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# Risk Prediction Models of Low Back Pain and Nephrolithiasis

# 요통 및 신장결석에 대한 위험도 예측 모형

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# Risk Prediction Models of Low Back Pain and Nephrolithiasis

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# Abstract

# Risk Prediction Models of Low Back Pain and Nephrolithiasis

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**Background**

A Complex Chronic Disease is a condition that involves multiple morbidities requiring the attention of multiple health care and facilities including community or home-based care. Prevention and mitigation of the effect of a single chronic condition, or constellation of conditions, requires improved measurement, and prediction. In developed nations, the prevalence of chronic diseases is increasing due to rapid aging of the population and the greater longevity of people with chronic conditions. Due to epidemiological transition, degenerative and life-style-related diseases have superseded infectious diseases in terms of morbidity and mortality in developed countries. These conditions have resulted into considerable cost both to individuals and to society through substantial health care needs and life-long disability. Thus, there is need to develop strategies to deal with age-

related conditions, especially considering the rapidly ageing population and the associated increase in health care expenditure. Low back pain was one of the most important contributors to the Korean DALYs in 2013, while the prevalence of nephrolithiasis and burden of disease has increased in Korea over the past 20 years. This study focused on two complex diseases; low back pain and nephrolithiasis, attempting to provide means of estimating risks and preventing these conditions.

**Low Back Pain**

**Introduction**: Low back pain is a common debilitating condition with a considerable economic burden to society, and accounting for over 10% of total insurance claims in Korea. Low back pain occurs in approximately 60–80% of people at some points in their lives, with a potential childhood onset, and an estimated 6-10% of acute low back pain patients developing chronic low back pain or experiencing repeated fluctuating pain episodes. There is still a knowledge gap regarding risk factors associated with onset of low back pain and its recurrence. Recently, longitudinal studies recommended assessing lipid profiles, atherosclerosis, hypertension, diabetes mellitus, and their relationship with low back pain. A 2018 systematic review by McIntosh *et al*., reported absence of validated prediction models for chronic low back pain. This study aimed at derivation and validation of prediction models and simplified risk scores to estimate future risk of developing low back pain, its recurrence, and chronicity using data from general medical practice. The study also aimed to assess the

association between risk factors for metabolic syndrome components and low back pain.

**Methods**: A population based prospective cohort study using routinely collected data from general medical practice in Korea. A total of 502,342 participants from National Health Insurance Service–National Sample Cohort (NHIS-NSC) enrolled from 2002 to 2010. Cox proportional hazards model and Prentice, Williams and Peterson Gap Time models were used in the analysis.

**Results**: During a median follow-up of 8.4 years (Range:1.49 to 8.99), there were 138,217 (31.5%) and 60,204 (13.2%) participants who experienced first onset of low back pain and chronic low back pain among 438,713 and 455,619 participants who were free of low back pain and chronic low back pain at baseline. From 503,482 participants, a consecutive cohort of 170,279 (33.8%) low back pain patients was constituted, and 49,462 (29.0%) and 106,927 (62.8%) patients experienced recurrent low back pain episodes within twelve (12) months and five (5) years of follow up, respectively. Metabolic syndrome components and premorbid conditions were associated with and predicted low back pain, although the direction of associations varied in univariate and multivariate analyses. The prediction equations of first onset of low back pain comprised of age, sex, and income grade, alcohol consumption, smoking status, physical exercise, body mass index, total cholesterol, fasting blood glucose, blood pressure and medical history of diseases. The prediction equations for 5-year low back pain recurrence comprised of age, sex, income grade, smoking status, alcohol consumption, body

mass index, total cholesterol, hypertension, physical activity, number of days of low back pain treatment and medical history of diseases. The Harrell's C-statistics for the prediction equations in the validation cohorts were 0.804 (95% CI, 0.796-0.812), 0.643 (95% CI, 0.629-0.656), 0.857 (95% CI, 0.847-0.866) and 0.759 (95% CI, 0.745-0.774) for first onset of low back pain, chronic low back pain, 5-year recurrent low back pain and 12-months low back pain recurrence, respectively. Based on simplified points based risk scores, age, disc degeneration, and sex conferred highest risk points for low back pain onset, whereas age, total days of prescription and disc degeneration conferred highest risk for 5-year recurrence.

**Conclusion**: This study implies low back pain is predictable, preventable and treatment of initial episode can effectively reduce risk of recurrence. The study also provides evidence that metabolic syndrome components are associated with low back pain outcomes and premorbid conditions are predictive of future low back pain, chronicity and its recurrence. Of particular interest, there was an inverse association between hypertension and chronic low back pain. However, there are some differences in predictors of onset, predictors of recurrence and chronicity of low back pain. Five low back pain prediction models that can estimate individuals' risk of developing and experiencing recurrent episodes have been developed and validated in a nationwide sample cohort using data from general practice. However, the derived equations cannot substitute the clinical expertise, but rather augment precision in clinical decision-making. Knowledge of the overall health status of a patient with respect

to low back pain risk and expert knowledge from clinical practitioners will create a much clearer picture than either one alone. These variables in the models can easily be obtained in clinical practice and the points system is simple to use. This study also offers an opportunity for external validation or updating the models by incorporating other risk predictors in other settings especially in this era of precision medicine.

**Nephrolithiasis**

**Introduction:** Nephrolithiasis is the presence of renal calculi in the urinary tract and kidneys caused by disruptions in the balance between solubility and precipitation of salts. Nephrolithiasis is a multifactorial disorder with complex aetiology and with a prevalence approximating 10% in Western countries. A study by Romero *et al*. reported a 5.0% prevalence of nephrolithiasis in South Korea and the disease burden has been increasing but to date no population specific nephrolithiasis risk prediction models have been developed and validated in Korea. Nephrolithiasis has been linked to metabolic syndrome, although conclusions have not been drawn. Well-validated risk prediction models help to identify individuals at high risk of diseases and to take preventive measures. Despite the abundant epidemiologic research on nephrolithiasis, longitudinal studies have not attempted to develop and validate nephrolithiasis risk prediction models using routinely collected medical data. This study aimed to develop and validate nephrolithiasis prediction equations and simplified risk scores from risk predictors that individuals and clinicians are likely to know. In addition, the study aimed to assess the

relationship between metabolic syndrome risk factors, premorbid conditions, and nephrolithiasis.

**Methods:** A prospective population based cohort study in Korea. A total of 502,342 participants from the National Health Insurance Service–National Sample Cohort (NHIS-NSC) enrolled from 2002 to 2010. Cox proportional hazard model was used in the analysis.

**Results:** During a median follow-up of 8.5 years (Range=2.0-8.9) and among 496,971 participants, there were 18,205 (3.7%) cases of nephrolithiasis. Metabolic syndrome components and premorbid conditions were associated with and predicted nephrolithiasis, although the strength of associations varied in univariate and multivariate analyses. The risk predictors in the parsimonious model for newly diagnosed nephrolithiasis included age, sex, income grade, alcohol consumption, body mass index, total cholesterol, fasting blood glucose, history of diagnosed gout, hyperparathyroidism and inflammatory bowel disease. The Harrell's C-statistic was 0.820 (95% CI, 0.806-0.834) and 0.819 (95% CI, 0.798-0.838) in the derivation and validation cohorts, respectively. Using the optimal threshold determined by Youden's index to define high-risk individuals, the model's sensitivity and specificity in the validation cohort were 76.5% (95% CI, 75.4% to 77.5%) and 62.0% (95% CI, 61.8% to 62.3%), respectively. During the median follow-up period, there were 7,086 (30.1%) recurrent cases of nephrolithiasis in the consecutive cohort of 23,576 patients. The cumulative risk of nephrolithiasis recurrence increased from 19.8 (95% CI, 19.3 to 20.4) to 37.6 (95% CI, 36.8 to 38.3) during a 5-year follow

up period. The parsimonious model for 5-year nephrolithiasis recurrence comprised of sex, age, body mass index, and total number of days of prescription. The Harrell's C-statistic was 0.926 (95% CI, 0.907-0.945) and 0.909 (95% CI, 0.879-0.935) for derivation and validation cohorts, respectively. Using the optimal threshold determined by Youden's index to define high-risk individuals, the model's sensitivity and specificity in the validation cohort were 66.0% (95% CI, 64.1% to 68.0%) and 77.5% (95% CI, 76.4% to 78.6%), respectively. Based on the simplified points based nephrolithiasis risk scores, age, sex, and body mass index conferred highest risk points for newly diagnosed nephrolithiasis, whereas total days of prescription, sex, and age conferred highest risk for 5-year nephrolithiasis recurrence.

**Conclusion**

This study implies nephrolithiasis might be a predictable condition, and the models might be used to screen a high-risk group. The derived prediction equations can be availed to general population in form of web-based calculator or used by medical practitioners to assess nephrolithiasis risk among health individuals and prognosis among patients who have recently developed nephrolithiasis. Knowledge of the overall health status of a patient with respect to nephrolithiasis risk and expert knowledge from clinical practitioners will create a much clearer picture than either one alone. These variables in the derived models can easily be obtained in clinical practice and the points system is simple to use. This study also offers an

opportunity for external validation or updating the model by incorporating other risk predictors in other settings especially in this era of precision medicine.

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**Keywords:** Complex Diseases, Low Back Pain, Nephrolithiasis, Chronic Disease, Episode, Recurrence, Prediction, Predictors, Prognosis, Risk Score, Derivation, Validation.

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**Abbreviations**

| | |
|---|---|
| BMD | Bone mineral density |
| CD | Complex diseases |
| CCD | Complex Chronic Diseases |
| CDC | Centers for Disease Control and Prevention |
| DALYs | Disability-Adjusted Life Years |
| DBP | Diastolic Blood Pressure |
| IBD | Inflammatory Bowel Disease |
| FBG | Fasting Blood Glucose |
| IVD | Intervertebral Disc |
| IVDD | Intervertebral Disc Degeneration |
| cLBP | Chronic Low Back Pain |
| KLWC | Korea Labor Welfare Corporation |
| KNHIS | Korean National Health Insurance Services |
| LBP | Low Back Pain |
| LDD | Lumbar Disc Degeneration |
| KCDC | Korea Centers for Disease Control and Prevention |
| KNIH | Korea National Institute of Health |
| RFS | Recurrence Free Survival |
| SBP | Systolic Blood Pressure |
| WHO | World Health Organization |

# I. Introduction

## 1.1 Background

A Complex Chronic Disease (CCD) a disease or condition that involves multiple morbidities requiring the attention of multiple health care, and facilities including community or home-based care. Patients or individuals with CCD present with functional limitations, disabilities and unique needs to the health care systems [1]. Chronic conditions are characterized by persistent and recurring health problems, a non-self-limited nature and long duration measured in months and years, not days or weeks [2]. Prevention and mitigation of the effect of a constellation of conditions or a single chronic condition requires improvement in measurement [3], and prediction. Pathogenesis of complex diseases involves integration of genetic and environmental factors over time [4]. The prevalence of chronic diseases varies across geographic region and time [5-7], and the incidence and prevalence rates in the developed world has been increasing in recent years [8]. In developed nations, the prevalence of chronic diseases has been increasing due to demographic changes as a result of rapidly aging population and the greater longevity of people with chronic conditions [9]. In addition to an increase in the number patients with specific diseases, multimorbidity is on rise, that is, the presence of multiple diseases in the same individual is on rise [10]. Due to epidemiological transition, degenerative and life-style-related diseases have superseded infectious diseases in terms of morbidity and mortality in developed countries [11]. These conditions have resulted into considerable cost to both

individuals and society through substantial health care needs and life-long disability, thus, urgent strategies should be developed to deal with age-related conditions, especially considering the rapidly ageing population and the associated increase in health care expenditures [12-14]. Low back pain was the most important contributors to the Korean DALYs in 2013 and the burden was highest in women [5], and nephrolithiasis disease burden has been increasing in Korea in past 20 years [15]. This study focussed on two complex diseases; low back pain and Nephrolithiasis, attempting to provide means of estimating risks and preventing these conditions.

Both low back pain and nephrolithiasis are recurrent and episodic conditions [16, 17], and the risk factors for onset, transition to chronicity or recurrence may be different, making prediction by a single model less accurate. Therefore, prediction of both low back pain and nephrolithiasis requires application of models that can capture the different outcomes presented in clinical practice. This study also aimed to provide prediction tools that can be utilised to predict the risk of chronic, intermittent, and episodic nature of both low back pain and nephrolithiasis using cox proportional hazard model and the extended cox proportional hazard models (Prentice -Williams and Peterson Models).

## 1.2 Low Back Pain

### 1.2.1 Background

Low back pain refers muscle tension, pain, or stiffness localized above the inferior gluteal folds and below the costal margin and may present with or without sciatica [18]. Previous studies have defined chronic low back pain (cLBP) as persistence of low back pain for 3 months [19-21], for six or more months including recurrent or seasonal episodes [22]. Low back pain (LBP) is a common musculoskeletal disorder causing disability, severe pain, and prolonged sick leave at personal and social expense [23]. Back problems are the leading cause of job-related disability and rank second in causing disability [24]. Approximately 60–80% of people experience low back pain during their lifetime [25], with a potential childhood onset [26], and an estimated 6-10% of acute LBP patients experience recurrent episodes or develop cLBP [16]. The annual and point prevalence of LBP were approximated to be 45% and 30%, respectively [27]. Lee *et al.,* reported a 17.1% total prevalence of LBP in South Korea with high prevalence in females (21.0%) than males (12.1%) [28], whereas among hypertensive individuals, lifetime prevalence was 34.4% [29]. The reported prevalence of LBP varies substantially depending on the case definition used [30].

LBP is a common complex and multi-factorial disorder [31, 32]. Despite the magnitude of the problem, the structural origin of most low back episodes is unknown, and the structural abnormalities have poor correlation with symptoms

[33], and often considered non-specific in origin [34], caused by certain diseases, injuries, sepsis and malignancy [35]. It has been estimated that 5–15% of LBP is attributable to specific causes [25, 36], whereas the remaining 85–95% of cases are non-specific in origin [37, 38].

Risk factors associated with low back pain include; female sex [39], older age [40], smoking [41], high job strain and job characteristics [42], high bodyweight [43], previous episodes of low back pain [42], psychological stress [44], and depression [45], physical inactivity [46], and income grade [47]. In addition, some comorbidities are associated with LBP including; coronary artery disease [48], dyslipidemia [49], diabetes mellitus [19], and disc degeneration [50], history of back injury [51], previous low back pain episodes [52, 53], bone mineral density disorders (BMD) [54], spinal stenosis [55], and spondylolisthesis [53]. Prediction models are useful in informing patients and physicians about individual's probability of having or developing a certain condition or disease and help them in decision-making [56].

### 1.2.2 Statement of the problem

Though a number of studies have been conducted on low back pain, previous studies recommended longitudinal studies to assess lipid profiles [57], atherosclerosis [58], hypertension [21, 29], diabetes mellitus [19], and their relationship with low back pain. A 2018 systematic review by McIntosh *et al*., reported lack of prognostic model validation in low back pain prediction studies

[59]. There is still a knowledge gap regarding risk factors associated with onset of low back pain, chronicity and its recurrence.

Prediction models estimate disease probability or any outcome or relate risk to the indication of a diagnostic test or treatment choice. Medical practitioners can use clinical prediction models to classify patients according to their probability of a given disease or in decision making regarding treatment benefits [60]. Prediction models should include factors that are predictive of a disease, feasible, realistic, and easily available; and the outcome of interest should be relevant and applicable in clinical practice. The predictors can include medical history, physical examination findings, and laboratory results [61, 62].

Well-validated risk prediction models help to identify individuals at high risk of diseases and aid decision making in relation to preventive measures. Studies have assessed risk factors associated with low back pain, but few have attempted to develop and validate prediction models of low back pain and its recurrence [59]. This study aimed to develop prediction models to estimate the 8-year risk of developing low back pain, its chronicity, and recurrence in a large population-based cohort study using data from general medical practice. Prediction models developed and evaluated can be incorporated into risk prediction tools and availed to the general population in form of web based electronic calculators or computerized systems in health facilities to assist in disease diagnosis and risk prediction. This study also aimed to provide prediction tools that can take care of the chronic, intermittent, and episodic nature of low back pain.

### 1.2.3 Main objective

This study aimed to assess risk factors associated with low back pain, and to develop and validate prediction equations to estimate the 8-year future risk of developing low back pain, its recurrence, and chronicity through a large population-based cohort study using routinely collected data from general medical practice.

### 1.2.4 Specific objectives

i. To derive and validate prediction equations and simplified risk scores to estimate the 8-year risk of developing low back pain, risk of twelve-months recurrence (12 months), five-year recurrence risk (5 years) and the risk of chronic low back pain in the Korean population using routinely collected health data.

ii. To assess the relationship between low back pain outcomes and the risk factors of metabolic syndrome.

iii. To assess the relationship between low back pain outcomes and premorbid conditions. This study focused on fasting blood glucose or history of diabetes mellitus, blood pressure or hypertension, dyslipidaemia, coronary artery disease, and disc degeneration, history of back injuries, spondylolisthesis, bone mineral density disorders, and spinal stenosis.

### 1.2.5 Research questions

i. Is the onset of low back pain, its recurrence, and chronicity predictable using data from general medical practice?

ii. Is metabolic syndrome or its risk factors associated with and predictive of low back pain outcomes?

iii. Do premorbid conditions predict onset, recurrence, and chronicity of low back pain?

iv. Are there any significant differences in the predictors of onset, predictors of chronicity or persistence, and predictors of recurrence of low back pain?

## 1.3 Nephrolithiasis

### 1.3.1 Background

Nephrolithiasis, urolithiasis or kidney stone, refers to the presence of renal calculi caused by disruptions in the balance between solubility and salts precipitation in the urinary tract and kidneys [63]. Nephrolithiasis is a common disorder with a prevalence approximating 10% in Western countries [64], and with a 50% recurrence rate at 5–10 years, which necessitates frequent urological treatments [65]. The incidence of nephrolithiasis peaks between age 20 and 30 years [63], but varies with sex and race [66]. Men have a twofold risk of stone formation compared to women, having a peak age of 30 years whereas women have a bimodal age distribution, with peaks at 35 and 55 years [67]. Generally, nephrolithiasis affects all age groups, sexes, and races [17, 68], although there is a high prevalence in men than in women within the age of 20–49 years [69].

Nephrolithiasis is highly prevalent in wealthy countries and is considered as a disease of affluence [70, 71], with substantial direct and indirect costs among working age adults [72]. The reported lifetime prevalence of nephrolithiasis in developed world ranges from 10–12% in men and 5–6% in women [73, 74]. A study by Romero *et al.,* reported a 5.0% prevalence of nephrolithiasis in South Korea [68], whereas Hyeon *et al.,* reported the expected lifetime prevalence of 6.0% and 1.8% among Korean men and women, respectively [75]. Recently, a worldwide increase in occurrence of kidney stone disease has been reported [69]. Despite the abundant epidemiological research on nephrolithiasis, longitudinal

studies have not attempted to develop and validate nephrolithiasis prediction models using data from general medical practice.

### 1.3.2 Statement of the problem

Although the prevalence and disease burden of nephrolithiasis has been increasing in Korea [15], to date no population specific nephrolithiasis risk prediction equations have been developed and validated in Korea. Nephrolithiasis is an increasing urological disorder, affecting approximately 12% of the world population [76]. The relapsing rate of secondary stone formations is estimated to be 10–23% per year, 50% in 5–10 years, and 75% in 20 years among patients [17]. Therefore, treatment and time lost from work involves substantial cost imposing an impact on the quality of life and nation's economy [76].

The pathogenesis of nephrolithiasis is complex and is a sequelae of several physicochemical events including supersaturation, nucleation, growth, aggregation, and retention of urinary stone constituents within tubular cells [76]. Previous studies have suggested nephrolithiasis to be a systemic disorder linked to metabolic syndrome [77], although conclusions have not been drawn. In addition, previous studies recommended further investigations to clarify on the relationship between calcium nephrolithiasis and metabolic syndrome [78], as well as the genetic basis of nephrolithiasis [79].

The prevention of nephrolithiasis recurrence requires better understanding of the mechanisms involved in stone formation [80], and putative risk factors. The

importance of understanding pathomechanisms of nephrolithiasis associated with stone inhibitors or promoters has been suggested to be crucial for discovering stone-removing medications [76]. Furthermore, understanding the pathophysiology, pathogenesis, and genetic basis of kidney stone formation could lead to discovery of novel drugs and strategies to manage urolithiasis [76].

Epidemiologic risk prediction models can aid in identification of individuals at risk of developing different medical conditions, thereby assisting medical practitioners in advising patients and institution of preventive measures. Previous studies have assessed several risk factors associated with nephrolithiasis but none has attempted to develop and validate prediction models using data from general medical practice in a large population-based setting. However, Kazemi *et al*., developed a model to predict stone type among kidney stone patients [81], but the risk of nephrolithiasis onset has not been studied using large prospective designs. Prediction of risk of developing nephrolithiasis can inform individuals about their risks, thereby promoting lifestyle adjustments to reduce associated risks, society costs, and associated comorbidities. To date, there is no population specific nephrolithiasis risk prediction models developed and evaluated using routinely collected medical data in Korea.

### 1.3.3 Main Objective

This study aimed to develop and validate nephrolithiasis prediction models from risk predictors that individuals from general population and clinicians are likely to know. The study also aimed to investigate associations between premorbidities, risk factors of metabolic syndrome components, and onset of nephrolithiasis.

### 1.3.4 Specific objectives

i. To derive and validate prediction models and simplified risk scores to estimate the 8-year risk of developing nephrolithiasis among apparently healthy individuals and its recurrence in Korea population.

ii. To examine the relationship between nephrolithiasis and premorbid conditions including diagnosed or medical history of coronary artery disease, gout, hyperparathyroidism, inflammatory bowel disease or ulcerative colitis and chronic kidney disease.

iii. To examine the relationship between risk factors of metabolic syndrome components and nephrolithiasis.

### 1.3.5 Research questions

i. Is nephrolithiasis predictable using data from general medical practice?

ii. Do premorbid conditions accurately predict onset of nephrolithiasis?

iii. Do risk factors of metabolic syndrome components predict onset of nephrolithiasis?

# II. Literature Review

## 2.1 Literature Review: Low Back Pain

### 2.1.1 Epidemiology of low back pain

Low back pain (LBP) is one of the commonest and challenging problems in medical care [82]. In 2010, LBP ranked highest in terms of global disability [14], with tremendous societal costs due to lost productivity and suffering [83]. LBP accounts for 90% of the total costs associated with absenteeism in Europe [84], and ranks as one of the greatest contributors to global disability [14]. Kim *et al*., found low back pain accounting for 10.2% of the total insurance benefit in Korea [85]. There is a large variation in prevalence of LBP, which is attributed to differences in study designs and settings amongst studies [86], differences in case definitions [30], and therefore general conclusions about LBP prevalence have not been drawn [87].

Low back pain is a global health problem affecting between 50% and 80% of people at some time in their lives [25, 88]. The annual incidence of low back pain in most developed countries varies between 4% and 5% [89]. The lifetime prevalence of low back pain among adults in Australia was estimated to be 79.2% [90], whereas in developing countries the mean lifetime prevalence was 62% [91]. A low prevalence of LBP among children and adolescents has been reported compared to adults, but recent trends show an increase in prevalence among the former and the prevalence peaks between 35 and 55 years of age [92-94]. The annual and point prevalence of LBP were approximated to be 45% and 30% [27], respectively, whereas another study estimated between 70% and 85% of the general population experiencing an episode of LBP persisting for more than 3

months [25]. Previous studies found an increase in LBP prevalence [95, 96]. However, some authors believe that the actual prevalence may not have changed, but the reporting has; or that it could be resultant of a change in questions used to assess the prevalence; or even resulting from real increase in LBP prevalence due to lifestyle changes of the populations [97]. A study conducted in Korea reported total prevalence of LBP at 16.6% with a remarkable disparity between men and women at 10.8% and 21.1%, respectively for self-reported back pain in the past 3 months [21], which was not different from the 15% prevalence reported in Korean population more than a decade ago [98].

### 2.1.2 Natural history of low back pain

Low back pain is a symptom, not a diagnosis, and usually with underlying structural abnormality [99]. The course of chronic low back pain is highly variable [100], and the best description of LBP should consider the quality of symptoms that accompany the pain and its duration [99]. The acute form of LBP has been defined as pain with immediate onset and lasting for 0-3 months, the sub-acute form as LBP with slow onset and lasting for 0-3 months, chronic LBP as persistence of pain for at least 3 months duration and recurrent pain as pain occurring after pain free interval [101]. However, most definitions of low back pain have ambiguities [102].

Previous studies have suggested low back pain to be episodic or recurrent [102, 103], and with approximately 36% recurrence rate within 12 months [104].

Experiencing more than two previous episodes of low back pain triples probability of a recurrence within 12 months [52]. The subacute low back pain or mild recurrent form usually has little impact on patient's well-being or function [99, 100]. However, recurrence is associated with multiple treatments and experiencing work related time loss, which are costly both to individuals and to the society [105].

The low back pain recurrence is different from both persistence of the original pain episode and a flare-up of the original episode. For an episode to be truly recurrent, a patient should first recover from the original episode and then experience a new low back pain episode [105, 106]. A systematic review suggested a minimum recovery period of 30 days pain-free period to denote the beginning of a new episode [106], but for record based studies, 3 months duration has been recommended [106]. However, most studies do not include recovery in recurrence definition which makes it difficult to differentiate between recurrences and persistence of low back pain [105].

## 2.2 Risk factors and pathogenesis of low back pain

### 2.2.1 Association between demographic risk factors and low back pain.

#### 2.2.1.1 Sex

Studies have reported sex differences in prevalence of LBP, with a high prevalence in women compared to men [107, 108]. Leveille *et al*., reported women to be greatly affected by many chronic pain conditions including those of musculoskeletal system in comparison with men [108]. The sex disparity is

partially attributed to sex differences in pain threshold, with women having a lower threshold compared to men [109-112]. A biopsychosocial model of chronic pain attributes sex differences in pain to interactions between biological, psychological, and sociocultural factors [39, 113]. Menstrual cycle associated fluctuations in pain sensitivity could be a plausible explanation for sex differences in pain reported in younger adults [114].

Several causes of LBP related to female sex have been reported including biologic response to pregnancy and parturition, physical stress of child-rearing and perimenopausal abdominal weight gain [107]. There is a significant difference in body composition between men and women [115, 116], with a stronger association between obesity and LBP in women compared with men [117]. The sex difference in the observed association between obesity and back pain is related to differences in hormonal influences and pain perception [118]. The difference in low back pain prevalence between school girls and boys was attributed to psychological factors, female hormone fluctuation, and menstruation [97].

Sex differences in body fat deposition are evident even at the foetal stage, becoming prominent during puberty [119], which may increase sex differences in risk of low back pain through other pathways. Sex differences in body composition has been attributed to the action of sex steroid hormones; which are responsible for dimorphisms during pubertal development, and reduction in free testosterone levels was associated with an increase in fat mass [120], which is associated with low

back pain. On the contrary, intervertebral disc degeneration (IVDD) which is strongly associated with LBP [121], is more severe and occurs at an earlier age in men compared to women [122]. The difference in severity has been attributed to increased mechanical stress and physical injury in men, although after menopause (49–50 years), lumbar discs degenerate at a faster rate in females [123-125].

#### 2.2.1.2 Age

The prevalence of widespread pain increases with age, peaking in the seventh and eighth decades [126, 127]. The advancement in age alters blood supply to discs [128], and occlusion of blood supply to intervertebral discs is strongly associated with LBP [129]. Generally, the incidence of low back pain increases with advancement in age toward the ages of 50-60s, thereafter decreasing gradually [130-132].

#### 2.2.1.3 Socioeconomic status

A previous study suggested a relationship between socioeconomic status and low back pain including occupational exposures [133]. Biomechanical loading has been suggested as the most important occupational factor predicting both recurrent low back pain and sick leave attributed to back disorders [134]. In addition, exposure to manual materials handling activities is an important risk factor consistently associated with work-related back disorders [135], with employees involved in such jobs more often on sick leave due to back pain [136, 137]. Physical load during work and leisure time are risk factors for back pain [138], and

reduction in physical load can reduce the burden of low back pain by 13–18% [139]. Furthermore, social class, low levels of educational and low-income are associated with LBP [140, 141]. However, a study conducted in Korea found no association between income levels and low back pain [28].

### 2.3 Association between lifestyle risk factors and low back pain

#### 2.3.1 Cigarette Smoking

Several lifestyle risk factors are associated with LBP [142]. Genetic studies of identical twins found an association between smoking and disc degeneration (DD) [129, 143], and smoking is associated with disc herniation [144], both of which are well-known risk factors for LBP. Two previous systematic reviews have produced equivocal results with one concluding that a positive association between cigarette smoking and LBP exists [145], whereas the other reported unclear findings [146]. However, most causal factors of multifactorial diseases have relatively weak effects [147]. Some studies assessing effect of smoking and occupation factors have reported an association between smoking and low back pain only in people with heavy physical work [148]. Iwahashi *et al.*, experimentally proved nicotine effects on the intervertebral disc in rabbits [149], which is suggestive of a causal role of smoking in the pathogenesis of low back pain.

#### 2.3.2 Alcohol consumption

The mechanisms of action and modulation of effects of alcohol on pain perception is unknown [150]. However, consumption of alcohol in excess is

associated with social and psychological problems that may significantly influence the pathogenesis of chronic LBP [151-153]. Alcohol consumption may be associated with LBP only in people with alcohol consumption dependence [154]. Alcohol dependence and chronic pain share common neural circuits, therefore chronic pain states may affect alcohol use patterns [155, 156]. In addition, alcohol use and stress influence onset of neuropathic pain [155]. Alcohol consumption increases both arousal and sympathetic activity of nervous system [157], and the latter has been implicated in certain forms of neuropathic pain [158]. However, a systematic review found no positive link between alcohol consumption and low back pain [159].

### 2.3.3 Physical activity

Physical inactivity accounts for 6% of deaths globally, ranking as the fourth risk factor in terms of global mortality [160]. Physical inactivity is linked with narrowing of the intervertebral discs and fat infiltration in the paraspinal muscles [161], which are associated with LBP [161]. Physical activity (PA) is recommended in primary care management of both the acute and chronic forms of LBP [162, 163]. There is evidence supporting continued physical activity as a key element of self-management in cLBP pain populations [164].

In other studies, the potential role of physical activity in the incidence of LBP was investigated [165-167], with no definitive conclusions. A previous study reported a weak positive association between physical activity and LBP [168]. The

occurrence of LBP is related to the nature and intensity of the physical activities undertaken [169]. A moderate frequency of exercise (1-5 times/week) was associated with a lower LBP risk compared with a higher or a lower exercise frequency [170]. However, in a study conducted in Korea, Lee *et al.,* found no association between physical activity and LBP [28].

### 2.4. Association between anthropometric measures and low back pain.

There mechanisms that have been proposed to explain the associations between anthropometric measures and LBP [117]. Heavy mechanical load may increase compressive forces or result into increased shear on lumbar spine structures [117]. Disc degeneration and associated structural modifications [171], or modic changes in vertebral endplates [172], may be related to increasing loads. Non-subcutaneous fat deposition may be associated with atherosclerosis [173], which may occlude blood supply to the lumbar region [174], thereby contributing to the pathogenesis of LBP. Accumulation of fat tissue may result in increased production of acute-phase reactants and cytokines [175], thereby activating pro-inflammatory pathways resulting in pain.

#### 2.4.1 Body Mass Index

Low back pain may be influenced by obesity through pathophysiology of diseases of tendons and ligaments during aging process [176]. A systematic review reported lack of information on temporality or reversibility and there was no consistent relationship between LBP and body weight [177]. However, a meta-

analysis conducted in 2010 suggested an increased risk of low back pain for both overweight and obesity [117]. An increased BMI is an established risk factor for LDD which is associated with LBP [178], although the strength of this association has been disputed [179].

### 2.4.2 Body weight and height

Weight accumulation exerts a greater mechanical load on joints and other structures, thereby increasing the rate of degeneration through excessive tear and wear [180]. In addition, accumulation of adipose tissue, especially in visceral compartments, contributes to inflammation mediated through a decrease in anti-inflammatory adipocytes and an increase in pro-inflammatory cytokines [181], which is associated with low back pain [182]. A prospective study indicated that simple body weight might equally provide a basis for describing low back pain risk as BMI [183].

A previous study reported an association between body height and LBP [20], although an earlier study found equivocal results for both low back pain and sciatica [184], in relation to body height. Tallness has been suggested as a risk predictor for back surgery [25, 185], disk instability under external loading [37], as well as alterations of facet joints in patients with lumbar disc hernia [38]. An earlier study found no significant interactions between waist circumference and height or waist to hip ratio and BMI on low back pain outcomes [186], suggestive of independence of height in predicting low back pain.

### 2.4.3 Waist circumference, Waist-hip-ratio and Waist to Height Ratio

Anthropometric measures such as waist circumference [187], and waist-hip-ratio [188], have shown stronger associations with mortality than body mass index. Studies found an association between LBP and hip circumference (HC) among women [189], and waist-hip-ratio [190]. An inverse association between waist-hip-ratio and LBP has been reported [191], whereas waist circumference (WC) showed a strong association with LBP among women compared to BMI and waist-hip-ratio [186]. In a study that assessed the associations with BMI, WC and HC among young adults, WC was the only positive association after a complete mutual adjustment [189]. However, these associations may represent commonality in the underlying relationship between LBP and total fat mass, suggestive that increase in structural or mechanical loads on the spine remarkably contribute to the pathogenesis of LBP among women [20]. There is need to assess the association between these alternative measures of obesity and LBP in order to understand the pathogenesis of low back pain.

## 2.5. Metabolic syndrome components and risk factors

Metabolic Syndrome (MetS) has been reported to increase the risk of atherosclerosis events [192], which are associated with LBP [193]. MetS may increase the risk of disc degeneration in the entire body [194], due to insufficient nutrient supply to disc cells [195-197], thereby contributing to the pathogenesis of low back pain. A previous study found an increased risk of cLBP in people with a

history of cardiovascular diseases [21]. In addition, high total cholesterol [49, 198], high LDL cholesterol [49, 198], low HDL cholesterol [57], high triglycerides [49, 198], diabetes [144], and hypertension [144, 190], are also independently associated with LBP. Metabolic syndrome may increase low back pain risk through several mechanism as described below.

### 2.5.1 Diabetes mellitus

The association between diabetes mellitus and spinal disorders including cLBP has not been thoroughly investigated to examine the pathophysiology between these conditions and the role of shared risk factors [19]. An earlier study found no association between diabetes and LBP [199], whereas a recent study found some evidence supporting a possible involvement of type 2 diabetes mellitus (T2D) in the aetiology of LBP [22], and disc degeneration [200]. T2D is also associated with spinal stenosis [201], a condition associated with cLBP [202, 203]. In addition, neuropathic and musculoskeletal pains are common conditions among adults with diabetes mellitus [204].

Diabetes mellitus was linked to a lower density of proteoglycans and undersulfated glycosaminoglycans of the IVDs, which may alter the mechanical properties of the tissues and increase susceptibility to disc prolapse and consequent mechanical back pain [205]. On the contrary, metformin, a commonly prescribed anti-diabetic medication may have anti-inflammatory properties, which can potentially mitigate some symptoms mediated by inflammatory degenerative changes [206].

### 2.5.2 Hypertension

There is high prevalence of both hypertension and musculoskeletal conditions in adult populations [29]. Unlike most cardiovascular disease risk factors, a lower prevalence and an inverse relationship between LBP and blood pressure among hypertensive individuals compared to normotensives has been reported [29]. There is evidence from studies supporting the hypertension-related hypalgesia theory that associates increased blood pressure with higher pain thresholds [29, 207].

Sheps *et al.,* studied the relationship between blood pressure and pain perception and found an increase in blood pressure associated with hypalgesic mechanism [96]. Furthermore, the difference in levels of plasma beta-endorphins between hypertensives and normotensives was reported to signify the relationship with endogenous opioids [208], which may partly explain differences in pain states. The production of antinociceptions also supports hypertension-related hypalgesia [209], although definite conclusions have not been reached [109, 112].

Stimulation of baroreflex arch caused by increased blood pressure inhibits pain transmission [265], which may be through interactions with brain centres that control cardiovascular reflexes in the brainstem and nociception. One study found a relationship between unstimulated baroreceptive sensitivity and pain thresholds [209]. The endogenous opioid activity that contributes to reduced pain sensitivity may be involved in hypertension-associated hypalgesia [266], and the mechanism of action of endogenous opioids is related to baroreceptors [57]. The endogenous

opioids play a critical role in the interaction between resting blood pressure and pain sensitivity, and endogenous opioid dysfunction is related to the pathogenesis of chronic pain [24].

The relationship between pain and blood pressure may be a result of a neurotransmitter involvement such as catecholamine [57], and genetic factors may play a role in this complex phenotype. The metabolism of catecholamine is regulated by catechol-O-methyltransferase (COMT) gene, and polymorphism of this gene is involved in the modification of pain response [210, 211], and blood pressure control [212]. In a recent study, hypertension especially DBP had a negative correlation with LBP irrespective of sex [21]. Medication with antihypertensive drugs has not demonstrated a significant reduction of hypoalgesia [213]. There is an inverse relationship between hypertension and chronic musculoskeletal conditions such as cLBP [214], and between systolic blood pressure (SBP) or diastolic blood pressure (DBP) and prevalence of musculoskeletal disorders including LBP [198]. However, a prospective study found no associations between hypertension and LBP [190], whereas some other studies found a positive association [198, 215]. Therefore, there remains a considerable debate regarding the physiology in the pain sensitivity-hypertension relationship.

### 2.5.3 Lipid profiles and related structural changes

Low Back Pain patients often have missing or narrow lumbar and sacral arteries [216], and calcification in the abdominal aorta or lumbar artery disease [174, 193]. LBP is associated with atherosclerosis due to reduction in blood supply, which consequently leads to disc degeneration [217]. Therefore, atherosclerosis risk factors are plausibly associated with LBP but results from studies are inconclusive [190, 218]. Atheromatous plaques are present in the abdominal aorta early in adult life, and by the age of 20 years, approximately 10% of the population in the developed countries have advanced lesions in the abdominal aorta [219]. The fastest increase and complications of lesions such as formation of plaques with necrosis, ulcerations, thrombi and calcifications occurs mainly after the fourth decade of life [89].

Atherosclerosis hypothesis was suggested on the basis that ischemia of the lumbar spine can cause degeneration of spine structures resulting into pain disorders [219]. Lipid levels may be involved in the pathogenesis of LBP by other mechanisms other than through atherosclerosis because dyslipidemia is related to inflammation [220], which may be linked to LBP in other pathways [211]. Heuch *et al*., recommended large prospective studies to assess potential relationships between lipid levels and LBP risk [57]. However, a study conducted in Korea found no association between chronic LBP and the Framingham risk score components used to predict the danger of cardiovascular diseases [21]. Medication and treatments for certain conditions may also influence the pathogenesis of LBP,

and statin use may retard the process of disc degeneration [209], thereby reducing risk of LBP. Shcherbina *et al*., recently recommended prospective studies to specifically investigate atherosclerosis and the risk of low back pain [58].

### 2.5.4 Coronary artery disease

The relationship between coronary heart disease (CAD) and LBP is controversial with some studies reporting a relationship between back pain severity and CAD [221], and between LBP and CAD associated mortality rate [222, 223], whereas other studies have not found any association [224, 225]. A recent study found a higher prevalence of CAD among individuals with spinal pain [22], as opposed to LBP alone [40, 226]. Furthermore, chronic musculoskeletal pain [227-229] and wide spread pain are associated with CAD [230-232]. A Spanish Co-Twin Control Study reported an association between cLBP and lifetime myocardial infarction and coronary heart diseases [48]. There is need to reassess the relationship between LBP and CAD in a large population based study.

## 2.6 Comorbidity, premorbid diseases, psychosocial and hereditary risk factors

### 2.6.1 Disc degeneration

Disc degeneration is the principal risk factor underlying onset of LBP [94, 146, 215-219]. Degenerative changes in the lumbar intervertebral discs are among the major causes of cLBP [121]. Intervertebral disc degeneration (IVDD) is a multifactorial and complex condition with risk factors such as aging, spine deformities and diseases, spine injuries, and genetic factors involved in its pathogenesis [233], and these are associated with LBP. Disc degeneration results

into disc disruption and discogenic pain syndrome and these together with non-nerve root referred LBP account for 26%-65.8% of chronic LBP cases in practice [234-237].

The pathogenesis of lumbar disc degeneration (LDD) involves degradation of the normal disc matrix into a disorganized fibrous and less cartilaginous disc which progresses to form clefts and fissures consequently affecting disc integrity [238]. These structural degenerative changes may contribute to the relationships between obesity and LBP [117], and obesity may modify the association between disc degeneration and LBP. The prevalence of LDD increases with age, and a linear trend of LBP incidence is reported to peak after 45 years [179]. However, disc degeneration may develop without LBP symptoms and patients may experience LBP without radiologically observable disc degeneration [239].

### 2.6.2 History of back injuries

A previous study reported a positive association between history of low back injury and future risk of LBP [51], and presentation with LBP following motor vehicle collision is a common finding in approximately 37% of accidents victims [240]. In another study, 60.4% of individuals injured in traffic accident reported LBP within 30 days [241]. Previous studies found a relationship between prior low back injury and current LBP [242, 243], but data from long prospective studies is still inadequate.

### 2.6.3 Spinal stenosis

Porter *et al*., reported a high frequency of small spinal canals among patients seeking treatment for back pain and canal size is a risk factor for severe back pain in early working life [244]. Visuri *et al.*, found stenosis of the nerve root canals at level L5/S1 frequent among cLBP patients [55]. Both developmental stenosis and degenerative changes may contribute to the pathogenesis of LBP [55]. The size of spinal canal greatly influences disc pathology in LBP patients and structural stenosis of lumbar spinal canal can worsen long-term prognosis of low back pain [245].

### 2.6.4 Spondylolisthesis

Spondylolysis is an anatomic defect in the vertebral pars interarticularis, and is frequently observed in the lowest lumbar vertebrae whereas spondylolisthesis is the displacement of a vertebral body on the one below it, mainly caused by spondylolysis and spondylolytic degeneration [246]. A previous study found a positive relationship between spondylolisthesis and LBP [53]. Lumbar spondylolysis and spondylolisthesis are common findings during clinical examination of LBP patients [246]. Both spondylolysis and spondylolisthesis are prevalent in the general population, and though sometimes asymptomatic, the relationship between these conditions and clinically significant LBP is still a controversy [246]. Previous studies reported an estimated 25% of individuals with spondylolysis experiencing at least one episode of significant back pain at some point in their lifetime. Furthermore, individuals engaged in certain sporting

activities have increased risk of developing symptomatic LBP associated with spondylolysis [247, 248].

### 2.6.5 Bone mineral density disorders

Manabe *et al.*, reported an association between increased bone mineral density (BMD) and LBP in middle-aged women after adjusting for several risk factors [54]. Both high and low bone mineral densities (BMD) as well as osteoporosis are important public health problems when considering the musculoskeletal symptoms in middle-aged women [54]. There is a correlation between levels of bone density in lumbar spine and distal radius [249, 250], and radial BMD predicts both vertebral deformity [249], and degenerative changes of the lumbar spine [251, 252]. Osteoporosis is a characteristic condition of diminishing bone content and increasing damage to the bone architecture [253]. Vertebral deformity is one of the cardinal manifestations of osteoporosis and its prevalence increases with age [254, 255]. Cockerill *et al*., suggested that LBP and disability could be attributed to vertebral deformities [256, 257].

### 2.6.6 Systemic inflammation

Different pain conditions are associated with elevated serum levels of pro-inflammatory biomarkers, such as cytokines and c-reactive protein (CRP) [258]. Cytokines are regulatory proteins (pro-inflammatory biomarkers) which modulate the inflammatory response of the immune system [9]. Studies have produced some evidence suggesting pro- and anti-inflammatory cytokines modulation of central

and peripheral pain [259]. A previous study found a significant increase in plasma levels of interleukin (IL)-6 among LBP patients [260], which has been confirmed in a systematic review [261].

### 2.6.7 Psychological factors

Psychological factors influence pathogenesis of LBP [151-153]. In addition, psychological factors are associated with LBP treatment outcomes [262], and may influence the persistence and recurrence of LBP. This relationship is emphasised in bio-psychosocial model [263], and the fear avoidance model [264]. Based on the bio-psychosocial model, patient's functioning is influenced by biological, psychological, and social factors. Psychological factors such as distress [265], self-efficacy, fear-avoidance beliefs, coping styles and cognitive factors are presumed to significantly influence back pain disability compared to biomedical or biomechanical factors [266, 267].

There is an assumption that psychological factors are strongly related to disability in patients with chronic LBP [264]. The relationship between psychological factors and disability in patients with cLBP has been investigated but results are contradictory [263, 268]. Some studies reported moderate association between psychological factors and self-reported disability in cLBP patients [269, 270], whereas the relationship was not confirmed in other studies due to weak associations [271, 272]. There is also evidence supporting a

biopsychosocial interaction between emotional disorders and obesity with LBP [34], which suggests that the association may be mediated through other risk factors.

### 2.6.8 Genetics and heredity

The manifestation of chronic back pain depends on psychosocial, structural, occupational, and genetic factors [273]. A previous study reported an association between having a sibling with cLBP and presence of LBP [274]. Genetic influences are modulated by genes controlling the immune response or influencing intervertebral disc degeneration and genes involved in pain perception, signaling and psychological processing [275]. Therefore, genetics may modulate the pathogenesis of LBP through different pathways.

Heritability of back pain ranges from 30% to 45% [275, 276]. There is also a strong heritability of disc degenerative changes among twins [277]. Genes related to structural proteins of the discs (collagens and aggrecan) and genes controlling inflammation and matrix degradation are associated with pathologic and radiographic changes of LDD [278-281]. Genetic variants coding for inflammatory mediators are associated with different LDD phenotypes [280, 281], and may influence pathogenesis of LBP. These genetic variants are involved in peripheral modulation of pain [282]. Interleukin 18 (IL18) also induces synthesis of tumor necrosis factor-alpha (TNFα) which is involved in the pathogenesis of discogenic pain [283]. In addition, COX2 gene (PTGS2) may be involved in disc herniation through up regulation of prostaglandin E2 (PGE2) [284], and in the peripheral

modulation of pain [282]. Furthermore, a meta-analysis found evidence supporting the association between PARK2 gene and degeneration of the intervertebral disc, which is thought to be mediated through methylation of the PARK2 promoter [285].

# 2.7 Literature Review: Nephrolithiasis

### 2.7.1 Epidemiology of Nephrolithiasis

Nephrolithiasis, kidney stone or urolithiasis refers to the presence of renal calculi resulting from disruptions in the balance between precipitation and solubility of salts in the urinary tract and kidneys [63]. The incidence of nephrolithiasis peaks between age 20 and 30 years [63], but varies with sex and race [66]. Men have a twofold risk of stone formation compared to women, having a peak age of 30 years while women have a bimodal age distribution, with peaks at 35 and 55 years [67]. Nephrolithiasis or kidney stone disease is a common health disorder in developed countries with a reported lifetime prevalence of 10–12% in men and 5–6% in women [73, 74], and is considered as a disease of affluence [70, 71], with substantial direct and indirect costs among working age adults [72]. A study by Romero *et al*., reported a 5.0% prevalence of nephrolithiasis in South Korea [68], whereas Hyeon *et al*. reported the expected lifetime prevalence of 6.0% and 1.8% among Korean men and women, respectively [75].

Recently, a worldwide increase in occurrence of kidney stone disease has been reported [69], and incidental detection of uric acid renal stones has become more prevalent in Korea in the past 20 years [15, 286]. In the United States, the prevalence of nephrolithiasis was 8.8%, with a significantly growing incidence [287]. Nephrolithiasis is associated with high morbidity and healthcare spending [288]. Despite the abundant epidemiological research on nephrolithiasis, longitudinal studies have not attempted using routinely collected medical data to develop and validate nephrolithiasis prediction tools.

### 2.7.2 Risk factors and pathogenesis of nephrolithiasis

Nephrolithiasis is a multifactorial disorder [76], with constitutional, environmental, and genetic factors playing significant roles in the aetiology and pathogenesis of renal stones [289, 290]. In addition, metabolic risk factors contribute to the pathogenesis of kidney stone formation [289]. Risk factors associated with nephrolithiasis include; male sex, age and race [68], high socioeconomic status [291], body mass index [292], blood pressure levels [291, 292], diagnosed hypertension [292], diabetes and gout [292], chronic kidney disease [292], hyperparathyroidism [293], Crohn's disease and ulcerative colitis [294, 295], smoking [296], alcohol consumption [297], and metabolic syndrome [298]. In addition, nephrolithiasis risk factors may be genetic or related to specific diseases, for instance idiopathic hypercalciuria, medullary kidney disease, polycystic kidney disease, hyperoxalosis, Dent's disease, irritable bowel disease (IBD), hyperparathyroidism, and renal tubular acidosis, or sarcoidosis [63].

Nephroliths (calculi) are mineral concretions in the pelvis and renal calyces, which may be free or attached to the renal papillae [80]. Stones that develop in the urinary tract (nephrolithiasis or urolithiasis) form due to excessive supersaturation of with respect to a mineral, leading to crystal formation, aggregation, growth and retention within the kidneys [299]. In addition, urine supersaturation can result from relatively insoluble drugs or their metabolites, leading to crystallization in the renal collecting ducts (iatrogenic stones) [300].

The probability of stones occurrence increases when one or more factors are present that lead sequentially to supersaturation of the urine, the formation of crystals, and their subsequent aggregation into a clinically detectable stone. However, individuals without nephrolithiasis may excrete crystals; although calcium oxalate stone formers have a higher risk of crystalluria, and the presence of crystalluria significantly increases the risk of stone formation [301]. Although nephrolithiasis is a recurrent condition, recurrence is preventable by medication or dietary interventions [66].

## 2.8 Association between demographic factors and nephrolithiasis

### 2.8.1 Sex

Men have a twofold risk of stone formation compared to women, with a peak age of 30 years while women have a bimodal age distribution, with peaks at 35 and 55 years [67]. A previous study has attributed the rapid increase in stone disease treatments in women to increasing obesity, dietary changes, and decreased fluid intake [302]. In addition, estrogen may play a role in the pathogenesis of nephrolithiasis [303], and estrogen therapy may potentially decrease nephrolithiasis recurrence risk in postmenopausal women through reducing calcium oxalate saturation and lowering urinary calcium [304]. On the contrary, there is an inverse association between low-testosterone and nephrolithiasis [305]. These associations may explain the sex differences in relation to nephrolithiasis risk.

### 2.8.2 Age

Nephrolithiasis is unusual in children, with an incidence of approximately 0.15% [306], significantly lower than the incidence among adults. However, approximately 40% of children with nephrolithiasis have a positive family history, suggestive of genetic predisposition [307]. Generally, the incidence of nephrolithiasis peaks between age 20 and 30 years [63], but varies with sex and race [66]. Advancement in age is accompanied with taking medications for various age related diseases and vitamin supplements, both of which can potentially alter metabolic profiles and increase susceptibility to stone formation [308].

### 2.8.3 Socioeconomic status

Eisner *et al.,* reported a positive association between increasing poverty and increased urine calcium, whereas increasing education was protective against urine calcium and supersaturation of calcium phosphate and calcium oxalate [309]. In another study, socioeconomic status was associated with history of kidney stones [287]. Some occupations such as factory work are associated with exposures to higher ambient temperatures. Mass *et al.,* reported that some workers have infrequent fluid intake because of limited access to bathroom facilities leading to low-volume-associated stones [310].

## 2.9 Association between lifestyle risk factors and nephrolithiasis

Dietary and lifestyle factors may play a significant role in the changing epidemiology of kidney stones [287]. Previous studies indicated an increase in

prevalence of kidney stones worldwide among adults but the reasons for this increase are not clear. Suggestions point to changes in lifestyles, dietary habits, and increased prevalence of obesity as contributory factors [311].

### 2.9.1 Cigarette Smoking

Cigarette smoking is described as the major preventable cause of morbidity and mortality in the world [290]. Cigarette smoke contains antigenic, cytotoxic, mutagenic, and carcinogenic substances, most of which significantly affect the physiology of human body, with a possibility of damaging almost every organ [312]. Cigarette smoking is an independent risk factor in the pathogenesis of nephrolithiasis [290, 313, 314].

### 2.9.2 Alcohol consumption

A previous meta-analysis found alcohol consumption protective against urolithiasis, and a dose-response relationship was observed [297]. There are studies that have reported on benefits of alcohol consumption in relation to several health outcomes [315]. On the contrary, alcohol metabolites may cause DNA damage, resulting in diseases [316]. Alcohol components and its metabolites are excreted through the urinary tract; therefore, a role of alcohol in pathogenesis of urinary disorders is possible. The basic mechanism of alcohol-induced calculi is hypercalciuria and hyperoxaluria contributing to calcium oxalate crystal formation [317].

The consumption of alcohol is also related to severe oxidative stress to renal tissue, which could be an inducement for renal stone formation [318]. However, alcohol consumption may dilute metabolites in the blood and urine, and the diuretic effect of alcohol could possibly increase the frequency of voiding, thereby decreasing the risk of diseases [297]. A previous study conducted in USA reported that the risk of kidney stone could decrease by 59% with every increased 240 ml intake of red wine [319]. In addition, an increase in total fluid intake can reduce risk for kidney stones, but the choice of beverage may be important [319].

### 2.9.3 Physical activity

A previous study based on three large prospective cohorts found no associations between physical exercise, energy intake, and incidence of kidney stones [320]. In another study, results suggested a positive association between diabetes and adiposity and nephrolithiasis risk, but no association with physical activity [321]. However, physical activity may reduce weight gain [322], and the risk of type 2 diabetes [323], and may potentially reduce the risk of kidney stones [321].

## 2.10 Association between anthropometric measures and nephrolithiasis.

Nowfar *et al.,* found obesity associated with nephrolithiasis risk irrespective of age and sex, although a higher prevalence was reported in obese women as compared with obese men [324]. Generally, obesity prevalence increased from

30.5% to 35.7% between 2000 and 2010 [324], and is a potentially modifiable risk factor that affects pathogenesis and progression of kidney-related diseases [325].

### 2.10.1 Body Mass Index

A previous study reported that an increase in BMI increases the risk of calcium phosphate, calcium oxalate monohydrate and dihydrate and uric acid stones with positive correlations between BMI and urine calcium oxalate and sodium [326]. The magnitude of the increase in risk attributed to BMI is higher in women than in men [66]. Previous prospective studies found a correlation between incidence of urolithiasis and an increase in obesity [70, 288]. Powell *et al.*, found urinary pH, which is predictive of uric acid stones negatively correlated with body weight [327], and obesity induces insulin resistance, disturbs ammoniagenesis and Na+/H+ activities, thereby promoting the development of ureteral stones [328].

### 2.10.2 Waist and hip circumference, waist-hip-ratio and waist to height ratio

Taylor *et al.,* found a positive association between waist circumference (WC) and nephrolithiasis risk in men and in older and younger women [288]. Akarken *et al*., reported the ratio of visceral to subcutaneous adipose tissue as an emerging factor in the formation of kidney stones, in addition to hyperlipidemia, hypertension and obesity [329]. Furthermore, several studies have reported a positive association between a large WC and weight gain and nephrolithiasis risk [288, 330].

Adiposity is related to insulin resistance and evidence suggests involvement of insulin resistance in the nephrolithiasis etiology [331]. In a study conducted in Japan, insulin was associated with a history of kidney stones, suggestive that MetS components can potentially increase nephrolithiasis risk through hyperinsulinemia and insulin resistance [331]. Studies have investigated and reported a positive association between obesity and nephrolithiasis [325], but there no studies that have assessed the relationship between nephrolithiasis and alternative measures of obesity.

### 2.11 Association between metabolic syndrome and nephrolithiasis

Metabolic Syndrome (MetS) and its component including diabetes, obesity and hypertension, are interrelated clinical conditions that are independently associated with an increased risk of nephrolithiasis [288, 332, 333]. Metabolic syndrome (MetS) is a characteristic increase in values of serum glucose, lipids and blood pressure, as well as central obesity. MetS is associated with an increased risk of nephrolithiasis [298]. The risk of nephrolithiasis increases when two or more of these conditions act jointly [77, 334]. In addition, a previous study reported a positive association between a history of nephrolithiasis and cardiovascular disease [335], suggestive that nephrolithiasis may share some risk factors with these conditions. Most nephrolithiasis patients have increased arterial calcification and stiffness, which may explain the higher cardiovascular risk observed in stone formers [79]. The prevalence of MetS in Korea has increased significantly, from

24.9% in 1998, to 29.2% in 2001, 30.4% in 2005, and 31.3% in 2007 [336], which may result in increased incidence of nephrolithiasis.

### 2.11.1 Diabetes mellitus

Lieske *et al*., reported a bidirectional relationship between diabetes and urolithiasis, in which type 2 diabetes (T2D) increases urolithiasis risk, and a high T2D prevalence in patients with nephrolithiasis [333]. Another study confirmed an increased incidence of nephrolithiasis among diabetic people, which was independent of age and BMI [337]. Furthermore, presence of T2D was identified as the strongest risk factor in the pathogenesis of uric acid stones [338].

The association of diabetes and MetS with uric acid urolithiasis may involve insulin resistance, which is a principle metabolism disorder in both diabetes and MetS, and disrupts ammoniagenesis resulting in low urine pH, thereby promoting uric acid stone formation [287]. Cameron *et al*., reaffirmed an inverse relationship between urine pH and body weight, and deducted that the main nephrolithiasis risk factor in patients with T2D is a low urine pH [339]. Increased net acid excretion and reduced renal ammonium are the pathomechanisms for urinary pH in uric acid urolithiasis. Insulin resistance can impair the production and transport of ammonia but the underlying mechanism of increased acid production remains unknown [79]. However, an earlier study reported that insulin reduces calcium reabsorption by acting on the renal tubules [340].

### 2.11.2 Hypertension

Hypertension is individually associated with an increased risk of nephrolithiasis [333], independent of renal function, body mass and age [341, 342]. Kohjimoto *et al*., confirmed a correlation between hypertension and nephrolithiasis recurrence independent of MetS traits, sex and age [343]. Although the pathomechanisms underlying this relationship remains uncertain, the association between hypertension and nephrolithiasis appears to be bidirectional [341, 344].

### 2.11.3 Lipid profiles and Coronary Artery Disease

Kohjimoto *et al*., found an association between dyslipidemia and multiple nephrolithiasis recurrence independent of MetS traits, sex and age [343]. Epidemiological studies have linked hyperlipidemia and urine metabolic profiles and stone composition [345]. These correlations between dyslipidemia and nephrolithiasis are indicative of possible participation of a common mechanism such as inflammation, oxidative stress, and insulin resistance that may contribute to pathogenesis of nephrolithiasis in metabolic syndrome [343].

A previous study reported a correlation between serum concentrations of lipid components and urinary changes [345]. Furthermore, high total cholesterol was predictive of high urinary calcium and potassium, whereas low HDL or high triglyceride levels showed correlation with increased oxalate, urine sodium, uric acid, and a lower urine pH [345]. In addition, a high triglyceride level or total cholesterol was associated with an increased risk of uric acid stone formation [345].

Cho *et al*., found a significantly increased serum uric acid, lower urine pH, and increased percentage of uric acid stones in MetS patients [332]. In animal studies, pathogenesis between hyperlipidemia and kidney stones in rats has been explained by inflammation and damage in renal tubular cells [346]. On the contrary, MetS and hypertension were independent risk factors in nephrolithiasis, but not for the other characteristic parameters of metabolic syndrome [298].

## 2.12 Association between diseases, medication, genetics, and nephrolithiasis

### 2.12.1 Chronic Kidney Disease

A history of nephrolithiasis increases the risk of Chronic Kidney Disease (CKD)[347]. The kidneys function in excretion of metabolic wastes such as oxalate and calcium at supersaturated concentrations preventing precipitation of crystals, therefore, stone formation may be a form of malfunction or sign of a diseased kidney [348]. A previous study has recommended further studies to investigate underlying mechanisms underlying the relationship between nephrolithiasis and CKD, which may aid identification of effective preventive and therapeutic measures [347].

### 2.12.2 Primary hyperparathyroidism

Primary hyperparathyroidism (PHPT), renal tubular acidosis, and Crohn's disease increase the risk of calcium containing nephroliths. The prevalence of primary hyperparathyroidism among stone formers was approximated to be 5% [293], and renal impairment is a common finding in primary hyperparathyroidism

[349]. Gopal *et al*., reported nephrocalcinosis in 40.5% and presenting as a complaint in 15.1% of the hyperparathyroidism patients, respectively [350].

### 2.12.3 Inflammatory bowel disease and ulcerative colitis

There is an association between chronic diseases characterized by intermittent diarrhea such as Crohn's disease and ulcerative colitis, and the formation of renal calculi [294]. Inflammatory bowel disease (IBD) is characterized by malabsorption and diarrhea which increases the risk of renal calculi formation [351]. Nephrolithiasis is highly prevalent among patients with IBD (7%–15%) than in the general population (1%–15%), typically in patients with persistent severe small intestine enteritis or history of extensive small bowel resection [351, 352]. The incidence of urinary tract calculi is reportedly higher in patients with IBD than in the general population [353]. Furthermore, patients with history of ostomy are at increased risk of developing urate stones than calcium oxalate stones [352, 354, 355]. Among patients with Crohn's disease (CD) of the terminal ileum, 7–15% have episodes of renal stones [356].

### 2.12.4 Premorbid Gout

A history of gout increases nephrolithiasis risk, both calcium oxalate and urate. Kramer *et al*., reported that gout patients are 50% more likely to have a history of nephrolithiasis [357], but in prospective examination, a history of gout was associated with a twofold risk of nephrolithiasis independent of weight, diet and medications [358]. Although the mechanism for this relationship is unknown,

acid-base defects and insulin resistance are suspected [66]. People with gouty arthritis may form nephroliths [76].

### 2.12.5 Bone mineral density

Nephrolithiasis is associated with low bone mineral density (BMD) and fractures risk [359]. Low bone mineral density is independently associated with incident nephrolithiasis [360]. There is an inverse association between high potassium intake and urinary tract stones and osteoporosis [361, 362]. Vertebral fractures and urinary tract stones are highly prevalent in hyperparathyroidism [363], which is associated with nephrolithiasis [350]. A previous study reported an association between increased rates of low BMD and nephrolithiasis in children [364]. The role of estrogen on bone integrity is a possible explanatory mechanism in the observed association between BMD and nephrolithiasis [303]. However, further studies were recommended to confirm the possibility of a potentially common underlying pathomechanism leading to extraosseous calcium deposition and osteoporosis in nephrolithiasis [365].

### 2.12.6 Drug-Induced Stones

Drug-Induced stones account for approximately 1% of all stone types [366]. Drugs such as atazanavir, triamterene, guaifenesin, and sulfa drugs can induce kidney stones. A previous study found people who take the protease inhibitor indinavir sulphate, a drug used to treat HIV infection, at risk of nephrolithiasis [367]. These lithogenic drugs or their metabolites can form a nidus or superimpose

on preexisting renal calculi. On the other hand, these drugs may act through metabolic action by interfering with purine metabolisms or calcium oxalate, thereby inducing formation of nephroliths [368].

### 2.12.7 Genetics and family history

Genetic causes of renal stones are highly prevalent in children [369]. Calcium nephrolithiasis and idiopathic hypercalciuria are multifactorial complex diseases with 50% of their pathogenesis relating to a number of genes [370, 371]. Familial cases of renal stones are frequently observed in idiopathic calcium stone disease, and a positive family history of nephrolithiasis is reported in 15–20% of stone formers [372, 373]. The risk of stone formation is high (>2.5 times greater) in individuals with a family history of nephrolithiasis [373]. Previous study of monozygotic twins found heritability and genetic contributions of approximately 56% for nephrolithiasis [374], and 79% of children with nephrolithiasis have a first or second degree family history [375].

Genetic abnormalities leading to stone formation including primary hyperoxaluria and cystinuria contribute to the burden of disease in the kidney stone population [376]. In particular, cystine stones that are due to a genetic disorder of amino acid and cystine transport comprise less than 2% of all stone types. This condition is an autosomal recessive disorder caused by a defect in the rBAT gene on chromosome 2 [286], resulting in an excess of cystine in urinary excretions

[377], due to cystine leaking into urine or impairment of absorption of cystine in renal tubules.

# III. Methods and Materials

### 3.1 Study design, setting and cohort description

This study was a population based prospective cohort in Korea using data from National Health Insurance Service–National Sample Cohort (NHIS-NSC) collected from 1st, January 2002 to 31st, December 2010. The study considered all eligible participants and subjects with missing exposure data on some variables were included in the analysis after data imputation. For incident outcomes (prediction of first onset of low back pain or nephrolithiasis, which was first medical utilisation due to low back pain or nephrolithiasis), participants with history of the respective conditions at baseline were excluded. For each outcome, the data set was divided into derivation and validation cohorts employing the split sample method using a ratio of 2:1 with subjects assigned randomly [378]. The random splitting of the data ensured that each risk prediction model developed could be validated in a new data set from a different part of the intended population [378].

The NHIS-NSC comprises of members from different professions and demographic attributes, making it representative of the general Korean population. This database contains longitudinal anonymised patients' records of all claims data, including disease diagnostic codes, treatment details, monthly insurance premiums, prescriptions, laboratory clinical results, physician visits, and demographic information. The disease diagnostic codes are based on the Sixth Revision of the Korean Classification of Diseases (KCD-6), which is compatible with the Tenth

Revision of the International Classification of Diseases (ICD 10th Revision) [379]. The detailed description of this cohort profile has been published elsewhere [380].

### 3.2 Data extraction and choice of risk predictors

#### 3.2.1 Low back pain risk predictors

Based on literature reviews and established hypotheses, data on disease diagnosis, date of diagnosis, sex, age, insurance premium as a proxy for income grade (socioeconomic status), anthropometric measures, smoking status and alcohol consumption, physical activity, fasting blood glucose, total cholesterol, blood pressure measures, previous low back pain episodes and premorbid conditions including diabetes, coronary artery disease or ischemic heart disease (IHD), hypertension, disc generation, spondylolisthesis, history of back injury, bone mineral density disorders and spinal stenosis were extracted. Furthermore, medication information including total days of hospital admission, total days of prescription (treatment duration) and number of consultation visits were extracted.

#### 3.2.2 Nephrolithiasis risk predictors

Based on literature reviews and established hypotheses, data related to nephrolithiasis risk factors was extracted including disease diagnoses, date of diagnosis, sex, age, insurance premium as a proxy for income grade (socioeconomic status), anthropometric measures, smoking status, alcohol consumption, physical activity, fasting blood glucose, total cholesterol, blood pressure measures, and premorbid conditions including (diabetes, hypertension,

ulcerative colitis or inflammatory bowel disease (Chrohn's disease), chronic kidney disease, gout, hyperparathyroidism and coronary artery disease).

In this study, the date of onset was (1st, January, 2004) and the baseline period was between (1st January, 2002 to 31st December, 2003). For each participant, the first recorded data at baseline was used in the analysis and missing data was handled by imputation. This excluded the possibility of nephrolithiasis status influencing the values recorded for the risk factors. In order to ascertain premorbid conditions, ICD-10-CM diagnostic codes were used to extract diagnosis status for gout, chronic kidney disease, Chrohn's disease, diabetes, hypertension, coronary artery disease, and hyperparathyroidism.

### 3.3 Assessment and measurement of covariates

#### 3.3.1 Handling missing data and measurements of risk predictors

In longitudinal studies, data from repeated measurements of a given covariate within the same participant has remarkable correlation. Therefore, imputation of missing values based on neighboring values is a reliable approach than most imputation methods [381]. Using non-missing data of the same participant can aid in estimation of missing values in longitudinal imputation. In this study, missing values were imputed using fully condition specification (FCS) method by treating repeated measurements (same covariate measured at different dates in an individual) as distinct variables in the imputation model [382]. This approach has been referred to as "Just Another Variable" [382].

Non-linearity was handled by categorisation of variables into clinically meaningful groups. Body mass index (BMI) was categorised as (<18.5 kg/$m^2$, 18.5 kg/$m^2$-24.9kg/$m^2$, ≥25kg/$m^2$-29.9kg/$m^2$, ≥30kg/$m^2$); smoking was categorised as (never, former, and current smoking) whereas alcohol consumption was categorized into [Rarely (<2 times/month), moderate drinker (2-3 times/month) and heavy drinker (>3 times/month). Physical activity was categorised based on frequency per week into [Low (None), moderately active (1-2 times/week) and very active or high (≥3 times/week)], socioeconomic status was categorised based on insurance premium on scale of 100% to proxy income grade as (low <30%, medium 30-60% and high >60%). Hypertension status was categorised as [(SBP <120 mmHg and DBP <80 mmHg, SBP 120-139 mmHg or DBP 80-89 mmHg, SBP 140-159 mm Hg or DBP 90-99 mmHg, SBP ≥ 160 mmHg or ≥100 mmHg or medical utilisation due to hypertension (Rx)]. Fasting glucose was categorized as [(<100 mg/dL, 100-125mg/dL, ≥ 126 mg/dL or medical utilisation due to diabetes (Rx)]. Total cholesterol was categorised as (<200 mg/dL, 200 mg/dL-240 mg/dL, >240 mg/dL). For low back pain outcomes, baseline age was categorised as (<45 years, 45-54 years, 55-64 years and >64 years) whereas for nephrolithiasis, baseline age was categorised as (<25 years, 25-34 years, 35-44 years, 45-54 years and >54 years).

### 3.3.2 Low back pain premorbid predictors

Premorbid conditions were identified using ICD-10-CM diagnostic code lists for diabetes (E10-E14), coronary artery disease (I20-I25), hypertension (I10-I15) and IVDD as relevant selected codes between (M50-M518), disorders of bone mineral density and structure (M80-M85), spinal stenosis (M480.0-M480.8), spondylolisthesis (M4310-M4318) and [back or spine, hip and thigh injury as (S130- S139, S330-S3319 and S70-S79, respectively)] recorded before the end of baseline period. The study considered both primary and secondary diagnostic codes. Two years (1st January, 2002 to 31st December, 2003) were considered the baseline with the date of onset as 1st January 2004.

### 3.3.3 Nephrolithiasis premorbid predictors

History of diagnosed medical conditions was ascertained basing on the presence of ICD-10-CM diagnostic records for diabetes (E10-E14), hyperparathyroidism (E211-E215), hypertension (I10-I15), Coronary artery disease or Ischemic Heart Disease (I20-I25), chronic kidney disease (N18.1-N18.9), gout (M10.0-M10.17) and inflammatory bowel disease (IBD) as selected related codes between (K50-K52).

## 3.4 Case definition, prospective ascertainment, and exclusion criteria

### 3.4.1 Low Back Pain

Low back pain was ascertained using ICD-10-CM diagnostic codes (categories); including codes for low back pain (M54.5, M54.50, M54.51, M54.52,

M54.53, M54.54, M54.55, M54.56, M54.57, M54.58, M54.59, M54.9), codes for lumbago with sciatica (M54.4, M54.40, M54.41, M54.42, M54.43, M54.44, M54.45, M54.46, M54.47, M54.48, M54.49) and codes for sciatica (M54.3, M54.30, M54.31, M54.32, M54.33, M54.34, M54.35, M54.36, M54.37, M54.38, M54.39). The above categories have been used in case definitions of low back pain in other studies [383-385].

All the five low back pain outcomes in this study were treated as time-to-event outcomes. The outcomes were defined in accordance with previous proposed definitions [102]. Newly diagnosed or first onset of low back pain was defined as first occurrence of back pain in individuals without low back pain at baseline [102], 5-year recurrent low back pain was defined an episode or series of low back pain episodes occurring after at least 90 days (3 months) from the index low back pain diagnosis and occurring within 5 years [102], whereas recurrence within 12 months was defined as an episode or series of low back pain episodes between the third and twelfth month after the index date of diagnosis [102], and chronic low back pain defined as at least three consecutive episodes of low back pain with an interval of at least 90 days between the episodes and occurring over a period of more than 12 months [102]. In this study, a three (3 months) interval was used as standard for one episode duration as recommended [106], and multiple claims by the same participant within 3 months period were considered as a single episode.

The earliest recorded date of LBP diagnosis from any of the above codes was the index date for the diagnosis. For LBP onset, participants with no records of LBP were censored at the last recorded date, date of death or study end date and those with prior history of LBP recorded before 31st, December 2003 were excluded. Person years at risk were defined as the difference between the entry date and the right censoring date or date of event for first onset outcome and as the difference between the index date of diagnosis and date of recurrence for recurrence outcomes.

### 3.4.2 Nephrolithiasis

The outcomes of interest were time to first diagnosis of nephrolithiasis (first medical utilization due to nephrolithiasis) and time to nephrolithiasis recurrence. Nephrolithiasis (ICD-10-CM) diagnostic codes were extracted as codes N20.0 (calculus of kidney), N20.1 (calculus of ureter), N20.2 (calculus of kidney with calculus of ureter), N20.9 (unspecified urinary calculus), N21.0 (calculus in bladder), N21.1 (calculus in urethra), N21.8 (other lower urinary tract calculus), N21.9 (unspecified calculus of lower urinary tract), and N22.8 (calculus of urinary tract in other diseases classified elsewhere). Nephrolithiasis was ascertained based on any record of the above diagnostic codes. The case definition of nephrolithiasis based on the above (ICD-10-CM) diagnostic codes has been used in previous study [386].

Participants with any of the above diagnostic codes recorded after baseline date were considered as events whereas those with prior history of nephrolithiasis recorded within the baseline period (before 31st, December 2003) were also excluded from the study. Survival data provides a greater challenge due to invariable censoring observation times when participants' outcomes remain unascertained within the follow up period [387]. The earliest recorded date of nephrolithiasis diagnosis was the index date for the diagnosis and participants with no recorded nephrolithiasis or death without outcome of interest were censored at the last recorded date of examination (last hospital visit date), date of death or study end date (31, December 2010). Participants were followed from the first health examination date during the baseline period (2002 to 2003) until December 31st, 2010. The time to event was defined as the time from the first examination date or recorded date to nephrolithiasis diagnosis date, date of death or study end. Person years at risk were defined as the difference between the entry date and the right censoring date or date of event for first onset outcome and as the difference between the index date of diagnosis and date of recurrence for 5-year recurrence outcome.

### 3.5 Statistical analysis

#### 3.5.1 Descriptive statistics

The prediction equations were developed and validated in accordance with guidelines and protocols recommended by TRIPOD (Transparent Reporting of a Multivariable Prediction model for Individual Prognosis or Diagnosis)[388]. The

student's t-test for continuous variables and $\chi^2$-test for categorical variables were used to examine the differences in baseline characteristics between participants in the derivation and validation cohorts stratified based on the outcomes.

### 3.5.2 Derivation of low back pain prediction models

Prediction models typically use a pre-defined set of predictors or risk factors and a mathematical function or risk prediction equation, relating the predictors to the outcome (182). In this study, associations between LBP outcomes and risk factors were assessed using Cox proportional hazards model, and Prentice, Williams and Peterson Gap time models for modeling episodic events in longitudinal analysis [389]. Three analyses were conducted; (i) univariate analysis of each variable, (ii) partially adjusted model that adjusted for age and sex, and (iii) fully adjusted model that adjusted for age, sex, income grade, smoking status, physical activity and alcohol consumption. The aim was to find the most parsimonious sets of independent variables that are best predictive of the outcomes. Major violations of Cox proportions hazards assumption and functional form of covariates were tested by looking at cumulative martingale residues, Shoenfeld residue plots, log-log survival curves and Kolmogorov-type Supremum Test based on 1000 simulation patterns. Visual inspection did not show any major violation of the Cox Proportional Hazards assumption for any of the predictors in the final models, but there was non-linearity in some continuous variables. These variables were categorised into clinically meaningful groups. In this study, a single

imputation of missing data was conducted to replace missing values at baseline using observed data from the same participant during follow up time.

There was multicollinearity among some metabolic syndrome variables. Hierarchical cluster analysis and comparison of estimated coefficients for predictors in univariate and multivariate analysis was used for selection of suitable representative predictor for each cluster of correlated variables. The lowest risk levels for risk factors were set as reference categories. The representative variables were assessed in multivariate models and variables retained if they were significant at $\alpha$=0.15 using backward selection procedure in the derivation of parsimonious models for mow back pain outcomes. In addition, risk factors with extremely low prevalence (<0.1%) were excluded during model derivation to avoid problems associated with convergence, biased coefficient estimates, an increase in bias, higher variability, wider confidence intervals and a loss of power which would lead to a loss in accuracy and precision of risk estimates [390-392].

### 3.5.3 Derivation of nephrolithiasis prediction models

Cox proportional Hazards models were used to assess associations between risk predictors and nephrolithiasis outcomes. Time to event was defined as time between first recorded date (study entry date) and date of the first diagnosis of nephrolithiasis (medical utilisation due to nephrolithiasis) or time between index date of nephrolithiasis diagnosis and date of recurrence for the 5-year recurrence outcome. Three analyses were performed including univariate analysis, partially

adjusted models, which adjusted for age and sex, and a fully adjusted model, which adjusted for age, sex, income grade, smoking status, physical activity, and alcohol consumption. An initial assessment of Cox proportions hazards assumptions and functional form of continuous covariates for linearity using cumulative martingale, Shoenfeld residue plots, log-log survival curves and Kolmogorov-type Supremum test based on 1000 simulation patterns was performed. Non-linear continuous covariates were categorised into clinically meaningful categories.

Due to multicollinearity among metabolic syndrome variables, simultaneous adjustment for these covariates was not preformed and the variables were added to the fully adjusted models separately. Hierarchical clustering and assessment of estimated coefficients for predictors in the univariate analysis was used to select the most suitable representative predictor for each cluster. In this study, a less stringent criterion for variable retention was adopted to effectively reduce confounding [393], and the models were fitted and variables retained if they were significant at $\alpha$=0.15 using backward selection procedure in the derivation of parsimonious models for nephrolithiasis outcomes. In addition, risk factors with extremely low prevalence (<0.1%) were excluded during model derivation to avoid loss in accuracy and precision of risk estimates [390-392].

### 3.6 Validation and performance evaluation of risk prediction models

Prediction model estimates can be used for stratification of individuals or groups of individuals based on their risks [394]. Prediction models are mainly developed to guide healthcare professionals in decision-making regarding

management of conditions; including further testing, initiation or withholding treatment as well as informing individuals about their risks of having certain conditions (diagnosis) and developing or experiencing certain outcomes (prognosis) [395].

Model derivation and validation involves three phases: (i) derivation and internally validating of a prediction model; (ii) testing and where necessary, adjusting or updating the model for other individuals in other populations (external validation); (ii) evaluating the model's performance or impact on patient outcomes [394, 395]. Even though a prediction model may successfully predict the outcome of interest in the development sample even when internally validated, this is not confirmatory that the model is valuable [394, 396]. In most cases, when a model is applied to new individuals the performance of the prediction model is generally lower than the observed performance in the population from which the model was developed. Thus, the performance of developed and internally validated prediction models should be evaluated or validated in new individuals before they are implemented in guidelines or applied in clinical practice [397]. However, prediction models are not developed to replace doctors and other health care professionals, but to provide objective estimates of health outcome risks for both individuals (patients) and healthcare providers, thereby guiding them and assisting their subjective interpretations and intuitions [396, 398]. However, prediction models can affect individuals' health and cost-effectiveness of health care only when the information inform of predicted risks provided by the model change

individuals' and health care providers' behaviour or self-management decisions [61, 394].

The applications of prognostic models include; clinical decisions for individual patients regarding treatment options, providing information to patients and family members regarding possible course of a disease, creation of clinical risk groups for stratification of patients based on disease severity and risk adjustment when assessing the performance of health care systems [399]. Before a prediction model is applied in clinical practice, it should be validated by assessing its role [394] .

Model validation refers to the process of evaluating model performance, or a successful outcome where a model is certified as fit for the designed purpose [399]. Risk prediction models can be validated internally or externally. Internal validation involves reusing the entire dataset or parts of the dataset on which a model was derived in order to assess model overfit and correct or adjust for optimism in the performance of the model. On the other hand, external validation means assessing the performance of an existing model by applying the model to an independent dataset which was collected in a study separate from that which generated the data on which the original model is based, for instance data collected from a different geographical area, by different investigators, in a different cohort and time period [396, 400].

The evaluation and validating of model performance is based on; discrimination and calibration. Discrimination is the extent to which model risk

estimates distinguish different patient diagnoses or prognoses. Patients with high-predicted risk estimates should manifest with high event rates than patients at lower risk. Calibration measures prediction accuracy and well-calibrated prediction equations or risk score assigns correct event probability at all levels of predicted risk. On contrary, miscalibrated model under- or over-predicts the event probability, which may be global or miscalibration in the large [401], and sometimes depending on specific covariates or on the risk level. Discrimination is a more important aspect of the model than poor calibration because the calibration can be improved by model recalibration [396, 402], whereas discrimination cannot be altered. Therefore, discrimination measures should clearly and reliably identify models with poor discrimination.

### 3.6.1 Internal and external validation of prediction models

Prediction models determined in a single data set usually overestimates performance which can result from overfitting or due to unmeasured predictors [403]. Therefore, it is important to validate the model by quantifying its predictive performance in another population before applying it in clinical practice. In situations where the model performance in the validation set is poor, the model should be adjusted [404]. External validation refers to the process where the validation dataset is from a population or centre different from original sample that was used for the model development, whereas internal validation involves validation within the same data set used for model derivation usually by applying a form of re-sampling of the observed data. In addition, "temporal validation"

utilizes different observation periods for deriving and validating a model in the same population. Internal validation involves data splitting, cross-validation, and bootstrapping methods [405].

### 3.6.2 Data splitting strategies for predictive models

This involves randomly dividing the data into derivation and validation sets used for the purposes of model development and validation, respectively. The ratio between the derivation and validation set is a trade-off between having enough observations for the model fitting, which at least initially involves a larger number of predictors including interaction terms, and the validation process, in which only the parsimonious, and usually reduced model is being tested. The procedures for data splitting have been described [406], and validation set usually consists of 1/4 to 1/3 of the full dataset [396]. In this study, the data sets for the outcomes were randomly divided each into a derivation (2/3) and validation cohort (1/3) as recommended [378]. A larger derivation group of approximately 66.7% was chosen for the derivation sample in order to have an adequate sample size of observed events for the primary analysis.

### 3.6.3 Developing a simplified risk point score to predict outcomes

A simplified risk score was generated based on the magnitude of the regression coefficients. After deriving parsimonious models, different scores were developed following the steps proposed [407, 408]. For each variable significant on Cox regression analysis, a score was calculated by multiplying $\beta$ by 100 and rounding to the nearest integer. The total score was the sum of scores for each risk

factor. $S_0(t)$ was the outcome-free average survival probability at time $t$, which was estimated by Cox regression analysis. The risk score was developed and the total value of the points-based risk-scoring system was determined for each subject, then subjects were divided into five risk strata as used in many applications and clinical settings [408], although there is no universally agreed upon number of strata that are appropriate. The subjects were divided into five equally sized groups using the quintiles of the estimated risk score. In addition, the cumulative incidence risk of the outcomes of interest were estimated within each of the risk strata and Hazard Rations calculated for each strata using the lowest risk stratum as the reference stratum.

### 3.6.4 Model validation based on risk groups and stratification of participants

The Prognostic Index (PI) was used to create risk groups. Statistically, the Prognostic Index facilitates comparison of actual survival probabilities with estimates derived from the model [409]. The PI was centred on the 'average risk' by subtracting the mean from the observed prognostic index before categorisation. Kaplan-Meier curves for each risk stratum were used to assess variation in prognosis [387]. However, the grouping or categorisation of a continuous variable is associated with information loss especially at extreme risks [409]. Alternatively, survival curves can be derived directly from the Cox model; and comparison with Kaplan-Meier curves is a possible method for assessment of the model calibration [387]. The risk groups formed by categorising the PI were used to superimpose Kaplan-Meier survival curves for the groups in a single graph [387].

Though three or four groups are common [410], there is no agreement in literature regarding the number of risk groups to be created, and where or why to position the cut points [396], but modest number of risk groups is recommended compared to a large number. Two groups may be too few to satisfy the needs of research applications and clinical practice but too many groups will result into unstable survival curves and poor discrimination between neighbouring groups [387]. In addition, unequal group sizes may be preferable to equal groups, because they enable identification of individuals with extreme prognoses, thereby grouping together individuals with mainly similar prognoses [387]. In this study, in order to achieve a reasonable spread of risk, five risk strata or prognostic groups were created using cut-points on the PI determined by Cox's method [411], determined at $5^{th}$, $25^{th}$, $75^{th}$ and $95^{th}$ percentiles. The method is designed to reduce information loss that occurs with categorisation or grouping [387]. However, even for a correct model, the Kaplan-Meier curves for a given risk group be affected by residual confounding and may differ across datasets. Residual confounding occurs when the relationship between the Prognostic Index and the outcome is not completely accounted for by categorisation of the data into prognostic strata or groups; some inhomogeneity of prognosis remains within strata or groups [387]. Therefore, direct comparison between Kaplan-Meier curves for two datasets can be misleading. Residual confounding can be reduced by creating larger number of risk groups, but this has its own problems [387] .

### 3.6.5 Model Calibration based on Kaplan-Meier survival curves

Calibration measures how accurately the estimates or survival predictions from a model reflect the survival in the observed data [394, 396]. For well-calibrated models, the Prognostic Index should yield a similar level of risk over time and the survival curves should be similar in the derivation and validation datasets. A comparison of Kaplan-Meier plots roughly assesses model calibration and good calibration is when the survival curves for a given risk group agree well between the derivation and validation datasets [387]. The calibration assessment provided by comparing Kaplan-Meier curves between datasets is not a strict comparison between observed and predicted values because the Cox model does not directly predict the survival probabilities in this case. Instead, the PI derived from the Cox model provides only a rank ordering of risk, from which risk groups are created and the Kaplan-Meier method is used to estimate corresponding survival probabilities [387].

During validation of prognostic or predictive models, there are mainly two statistical approaches used to determine the prediction accuracy or model performance: calibration and discrimination [396]. In this study, the models developed from the derivation cohorts were applied to the validation cohorts and model performance was assessed based on Harrell's C-statistic, sensitivity and specificity, likelihood ratio, Brier score, and Hosmer-Lemeshow goodness-of-fit test (Nam and D'Agostino test for survival data).

### 3.6.6 Model calibration based on Nam and D'Agostino test and calibration plots

Calibration measures agreement between predicted probabilities and the actual outcomes [412]. The model calibration was assessed using Hosmer-Lemeshow (H-L) type $\chi^2$ statistic (Nam and D'Agostino $\chi^2$ statistic) which was extended and is applicable to survival data [413], and was calculated by dividing the data into 10 groups (deciles) based on the predicted probabilities from the model. The average predicted probability for each decile was compared to the actual risk probabilities of outcomes, and the associated calibration plots were obtained. Perfect predictions should be on the 45° line.

For assessing or testing whether the derived equations fit the data in each decile, the Nam and D'Agostino test is calculated as,

$$\chi^2_{ND}(t) = \sum_{g=1}^{\acute{G}} \frac{[KM_g(t) - \overline{p(t)}_g]^2 n_g}{\overline{p(t)}_g(1 - \overline{p(t)}_g)}$$

Where $KM_g(t)$ is the Kaplan-Meier failure probability in the $g$-th decile at time $t$, $\overline{p(t)}_g$ is the mean predicted probability of failure for subjects in $g$-th decile and $n_g$ is number of observations in a group $g$. In this equation, under the null $\chi^2_{ND}(t)$ is distributed as a Chi-square random variable with $\acute{G}$-1 degrees of freedom [414]. Therefore, the Nam and D'Agostino test is based on observed counts that are scaled up to compensate for censoring [414]. The Nam and

D'Agostino test does not make any specific modelling assumptions. Therefore, $\overline{p(t)}_g$ can be estimated in any survival modeling technique [414]. However, the performance of Nam and D'Agostino test depends on the form of baseline hazard and the censoring rate [414].

The above formula can be expressed as follows,

$$\chi^2_{ND}(t) = \sum_{g=1}^{G} \frac{[KM_g(t) - \overline{p(t)}_g]^2 n_g}{\overline{p(t)}_g(1 - \overline{p(t)}_g)}$$

$$= \sum_{g=1}^{G} \frac{[n_g KM_g(t) - n_g \overline{p(t)}_g]^2}{n_g \overline{p(t)}_g(1 - \overline{p(t)}_g)}$$

$$= \sum_{g=1}^{G} \frac{[\text{Observed}(t) - \text{Expected}(t)]^2}{n_g \overline{p(t)}_g(1 - \overline{p(t)}_g)}$$

Where $n_g KMg(t)$ is an estimator of the mean observed number of events by time $t$ in $n_g$ trials, assuming there is no censoring. The average number of events in each group is $n_g KMg(t)$ is the "observed" and $n_g \overline{p_g}$ is an estimate of the "expected" number of events assuming the model is correctly specified [414]. Hosmer-Lemeshow Goodness-of-Fit Statistics (Nam and D'Agostino test for survival data) evaluates model calibration; a large *P* value (>0.05) indicates a good match of predicted risk over observed risk.

### 3.7 Measures of discrimination and predictive accuracy

#### 3.7.1 Model discrimination based Harrell's C-Statistic

Discrimination is a model's ability to distinguish between non-events and events. The model discrimination performance was evaluated based on the overall concordance (Harrell's C-Statistic), which is a modification to the AUROC (Area Under the Receiver Operating characteristic Curve) adapted to survival data [415].

The Harrell's C-statistic is calculated using the formula below;

$$C = \frac{\sum_{i,j} \mathrm{I}(T_i > T_j) \,.\, \mathrm{I}(\eta_j > \eta_i) . \Delta_j}{\sum_{i,j} \mathrm{I}(T_i > T_j) . \Delta_j}$$

In the above equation, indices *i* and *j* represent pairs of observations in the sample. The C-statistic is the number of concordant pairs of observations divided by the number of comparable pairs [416] , and multiplication by the factor $\Delta j$ discards pairs of observations that are not comparable because the smaller survival time is censored ($\Delta j = 0$). The Harrell's *C*-statistic estimates the probability of the concordance$P(\eta_j > \eta_i | T_i > T_j)$, which compares the rankings of two independent pairs of survival times $T_i, T_j$ and predictions $\eta_i, \eta_j$. This performance measure evaluates the association between large values of $\eta_i$ and small values of $T_i$ and vice versa [416]. The Harrell' C-statistic corresponds to the area(s) under the time-dependent ROC curves [416-418]. A value of $C = 0.5$ corresponds to a non-informative prediction rule, whereas $C = 1.0$ corresponds to perfect association or prediction, and accounts for the entire observed survival times [416]. Harrell's C

is an easy-to-interpret performance measure coefficient which accounts for the whole range of the observed survival times [416].

### 3.7.2 Sensitivity and specificity

For each parsimonious model, the predictive sensitivities and specificities were also calculated with their confidence intervals [419]. For survival models, there exist extensions of cross-sectional sensitivity and specificity. However, instead of a simple binary outcome, $Y_i$=1, the survival time can be considered as a time-varying binary outcome by concentrating on the counting process represented as $N_i^*(t) = 1(T_i \leq t)$. The accuracy extensions can be categorised depending on whether the cases used to define time-dependent sensitivity are incident cases where $T_i = t$, or equivalently $dN_i^*(t) = 1$, is used to define cases (subjects experiencing the outcome of interest) for time $t$, or cumulative cases where $T_i \leq t$ or $N_i^*(t) = 1$ is used [417]. Heagerty *et al*., also considered whether controls are static, defined as subjects with $T_i > t^*$ for a fixed value of $t^*$, or whether controls are dynamic and defined for time t as subjects with $t^* > t$ [417].

Let superscripts $I$ and $\mathcal{D}$ denote incident sensitivity and dynamic specificity, respectively. Assuming a scalar marker value $\mathcal{M}_i$ is a predictor of the outcome, when considering the accuracy of a regression model, $\mathcal{M}_i = Z_i^T\beta$.

In case of incidents/dynamic cases, and for a baseline marker value, $\mathcal{M}_i$, Heagerty *et al*., proposed versions of time-dependent sensitivity and specificity [417], using the following definitions,

$$\text{Sensitivity}^{I}(\hat{c},t): P(\mathcal{M}_i > \hat{c} \mid T_i = t) = P(\mathcal{M}_i > \hat{c} \mid dN_i^*(t) = 1)$$

$$\text{Specificity}^{D}(\hat{c},): P(\mathcal{M}_i \leq \hat{c} \mid T_i > t) = P(\mathcal{M}_i \leq \hat{c} \mid N_i^*(t) = 0)$$

Based on the above approach a subject can be a control for an early time, $t < T_i$, and then be a case when $t = T_i$. This dynamic status parallels the multiple contributions that a subject can make to the partial likelihood function. In this case sensitivity measures the expected fraction of subjects with a marker greater than $\hat{c}$ among the subpopulation of individuals who die or experience the event of interest at time $t$, whereas specificity measures the fraction of subjects with a marker less than or equal to $\hat{c}$ among those who survive beyond time $t$. The incident sensitivity and dynamic specificity are defined by dichotomizing the risk set at time $t$ into those observed to die or experience the event of interest (cases) and those observed to survive (controls) [417].

Incident sensitivity and dynamic specificity are based on classification of the risk set at time $t$ into case(s) and controls, and thus, are a natural companion to hazard models. In addition, the definitions allow extension to time-dependent covariates using $P[\mathcal{M}_i(t) > \hat{c} | T_i = t]$ to define incident sensitivity and $P[\mathcal{M}_i(t) \leq \hat{c} | T_i > t]$ to define dynamic specificity with a longitudinal marker $\mathcal{M}_i(t)$ as well as allowing both time-specific accuracy summaries and time-averaged summaries that directly relate to the global concordance measure (C) [417].

### 3.7.3 Time-Dependent ROC Curves, Time-Dependent AUC and Concordance

Using incident/dynamic *(I/D)* ROC curves defined as the function $ROC_t^{I/D}(p)$, where $p$ represents the dynamic false-positive rate, and $ROC_t^{I/D}(p)$ denotes the incident true-positive rate. Assuming $\hat{c}^p$ to be the threshold that yields a false-positive rate of $p$:

$$P(\mathcal{M}_i > \hat{c}^p \mid T_i > t) = 1 - \text{specificity}^{\mathcal{D}}(\hat{c}^p, t) = p.$$

The true positive rate, $ROC_t^{I/D}(p)$, is the sensitivity obtained using the above threshold, or $ROC_t^{I/\mathcal{D}}(p)$ = sensitivity$^I(\hat{c}^p, t) = P(\mathcal{M}_i > \hat{c}^p \mid T_i = t)$. Using the true-positive rate and false-positive rate functions $TP_t^I(\hat{c})$ = sensitivity$^I(\hat{c}, t)$ and $TP_t^D(\hat{c})$ = $1 - specificity^D(\hat{c}, t)$, the *ROC* curve can be expressed as the composition of $TP_t^I(\hat{c})$ and the inverse function $[\text{TP}_t^{\mathcal{D}}]^{-1}(p) = \hat{c}^p$:

$$\text{ROC}_t^{\text{I}/\mathcal{D}}(p) = \text{TP}_t^{\text{I}}\{[\text{FP}_t^{\mathcal{D}}]^{-1}(p)\} \text{ for } p \in [0, 1].$$

The area under the I/$\mathcal{D}$ ROC curve for time $t$ is given as

$$\text{AUC}(t) = \int_0^1 ROC_t^{I/D}(p)dp$$

The above ROC methods can describe the ability of a marker to distinguish cases at time $t$ from controls at time $t$. Time-dependent ROC curves are related to the standard concordance summary C as described using the following equation:

$$\text{C} = P[\mathcal{M}_j > \mathcal{M}_k \mid T_j < T_k]$$

The above equation indicates the probability that the subject who died (experienced the outcome of interest) at the earlier time has a larger value of the marker and reflects the concepts of ROC analysis [417], although not the usual

concordance form, that is, $\mathrm{C} = P\left[\mathcal{M}_j > \mathcal{M}_k \middle| T_j > T_k\right]$. The assumption is that observations ($\mathcal{M}_j$,$T_j$) and ($\mathcal{M}_j$,$M_k$) are independent, and $T_j$ is continuous such that $P\left(T_k = T_j\right) = 0$. Assuming $P(x)$ to represent the probability, the concordance C is a weighted average of the area under time-specific ROC curves,

$$P[\mathcal{M}_j > \mathcal{M}_k | T_j < T_k]$$

$$= 2\int_t P[\{\mathcal{M}_j > \mathcal{M}_k\} \mid \{T_j = t\} \cap \{t < T_k\}] \times P[\{T_j = t\} \cap \{t < T_k\}]dt$$

$$= \int_t \mathrm{AUC}(t) \cdot w(t)dt = E_T[\mathrm{AUC}(T) \times 2 \times S(T)],$$

$$\text{where } w(t) = 2 \cdot f(t) \cdot S(t).$$

Based on the incident and dynamic (I/D) approach in calculation of sensitivity and specificity, AUC($t$) = $P(\mathcal{M}_j > \mathcal{M}_k | T_j = t, T_k > t)$ and assuming a fixed period of follow up (0, $\tau$). The concordance measure C can be modified to account for finite follow-up:

$$c^\tau = \int_0^\tau \mathrm{AUC}(t) \cdot w^\tau(t)dt,$$
$$w^\tau(t) = 2 \cdot f(t) \cdot S(t)/W^\tau$$

$$W^\tau = \int_0^\tau 2 \cdot f(t) \cdot S(t)dt = 1 - S^2(\tau),$$

The restricted concordance summary is the weighted average of the time-specific AUCs with the weights rescaled to integrate to 1.0 over the range (0, τ). This is a modification of the original concordance, where

$$C^\tau = P(\mathcal{M}_j > \mathcal{M}_k | T_j < T_k, T_j < \tau).$$

Therefore $C^\tau$ is the probability that the predictions for a random pair of

individuals are concordant with their outcomes, assuming the smaller event time occurs in (0, $\tau$) [417].

### 3.7.4 The Youden's J statistic and determination of risk thresholds

Determination of an optimal cut-point is critical for clinical decision making when dealing with prognostic or diagnostic biomarkers. For a certain biomarker measured at baseline with the purpose of identifying individuals who will develop or not experience a certain disease condition within a given time point $\tau$ of clinical interest, the Youden's Index can be used as an extension of ROC-based cut-point finding methods in this case of censored failure time outcome [420].

Lex $\mathcal{X}$ be a continuous biomarker of clinical interest and $\acute{c}$ be the cut-point above (or below) which individuals are classified as diseased and disease-free. The Youden function is the difference between the probability of $\mathcal{X} > \acute{c}$ in diseased individuals (sensitivity, *Sens*) and the complement to one of the probability of $\mathcal{X} \leq \acute{c}$ in disease-free individuals (specificity, *Spec*), i.e. *Sens* +*Spec*-1. The chosen $\acute{c}$ maximizing this function, or equivalently *Sens* + *Spec*, leads to a maximum value known as Youden index [421].

For a given individual, let $Z$ denote the survival time, defined as the time elapsed between an earlier or beginning time point, where the individual is health (disease or event-free), and the time of development of the disease. Let $\tau$ denote the time horizon of clinical interest. The definition of disease and health (disease-free) status depends on whether $Z \leq \tau$ or $Z > \tau$. The assumption is that an increase in values of the biomarker $\mathcal{X}$ possibly increases the risk of developing the disease or

experiencing the event of interest. Otherwise, take X's negative, without losing the generality. For any cut-point ç that defines a binary classification rule, a given individual is said to be testing positive or negative depending on whether $\mathcal{X} > ç$ or $\mathcal{X} \leq ç$. In this case, *Sens* and *Spec* at ç are defined as the probability of testing positive given that an individual is diseased

$$Sens(ç) = P[(\mathcal{X} > ç \mid \mathrm{Z}_i \leq \tau),$$

and as the probability of testing negative given that an individual is disease-free.

$$Spec(ç) = P[\mathcal{X} \leq ç \mid \mathrm{Z}_i > \tau]$$

The ROC curve is the plot of $Sens(ç)$ across 1- *Spec*(ç), for varying ç. The Youden function of c is the difference between $Sens(ç)$ and 1- *Spec*(ç):

$$\mathrm{J}(ç) = Sens(ç) + Spec(ç) - 1$$

J(ç) takes values between 0, when *Sens*(ç) = 1-*Spec*(ç), and 1 when *Sens*(ç) = *Spec*(ç) = 1. The Youden index J [421] is defined as the maximum of the Youden function [422], or equivalently of *Sens* (ç) + *Spec* (ç). In addition, Youden index J can be interpreted as the maximum net gain of the true positive fraction (*Sens*) with respect to the false positive fraction, i.e. 1-*Spec* [420].

### 3.7.5 Time-Dependent likelihood ratios for predictive performance evaluation

The likelihood ratio (LR) is ratio of conditional probabilities of obtaining a specific marker value given event or disease status (i.e., with and without event or disease) and is a method of summarizing predictive value of a marker by

quantifying the update to the odds of event obtained by incorporating knowledge of the new marker [423]. Smith *et al.,* proposed the time-dependent likelihood ratio (TD-LR) as a measure for the predictive value of continuous markers in survival analysis settings [423]. In survival analysis, characterizing the probability of an event during short, intermediate, and long timeframes based on knowledge of a specific biomarker can be done with separate values of the TD-LR than with a single hazard ratio value [423].

For the likelihood ratio (LR) for a binary event $D$ and a marker $X$. Let $D = 1$ if the event occurs and $D = 0$ otherwise and let $X$ be a marker (either binary or continuous). The LR for a given value of $X$ is defined as

$$\frac{P(X = x|D = 1)}{P(X = x|D = 0)}$$

For understanding the intuition behind using the LR as a measure of predictive value, consider the conditional odds of the event $D$ given a marker value $X = x$:

$$\frac{P(D = 1|X = x)}{P(D = 0|X = x)}$$

Based on Bayes' Theorem, the above odds can be reexpressed as a product of the LR as defined above and the prevalence-based or marginal odds of $D$, $\frac{P(D=1)}{P(D=0)}$:

$$\frac{P(D=1|X=x)}{P(D=0|X=x)} = \frac{P(X=x|D=1)}{P(X=x|D=0)} \text{ X } \frac{P(D=1)}{P(D=0)}$$

Therefore, the LR can be regarded as the "update" to the odds of event $D$ obtained by incorporating knowledge of the marker value. The initial likelihood of

an event is represented by the odds of the event based only on the prevalence of the event in the population, $\frac{P(D=1)}{P(D=0)}$, before incorporating the marker values and $\frac{P(X=x|D=1)}{P(X=x|D=0)}$ afterward [423].

The expectation is that useful or informative markers are Xs that dramatically change prevalence-based odds by incorporating knowledge of the marker value x and thus, the LR quantifies this update. The LR represents the extent to which the prevalence-based odds are adjusted by a given marker value [423]. When the LR is > 1, the given marker value is more common in the population experiencing the event (i.e., $D = 1$), so the odds based on prevalence are adjusted upward to yield the conditional odds of event given $x$ [423]. In addition, if the LR is < 1, the given marker value $x$ is observed more frequently amongst the population not experiencing the event (i.e., $D = 0$), so the odds based on prevalence are adjusted downward [423]. An LR of 1 indicates that a given marker value does not update the prevalence-based odds, making the marker not informative in prediction of the event of interest [423]. Thus, the LR is interpreted similarly to the Bayes factor, where the prevalence-based odds of event are considered the "prior", and the adjusted odds given knowledge of the marker value are the "posterior" [423], and the interpretation of the LR is similar for binary or continuous markers X [424].

For binary markers (positive or negative) and binary events, marker-positive LR and marker-negative LR can be expressed respectively in terms of true positive rate (TPR) and false positive rate (FPR):

$$LR(X=+) = \frac{P(X=+|D=1)}{P(X=+|D=0)} = \frac{TPR}{FPR}$$

$$LR(X=-) = \frac{P(X=-|D=1)}{P(X=-|D=0)} = \frac{1-TPR}{1-FPR}$$

The LRs are estimated with empirical estimators of the true positive rate and false positive rate. However, cases of binary or continuous markers for a binary event encompass many applications but do not address survival settings. In survival settings, interest lies not only in whether or not an event occurs, but in how long it takes to occur and individuals may be censored, in which case they do not experience the event of interest during the observation period [423].

For survival setting, let $T_i$ and $C_i$ denote failure time and censoring time for *i*th individual. Let $\delta_i$ be an event indicator equal to 1 if $T_i \leq C_i$ and 0 otherwise. Let $Z_i = min\,(T_i, C_i)$ denote the observed survival time. Let the counting process $D_i(t)$ = 1 if $T_i \leq$ t and $D_i(t)$ = 0 if $T_i > t$; that is, given time $t$, $D_i(t)$= 1 if individual $i$ experiences the event at or before time $t$. Lastly, let the marker value for the *i*th individual be $X_i$.

Using Bayes' Theorem the expression for the odds of a general event $D$ conditional on marker value $x$ can be expressed as a product of LR and the prevalence-based odds. The expression of the LR function as a product of conditional event probabilities and the prevalence-based odds can be given as:

$$LR(x) = \frac{P(X=x|D=1)}{P(X=x|D=0)} = \frac{P(D=1|X=x)}{P(D=0|X=x)} \text{ x } \frac{P(D=0)}{P(D=1)}$$

Thus, the time-dependent likelihood ratio (TD-LR) function at time $t$ and marker value $x$, $TD\text{-}LR(x,t)$ can be defined by substituting $D$ with $D(t)$ in the above expression for $LR(x)$ as follows:

$$TD\text{-}LR(x,t) = \frac{P(D(t)=1|X=x)}{P(D(t)=0|X=x)} \text{ x } \frac{P(D(t)=0)}{P(D(t)=1)}$$

The notation $D(t) = 1$ denotes the event or the condition of $(T \leq t)$ that is time-dependent and the notation $D(t) = 0$ denotes event-free,$(T > t)$ [423]. The TD-LR function retains much of the interpretation as that for the binary events, representing the update to the prevalence-based odds of event at or before time *t* obtained through measurement of the marker $X$ [423]. The above $TD\text{-}LR$ expression provides flexibility in allowing event status to change over time through $D(t)$. The TD-LR function allows a marker's predictive value to change over time; for instance, some marker values may be more predictive of events at or before later time points $t$ than they are of events at earlier $t$. Of great importance is the ability of TD-LR function to accommodate censoring by properly estimating $D(t)$, making it possible to use information from individuals censored before the time point of interest [423].

Smith *et al.,* proposed approaches for estimation of TD-LR function [423], using Kaplan-Meier (KM) nonparametric survival estimator [425] and survival estimates derived from Cox proportional hazards (Cox PH) models [426]. For a given $t$ and marker value $x$, $TD\text{-}LR(x,t)$, can be expressed using survival

probabilities because the event of $D(t) = 0$ or $D(t) = 1$, represents whether $(T > t)$ or $(T \leq t)$:

$$TD\text{-}LR(x,t) = \frac{1 - S(t|X = x)}{S(t|X = x)} \text{ x } \frac{S(t)}{1 - S(t)}$$

where $S(t) = P(T > t)$ denotes the survival function and $S(t|X = x) = P(T > t|X = x)$ the survival function conditional on marker value $x$. An estimator for the TD-LR function for a marker value $x$ at a given time $t$ can be obtained by combining the survival probability estimates from KM,$\hat{S}_{KM}(t)$, and Cox PH models, $\hat{S}_{Cox}(t|X = x)$:

$$TD\text{-}\widehat{LR}(x,t) = \frac{1-\hat{S}_{Cox}(t|X=x)}{\hat{S}_{Cox}(t|X=x)} \text{ x } \frac{\hat{S}_{KM}(t)}{1-\hat{S}_{KM}(t)}$$

Let $\mathcal{T}$ be the set of observed failure times in a sample. The Kaplan-Meier (KM) estimator of $S(t)$ can be expressed as:

$$\hat{S}_{KM}(t) = \prod_{s \in T\,, s \leq t} \left(1 - \frac{\sum_i I(Z_i = s)\delta_i}{\sum_i I(Z_i \geq s)}\right)$$

The estimated survival function conditional on marker value from the Cox PH model can be obtained [427] as:

$$\hat{S}_{Cox}(t|X = x) = \widehat{s_o(t)}^{\exp(\beta x)},$$

where $\widehat{s_o(t)} = \exp(-\widehat{\Lambda_o(t)})$ with $\widehat{\Lambda_o(t)}$ is the estimated baseline cumulative hazard function. The estimate $\beta$, a regression parameter relating the covariate $x$ to the hazard, is obtained through partial likelihood maximization and is used to estimate $\widehat{s_o(t)}$ by the method previously described [427].

LR is related to ROC curves [423]. ROC curves are used to compare the predictive ability of continuous markers for a binary event [428, 429]. For binary events, the use of the scale-invariant LR and placement value for standardizing marker values yields a mathematical relationship between ROC curves and the LR [430-432]. The same relationship holds for the TD-LR and the time-dependent ROC (TD-ROC) introduced by Heagerty *et al* [433, 434].

Let $F_{D(t)=1}(x)$ and $F_{D(t)=0}(x)$ be the cumulative distribution functions of the marker $X$ in the subsets of individuals experiencing the event *D* at or before $t$ and those not experiencing the event at or before $t$, respectively, and $f_{D(t)=1}(x)$ and $f_{D(t)=0}(x)$ denote the corresponding probability density functions for the marker values. Then, by definition,

$$TD\text{-}ROC(r,t) = 1 - F_{D(t)=1}(1 - F_{Dt(\cdot)=0}\,(r))^{-1})$$

where $r$ is a given false positive rate. The distribution function $F(\cdot)$, density function $f(\cdot)$ and the inverse function of $1 - F(\cdot)$ are for the marker X within the subset of $D(t) = 1$ or $D(t) = 1$, not as functions associated with the survival time $T$. Differentiating this expression with respect to $t$ using chain rule yields

$$TD\text{-}ROC'(r,t) = \frac{f_{D(t)=1}\left(F^{-1}_{D(t)=0}(1-r)\right)}{f_{D(t)=0}\left(F^{-1}_{D(t)=0}(1-r)\right)}.$$

Therefore, for a marker value $x$, time point $t$, take the false positive rate $r = U(x,t) = 1 - F_{D(t)=0}(x)$:

$$TD\text{-}ROC'(U(x,t),t) = \frac{f_{D(t)=1}\left(F^{-1}_{D(t)=0}(1-(1-F_{D(t)=0}(x)))\right)}{f_{D(t)=0}\left(F^{-1}_{D(t)=0}(1-(1-F_{D(t)=0}(x)))\right)}$$

$$= \frac{f_{D(t)=1}(x)}{f_{D(t)=0}(x)}$$

By reexpression of $f_{D(t)=1}(x)$ and $f_{D(t)=0}(x)$ as $P(X=x|D(t)=1)$ and $P(X=x|D(t)=0)$, the above expression becomes

$$= \frac{P(X=x|D(t)=1)}{P(X=x|D(t)=0)}$$

which can be expressed as $TD\text{-}LR(x,t)$ as in the formula obtained after applying Bayes' rule. This implies that at a given time $t$ and marker value $x$, $TD\text{-}LR(x,t)$ represents the derivative of the corresponding TD-ROC curve when the false positive rate takes the value at placement value $U(x,t)$ [423].

### 3.7.6 Model discrimination and calibration based on Brier score

The Brier score is a proper scoring rule [435] which simultaneously captures discrimination and calibration [436], with low values indicating better prediction. The Brier score is a measure of the squared deviation of survival estimate from the true probability [437] used in survival analysis accounting for censoring [438], and is a function of time. The Brier score does not depend on arbitrary definition of thresholds for the classification of individual risk scores to different risk groups [439]. However, the Brier score depends on prevalence and may give undesirable results where clinical consequences are discordant with prevalence [440].

The be score can be calculated in survival predictions [441{Graf, 1999 #1388]}. Let $T_i^*$ be the event time for subject $i$ and $f_i(t)$ be the density function of $T_i^*$. The survival function of subject $i$ is then calculated as

$$S_i(t) = P(T_i^* > t) = \int_t^\infty f_i(u)\, du.$$

In survival prediction models, the aim is to estimate $S_i(t)$ for all subjects. Let $\pi_i(t)$denote these estimates, and the $\pi_i(t)$'s as known (non-random) functions. To evaluate the predictive performance of the $\pi_i(t)$'s requires calculation of the mean squared error of the estimates to the true survival functions. For a data set with n subjects, this score is calculated as

$$MSE(t) = \frac{1}{n}\sum_{i=1}^{n}[S_i(t) - \pi_i(t)]^2.$$

However, $S_i(t)$ is usually unknown, and we instead observe event times $T_i^*$ drawn from the event time distribution[441]. The Brier score in absence of censoring approximates the true survival functions with step-functions with jumps at the event times, giving

$$BS(t) = \frac{1}{n}\sum_{i=1}^{n}[\mathbb{1}\{T_i^* > t\} - \pi_i(t)]^2.$$

$$= \frac{1}{n}\sum_{i=1}^{n}[\pi_i(t)^2\mathbb{1}\{T_i^* \le t\} + [1 - \pi_i(t)]^2\mathbb{1}\{T_i^* > t\}].$$

The expectation of the Brier score is calculated as

$$\mathbb{E}[BS(t)] = \frac{1}{n}\sum_{i=1}^{n} \mathbb{E}[\pi_i(t)^2 \mathbb{1}\{T_i^* \leq t\} + [1-\pi_i(t)]^2 \mathbb{1}\{T_i^* > t\}]$$

$$= \frac{1}{n}\sum_{i=1}^{n} [\pi_i(t)^2 \mathrm{P}\{T_i^* \leq t\} + [1-\pi_i(t)]^2 \mathrm{P}\{T_i^* > t\}]$$

$$= \frac{1}{n}\sum_{i=1}^{n} [\pi_i(t)^2 [1-S_i(t)] + [1-\pi_i(t)]^2 S_i(t)]$$

$$= \frac{1}{n}\sum_{i=1}^{n} ([S_i(t)-\pi_i(t)]^2 + S_i(t)[1-S_i(t)])$$

$$= MSE(t) + \frac{1}{n}\sum_{i=1}^{n} S_i(t)[1-S_i(t)].$$

Thus, the expected Brier score is the sum of the MSE and a given constant that is independent of survival estimates $\pi_i(t)$. This constant is the irreducible error of approximating the true survival functions $S_i(t)$ with the step-functions $\mathbb{1}\{T_i^* > t\}$. Therefore, minimization of the expected Brier score is equivalent to minimizing the MSE, and the minimum is obtained for the true survival functions, that is, $\pi_i(t)$=$S_i(t)$ [441].

In most of the practical settings in medical research, only a subset of the event times $T_i^*$ is observed. For some subjects, the event time occurs after some censoring time $C_i^*$. For survival modelling in such settings, the right-censored event time $T_i = min\{T_i^*, C_i^*\}$ and the event indicator $D_i = 1\{T_i^* \leq C_i^*\}$.When the event and censoring time coincide, the event is considered to observed in

conventional survival analysis[441]. Because of partial information available, the Brier score described above cannot be calculated but can be approximated by weighting the scores of the observed event times by the inverse probability of censoring [438, 442]. This approach is known as inverse probability of censoring weighting (IPCW), and the IPCW Brier score is given by

$$BS_{\text{IPCW}}(t) = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{\pi_i(t)^2\mathbb{1}\{T_i \le t, D_i = 1\}}{G_i(T_i-)} + \frac{[1-\pi_i(t)]^2\mathbb{1}\{T_i > t\}}{G_i(t)}\right].$$

where $G_i(t) = P(C_i^* > t) > 0$, denotes the survival function of the censoring distribution for subject $i$. Assuming $G_i(t)$'s to be known functions, the expectation of the IPCW Brier score can be calculated as

$$\mathbb{E}[BS_{\text{IPCW}}(t)] = \frac{1}{n}\sum_{i=1}^{n}\mathbb{E}\left[\frac{\pi_i(t)^2\mathbb{1}\{T_i \le t, D_i = 1\}}{G_i(T_i-)} + \frac{[1-\pi_i(t)]^2\mathbb{1}\{T_i > t\}}{G_i(t)}\right]$$

$$= \frac{1}{n}\sum_{i=1}^{n}\pi_i(t)^2\mathbb{E}\left[\frac{\mathbb{1}\{T_i^* \le t, T_i^* \le C_i^*\}}{G_i(T_i^*-)} + [1-\pi_i(t)]^2\frac{P\{T_i^* > t, C_i^* > t\}}{G_i(t)}\right]$$

$$= \frac{1}{n}\sum_{i=1}^{n}\pi_i(t)^2\int_0^t \frac{G_i(u-)f_i(u)}{G_i(u-)}du + [1-\pi_i(t)]^2\frac{G_i(t)S_i(t)}{G_i(t)}$$

$$= \frac{1}{n}\sum_{i=1}^{n}\pi_i(t)^2\,[1-S_i(t)] + [1-\pi_i(t)]^2 S_i(t)$$

$$= MSE(t) + \frac{1}{n}\sum_{i=1}^{n}S_i(t)[1-S_i(t)]$$

The above expression is similar to the the expectation of the uncensored Brier score, thus the IPCW Brier score can be used for approximation of the uncensored Brier Score [441].The Brier score ranges between 0.0 and 1.0, with the score = 0.0 representing a perfect model performance.

### 3.8 Calculation of personalized risk based on models and simplified risk scores

#### 3.8.1 Prediction equations

Risk prediction models from survival data combine predictors to estimate the absolute risk that an outcome of interest will occur within a given time period in an individual with a specific predictor profile [443, 444]. In the medical field, predictive or prognostic models have been developed to predict individualized risk of future events, including death, and to stratify individuals into risk categories [445]. The prediction of individualized outcomes increases the cost-effectiveness of treatment by assisting health care professionals in decision-making and offering patient advice [444, 446]. Basing on Cox proportional hazard models, the individualized probability of experiencing an outcome of interest within the years of follow up ($t$), can be estimated using the following equation:

$$P(\text{Outcome}) = 1 - S_o(t)^{\exp[(fx)]},$$

$$f(x) = \sum_i \beta_i x_i$$

Where $S_o(t)$ denotes the baseline survival probability at time ($t$) for an individual with all covariates equivalent to zero (0), $\beta_i$ denotes the change in log hazard rate (are the estimated $\beta$-coefficients) and $x_i$ denote values of predictors in

the model. Using the estimated coefficients $\beta_i$ and survival probabilities $S_o(t)$, personalized probabilities of experiencing the outcomes of interest can be calculated.

### 3.8.2 Simplified risk scores

To construct risk scores for the outcomes, the risk points associated with the presence of a given level of a risk factor were determined by multiplying the regression coefficient $\beta$ by 100 and rounding to the nearest integer, with the reference level assigned zero points. The total score for each participant was obtained by summation of scores for each predictor. The median risk score, the $25^{th}$ and $75^{th}$ percentiles were calculated. The Youden's Index was used to determine the optimal cut-off point to define high-risk individuals based on the simplified risk score. The threshold was used to determine the number of outcome events identified by application of the cut-off points. In addition, using Youden's Index determined cut-off value, sensitivity, specificity, positive and negative likelihood, positive and negative predictive values and accuracy were determined for the risk scores.

In addition, sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values and accuracy values were determined using cut-off thresholds at the $99^{th}$, $97^{th}$, $95^{th}$, $90^{th}$, $75^{th}$, $50^{th}$, $25^{th}$,$10^{th}$ and $5^{th}$ percentiles corresponding to the identification of individuals in top risk of 1%, 3%, 5%, 10%, 25%, 50%, 75%, 90%, and 95%. For each derived simplified risk score, a hypothetical risk profile was used to describe how the risk score can be applied in

practice. The $S_0(t)$ was outcome-free average survival probability at end of follow-up time ($t$), which was estimated by Cox regression analysis. Based on the point system, the probability of an outcome can be estimated as follows;

$$P(\text{Outcome}) = 1 - S_o(t)^{\exp[(Score/100)]},$$

Where score was the total number of risk points for a hypothetical risk profile.

### 3.8.3 Modelling of low back pain using Prentice-Williams-Peterson models

Prentice, Williams, and Peterson described two related approaches that are applicable in relating the hazard function to previous failure time history [447]. The methods are stratified Cox based approaches where the first considers the time since study entry (total time or calendar time scale) whereas the other incorporates the time since the previous event (gap time scale) [448]. For a clinical trial with two treatment groups and no consideration of further covariates, in the total time approach the hazard for an individual $i$ for the $jth$ recurrent event is modeled as

$$\lambda_{ij}(t) = \lambda_{0j}(t)\exp(\beta_j X_{ij})$$

$$i = 1, \dots, n, j = 1, \dots, k_i, k_i \leq k,$$

whereas in the gap time approach the hazard is modeled as

$$\lambda_{ij}(t) = \lambda_{0j}(t - t_{j-1})\exp(\beta_j x_{ij}),$$

$$i = 1, \dots, n, j = 1, \dots, k_i, k_i \leq k$$

The underlying model is not different from the common Cox proportional hazards model but for each recurrent event or episode $j = 1, \dots, k_i$ a separate hazard function is modeled with an own baseline hazard $\lambda_{0j}$ and a regression parameter or

coefficient $\beta_j$. Therefore, the hazards for a recurrent event (episode) may change after a previous event, which implies that the current risk to experience an event can potentially be influenced by the previous events [448]. The order number $j$ of an event defines a stratification variable within these approaches, in such a way that in stratum 1 there are all first event times, in stratum 2 there are all second event times, and so on[448]. A subject is at risk for the $j^{\text{th}}$ event only if that subject experienced a previous $(j-1)^{\text{th}}$ event. Therefore, in the above models the hazard at time $t$ for the $j^{\text{th}}$ recurrence are conditional on the entire previous events [448]. The partial likelihood is expressed as a product of the strata-specific partial likelihoods

$$L(\beta) = \prod_{j=1}^{k} L_j(\beta)$$

$$\text{where } L_j(\beta) = \prod_{i=1}^{n} \left( \frac{exp(\beta_j x_{ij})}{\sum_{l \epsilon R_j^{PWP}(T_{ij})} exp(\beta_j x_l)} \right)^{\delta_{ij}}$$

The risk sets are defined separately for each stratum. For the Prentice, Williams, and Peterson total time (PWP-TT) model, the risk set is given as

$$R_j^{PWP}(t) := \{l, l = 1, \ldots, n : T_{l(J-1)} < t \leq T_{lj}\},$$

whereas for the Prentice, Williams, and Peterson gap time (PWP-GT) model the risk set is given as

$$R_j^{PWP}(t) := \{l, l = 1, \ldots, n : (T_{lj} - T_{l(j-1)}) \geq t\},$$

Where again $T_{lj}$ are the distinct event times for individual $l, l =$

$1,\ldots,n$, and for the $j^{\text{th}}$ occurring event $j = 1,\ldots,k_l, k_l \leq k, l = 1,\ldots,n$. The maximal number of recurrent events for a subject given by $k$ determines the number of strata. The Prentice, Williams, and Peterson models [447] can be applied to estimate strata-specific treatment effects $\beta_J, j = 1,\ldots,k$. However, when analyzing a composite endpoint, one is usually interested in a single treatment effect estimator quantifying the net effect. Setting $\beta_1 = \beta_2 = \ldots = \beta_k = \beta$ within the above partial likelihood allows estimating a common parameter $\beta$ [448]. The corresponding treatment effect in terms of a hazard ratio $exp(\beta)$ also corresponds to a mixed effect denoted as $\theta MixPWP$. The implementation can be conduced by adapting the standard Cox proportional hazards model [448]. For the PWP-TT approach, an additional stratum variable that counts the number of events for each individual is required. For the gap time model all starting times are set to zero and the stopping time denotes the time since the previous event [448]. In this study, all analyses were conducted using SAS version 9.4 (SAS Inc., Cary, North Carolina, USA), (Python v3.7.1) and R v3.44.

# IV. Results

# 4.1 Prediction of first onset of low back pain

### 4.1 Prediction of first onset of low back pain.

In this study, the outcome of interest was first onset of low back pain defined as newly diagnosed low back pain among apparently healthy individuals at baseline. After data extraction, 63,629 out of 502,342 participants in the cohort had history of low back pain at baseline. This study aimed to predict onset of low back pain among apparently health people, therefore these participants were excluded from the analysis. The final analysis comprised of 438,713 participants.

#### 4.1.1 Description of the study population.

Table 1 shows baseline characteristics of the development and validation cohorts used in deriving prediction model for first onset of LBP. The extracted data comprised of 502,342 participants. At baseline, 63,629 participants with LBP history were excluded from the analysis. During a median follow-up of 8.4 years (Range:2.11 to 8.99), there were 92,190 (31.5%) and 46,027 (31.5%) newly diagnosed LBP cases among 292,701 and 146,012 participants in the derivation and validation cohorts, respectively. The total number of person-years of follow-up was 3,247,597 years. The mean (SD) of covariates and the distribution of the baseline characteristics among cohorts are presented (Table 1) .There were no discrepancies between the derivation and validation cohorts. However, there were differences observed between participants who developed LBP and those who did not (Table 1). Those who developed LBP had higher mean values of fasting glucose, total cholesterol, and blood pressure. The average follow up times were

approximately 8.4 years and 5.2 years among those who remained health and those who developed LBP, respectively (Table 1).

**Table 1. Baseline characteristic of participants in derivation and validation cohorts for newly diagnosed low back pain [mean (SD) or n (%)].**

| Covariate | Derivation Cohort (n=292,701 ) | | | Validation Cohort (n=146,012 ) | | |
|---|---|---|---|---|---|---|
| | **Without LBP** | **With LBP** | ***P* value** | **Without LBP** | **With LBP** | ***P* value** |
| | **200,511(68.5%)** | **92,190 (31.5%)** | | **99,985(68.5%)** | **46,027 (31.5%)** | |
| Years of follow up | 8.4 (1.2) | 5.2 (2.0) | <.0001 | 8.4 (1.2) | 5.3 (2.0) | <.0001 |
| Height (cm) | 164.7 (8.5) | 161.9 (9.0) | <.0001 | 164.7 (8.6) | 164.7 (8.6) | <.0001 |
| Weight (kgs) | 63.0 (11.2) | 62.2 (10.7) | <.0001 | 63.0 (11.2) | 62.1 (10.6) | <.0001 |
| BMI ($kg/m^2$) | 23.2 (3.2) | 23.7 (3.2) | <.0001 | 23.2 (3.2) | 23.7 (3.2) | <.0001 |
| SBP (mm Hg) | 122.0 (16.9) | 123.8 (17.4) | <.0001 | 122.1 (16.9) | 124.0 (17.4) | <.0001 |
| DBP (mm Hg) | 77.0 (11.4) | 77.6 (11.4) | <.0001 | 77.0 (11.4) | 77.8 (11.4) | <.0001 |
| FBG (mg/dL) | 92.7 (27.4) | 94.5 (27.8) | <.0001 | 92.7 (27.5) | 94.5 (27.7) | <.0001 |
| Total Cholesterol (mg/dL) | 189.8 (38.4) | 194.2 (38.4) | <.0001 | 189.6 (38.2) | 194.1 (38.3) | <.0001 |
| **Sex** | | | <.0001 | | | <.0001 |
| Male | 112,766 (56.2) | 41,197 (44.7) | | 56,238 (56.3) | 20,548 (44.6) | |
| Female | 87,745 (43.8) | 50,993 (55.3) | | 43,747 (43.7) | 25,479 (55.4) | |
| **Age** | | | <.0001 | | | <.0001 |
| <44 yrs. | 140,935 (70.3) | 45,889 (49.8) | | 70,142 (70.2) | 22,859 (49.7) | |
| 45-54 yrs | 33,874 (16.9) | 21,006 (22.8) | | 17,084 (17.1) | 10,286 (22.3) | |
| 55-64 yrs | 17,685 (8.8) | 15,967 (17.3) | | 8,730 (8.7) | 8,101 (17.6) | |
| ≥65 yrs | 8017 (4.0) | 9,328 (10.1) | | 4,029 (4.0) | 4,781 (10.4) | |
| **Insurance premium** | | | <.0001 | | | <.0001 |
| Low (<30%) | 28,775 (14.4) | 14,134 (15.3) | | 14,351 (14.4) | 7,079 (15.4) | |
| Medium (30-60%) | 72,466 (36.1) | 32,887 (35.7) | | 36,302 (36.3) | 16,352 (35.5) | |
| High (>60%) | 99,270 (49.5) | 45,169 (49.0) | | 49,332 (49.3) | 22,596 (49.1) | |
| **Physical Activity/Week** | | | <.0001 | | | <.0001 |
| Low (None) | 113,951 (56.8) | 55,065 (59.7) | | 56,607 (56.6) | 27,617 (60.0) | |
| Moderate(1-2times/week) | 72,168 (36.0) | 30,420 (33.0) | | 36,273 (36.3) | 15,117 (32.8) | |

| Covariate | Derivation Cohort (n=292,701 ) | | | Validation Cohort (n=146,012 ) | | |
|---|---|---|---|---|---|---|
| | **Without LBP** | **With LBP** | ***P* value** | **Without LBP** | **With LBP** | ***P* value** |
| | **200,511(68.5%)** | **92,190 (31.5%)** | | **99,985(68.5%)** | **46,027 (31.5%)** | |
| High (≥3 times/week) | 14,392 (7.2) | 6,705 (7.3) | | 7,105 (7.1) | 3,293 (7.2) | |
| **Smoking Status** | | | <.0001 | | | <.0001 |
| Never | 125,183 (62.4) | 65,920 (71.5) | | 62,419 (62.4) | 32,982 (71.7) | |
| Former Smoker | 9,502 (4.8) | 3,570 (3.9) | | 4,735 (4.7) | 1,812 (3.9) | |
| Current Smoker | 6, 826 (32.8) | 22,700 (24.6) | | 32,831 (32.9) | 11,233 (24.4) | |
| **Alcohol Consumption/Month** | | | <.0001 | | | <.0001 |
| Rarely (< 2 times) | 93,627 (46.7) | 51,249 (55.6) | | 46,602 (46.6) | 25,661 (55.7) | |
| Moderate drinker (2–3 times) | 86,400 (43.1) | 33,120 (35.9) | | 43,264 (43.3) | 16,467 (35.8) | |
| Heavy drinker ( > 3 times) | 20,484 (10.2) | 7,821 (8.5) | | 10,119 (10.1) | 3,899 (8.5) | |
| **Body Mass Index** | | | <.0001 | | | <.0001 |
| < 18.5 kg/$m^2$ | 12,859 (6.4) | 4,125 (4.5) | | 6,393 (6.4) | 2,043 (4.4) | |
| 18.5 kg/$m^2$-24.9 kg/$m^2$ | 132,720 (66.2) | 58,164 (63.1) | | 66,209 (66.2) | 29,173 (63.4) | |
| 25 kg/$m^2$-29.9 kgm$^2$ | 50,034 (25.0) | 27,127 (29.4) | | 25,013 (25.0) | 13,413 (29.1) | |
| ≥30 kg/$m^2$ | 4,898 (2.4) | 2,774 (3.0) | | 2,370 (2.4) | 1,398 (3.1) | |
| **Fasting Blood Glucose** | | | <.0001 | | | <.0001 |
| < 100mg/dL | 133,110 (66.4) | 58,711 (63.7) | | 6,6307 (66.3) | 29,226 (63.5) | |
| 100mg/dL-125 mg/dL | 47,069 (23.5) | 22,946 (24.9) | | 23,492 (23.5) | 11,504 (25.0) | |
| ≥126 mg/dL or Rx | 20,332 (10.1) | 10,533 (11.4) | | 10,186 (10.2) | 5,297 (11.5) | |
| **Blood Pressure/HTN** | | | <.0001 | | | <.0001 |
| SBP <120 and DBP <80 | 76,363 (38.1) | 32,178 (34.9) | | 38,029 (38.0) | 16,005 (34.8) | |
| SBP 120-139 or DBP 80-89 | 102,448 (51.1) | 48,340 (52.4) | | 51,172 (51.2) | 23,997 (52.1) | |
| SBP 140-159 or DBP 90-99 | 19,029 (9.5) | 10,245 (11.1) | | 9,451 (9.5) | 5,259 (11.4) | |
| SBP≥ 160 Or ≥ DBP100 or Rx | 2,671 (1.3) | 1,427 (1.6) | | 1,333 (1.3) | 766 (1.7) | |
| **Total cholesterol** | | | <.0001 | | | <.0001 |
| < 200 mg/dL | 124,133 (61.9) | 52,903 (57.4) | | 62,029 (62.0) | 26488 (57.5) | |
| 200 mg/dL /l-239 mg/dL | 56,157 (28.0) | 28,154 (30.5) | | 28,103 (28.1) | 14021 (30.5) | |

| Covariate | Derivation Cohort (n=292,701 ) | | | Validation Cohort (n=146,012 ) | | |
|---|---|---|---|---|---|---|
| | **Without LBP** | **With LBP** | ***P* value** | **Without LBP** | **With LBP** | ***P* value** |
| | **200,511(68.5%)** | **92,190 (31.5%)** | | **99,985(68.5%)** | **46,027 (31.5%)** | |
| ≥240 mg/dL | 20,221 (10.1) | 11,133 (12.1) | | 9,853 (9.9) | 5518 (12.0) | |
| **Diagnosed IHD** | | | <.0001 | | | <.0001 |
| No | 199,059 (99.3) | 90,873 (98.6) | | 99,300(99.3) | 45,375 (98.6) | |
| Yes | 1,452 (0.7) | 1,317 (1.4) | | 685 (0.7) | 652 (1.4) | |
| **Diagnosed IVDD** | | | <.0001 | | | <.0001 |
| No | 193,216 (96.4) | 83,531 (90.6) | | 96,303(96.3) | 41,591 (90.4) | |
| Yes | 7,295 (3.6) | 8,659 (9.4) | | 3,682 (3.7) | 8,118 (9.6) | |
| **History of Back Injuries** | | | <.0001 | | | <.0001 |
| No | 199,823 (99.7) | 91,459 (99.2) | | 99,656(99.67) | 45,641 (99.2) | |
| Yes | 688 (0.3) | 731 (0.8) | | 329 (0.33) | 386 (0.8) | |
| **BMD Disorder** | | | <.0001 | | | <.0001 |
| No | 196,828 (98.2) | 86,923 (94.3) | | 98,160 (98.2) | 43,327 (94.1) | |
| Yes | 3,683 (1.84) | 3,683 (5.7) | | 1,825 (1.8) | 2700 (5.9) | |
| **Spinal Stenosis** | | | <.0001 | | | <.0001 |
| No | 199,621 (99.6) | 90,561 (98.2) | | 99552(99.57) | 45193 (98.2) | |
| Yes | 890 (0.4) | 1,629 (1.8) | | 433 (0.43) | 834 (1.8) | |
| **Spondylolisthesis** | | | <.0001 | | | <.0001 |
| No | 200,434 (99.96) | 92,068 (99.9) | | 99,956(99.97) | 45,957 (99.8) | |
| Yes | 77 (0.04) | 122 (0.1) | <.0001 | 29 (0.03) | 70 (0.2) | <.0001 |

The student's *t*-test for continuous variables and $\chi^2$-test for categorical variables were used to examine the differences in baseline characteristics between participants in the derivation and validation cohorts stratified based on newly diagnosed low back pain outcome. Abbreviations: FBG, Fasting Blood Glucose; BMD, Bone Mineral Density; IHD, Ischemic Heart Disease; IVDD, Intervertebral Disc Degeneration;

### 4.1.2 Cumulative incidence probabilities of newly diagnosed low back pain

In the course of the overall follow-up period (8.99 years), the cumulative incidence risk of first onset of low back pain increased from 10.5 (95% CI, 10.4-10.6) in 2004 to 35.3 (95% CI, 35.1-35.5) at the end of the study period (December 31st 2010). In general, the risk of low back pain (first onset) increased with increase in length of follow up period. The details of the incidence trends and cumulative risks are presented (Table 2).

**Table 2. Follow-up times, cumulative incidence and incidence probabilities of first onset of low back pain**

| Calendar Year | Censored | Events | Total | CR* (95% CI) |
|---|---|---|---|---|
| 2004 | 5,199 | 45,775 | 50,974 | 10.5 (10.4-10.6) |
| 2005 | 3,029 | 19,948 | 22,977 | 15.1 (15.0-15.2) |
| 2006 | 6,541 | 18,737 | 25,278 | 19.5 (19.4-19.6) |
| 2007 | 9,531 | 17,442 | 26,973 | 23.7 (23.6-23.9) |
| 2008 | 19,619 | 17,414 | 37,033 | 28.1 (27.9-28.2) |
| 2009 | 114,083 | 16,844 | 130,927 | 33.3 (33.1-33.4) |
| 2010 | 142,494 | 2,057 | 144,551 | 35.3 (35.1-35.5) |
| **Totals** | **300,496** | **138,217** | **438,713** | |

CR*=Cumulative Risk

### 4.1.3 Association between risk predictors and first onset of low back pain

Tables 3 ⇓ present the estimated coefficients and hazard ratios of covariates. The prevalence of newly developed low back pain (first onset) was high among the old age categories (Table 1), and was associated with LBP in the univariate and multivariate analyses ($p<0.05$) (Table 3). In addition, female sex and low income were positively associated with first onset of low back pain ($p<0.05$) (Table 3).

Among lifestyle risk factors, smoking and alcohol consumption were inversely associated with LBP whereas physical inactivity was weakly associated with LBP ($p<0.05$) (Table 3).

Hypertension showed a positive association in the univariate analysis, which changed direction to an inverse association after adjusting for other risk factors ($p<0.05$) (Table 3). The prevalence of LBP was also lower in the hypertensive categories compared to the normotensive group (Table 1). Body mass index showed a stable positive association with LBP in all analyses, and a lower BMI showed an inverse association ($p<0.05$) (Table 3). Total cholesterol showed a positive association, which was weak in the adjusted models. On the other hand, fasting blood glucose (FBG) showed a positive association in the univariate analysis, which was inverse in fully adjusted model ($p<0.05$) (Table 3). In general, metabolic syndrome (MetS) variables were associated with first onset of LBP, although the direction and strengths of association varied ($p<0.05$) (Table 3).

With regard to premorbid conditions, IHD, disc degeneration, spondylolisthesis, history of back injury, spinal stenosis, and BMD were positively associated with first onset of low back pain ($p<0.05$) (Table 3). The direction of associations did not change in comparison with unadjusted models, although the associations were stronger in the unadjusted models. The details of the associations between first onset of low back and the risk predictors are presented ($p<0.05$) (Table 3).

**Table 3. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors in the univariate, partially adjusted and fully adjusted models for first onset of low back pain**

| Covariate | Unadjusted∗ | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value | β (SE) | HZ (95% CI) | *P* Value |
| **Sex** | | | | | | | | | |
| Female | 0.355 (0.005) | 1.43 (1.41-1.44) | <.0001 | 0.355 (0.005) | 1.43 (1.41-1.44) | <.0001 | 0.324 (0.007) | 1.38 (1.36-1.40) | <.0001 |
| **Age** | | | | | | | | | |
| <45 yrs. | **Reference** | **Reference** | | **Reference** | **Reference** | | **Reference** | **Reference** | |
| 45-54 yrs | 0.511 (0.007) | 1.67 (1.65-1.69) | <.0001 | 0.512 (0.007) | 1.67 (1.65-1.69) | <.0001 | 0.513 (0.007) | 1.67 (1.65-1.69) | <.0001 |
| 55-64 yrs | 0.825 (0.007) | 2.28 (2.25-2.32) | <.0001 | 0.832 (0.008) | 2.30 (2.27-2.33) | <.0001 | 0.826 (0.008) | 2.29 (2.25-2.32) | <.0001 |
| >65 yrs | 1.089 (0.009) | 2.97 (2.92-3.03) | <.0001 | 1.081 (0.009) | 2.95 (2.90-3.00) | <.0001 | 1.073 (0.009) | 2.92 (2.87-2.98) | <.0001 |
| **Income (Insurance)** | | | | | | | | | |
| High (>60%) | **Reference** | **Reference** | | **Reference** | **Reference** | | **Reference** | **Reference** | |
| Medium (30-60%) | -0.0006 (0.006) | 0.99 (0.98-1.01) | 0.9171 | 0.053 (0.006) | 1.05 (1.04-1.07) | <.0001 | 0.051 (0.006) | 1.05 (1.04-1.07) | <.0001 |
| Low (<30%) | 0.068 (0.008) | 1.07 (1.05-1.09) | <.0001 | 0.031 (0.008) | 1.03 (1.02-1.05) | <.0001 | 0.029 (0.008) | 1.03 (1.01-1.05) | 0.0002 |
| **Physical Activity/Week** | | | | | | | | | |
| High (≥3 times) | **Reference** | **Reference** | | **Reference** | **Reference** | | **Reference** | **Reference** | |
| Moderate (1-2 times) | -0.086 (0.011) | 0.92 (0.89-0.94) | <.0001 | -0.014 (0.011) | 0.99 (0.97-1.01) | 0.2057 | -0.014 (0.011) | 0.99 (0.97-1.01) | 0.2192 |
| Low (None) | 0.034 (0.011) | 1.03 (1.01-1.06) | 0.0015 | 0.023 (0.011) | 1.02 (1.00-1.05) | 0.0278 | 0.019 (0.011) | 1.02 (1.00-1.04) | 0.0818 |
| **Smoking Status** | | | | | | | | | |
| Never | **Reference** | **Reference** | | **Reference** | **Reference** | | **Reference** | **Reference** | |
| Former | -0.266 (0.014) | 0.77 (0.75-0.79) | <.0001 | -0.021 (0.015) | 0.98 (0.95-1.01) | 0.1462 | -0.017 (0.015) | 0.98 (0.96-1.01) | 0.2542 |
| Current Smoker | -0.333 (0.006) | 0.72 (0.71-0.73) | <.0001 | -0.014 (0.008) | 0.99 (0.97-1.00) | 0.0696 | -0.015 (0.008) | 0.99 (0.97-1.00) | 0.0674 |
| **Alcohol Consumption/Month** | | | | | | | | | |
| Rarely (<2 times) | **Reference** | **Reference** | | **Reference** | **Reference** | | **Reference** | **Reference** | |
| Moderate drinker (2–3 times) | -0.293 (0.006) | 0.75 (0.74-0.76) | <.0001 | -0.048 (0.006) | 0.95 (0.94-0.97) | <.0001 | -0.047 (0.006) | 0.95 (0.94-0.97) | <.0001 |
| Heavy drinker ( ≥ 4 times) | -0.281 (0.010) | 0.76 (0.74-0.77) | <.0001 | -0.016 (0.011) | 0.98 (0.96-1.00) | 0.1229 | -0.017 (0.011) | 0.98 (0.96-1.00) | 0.1056 |
| **Body Mass Index** | | | | | | | | | |

| Covariate | Unadjusted∗ | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value | β (SE) | HZ (95% CI) | *P* Value |
| < 18.5 kg/m$^2$ | -0.265 (0.013) | 0.77 (0.75-0.79) | <.0001 | -0.228 (0.013) | 0.80 (0.78-0.82) | <.0001 | -0.233 (0.013) | 0.79 (0.77-0.81) | <.0001 |
| 18.5 kg/m$^2$-24.9 kg/m$^2$ | **Reference** | **Reference** | | **Reference** | **Reference** | | **Reference** | **Reference** | |
| 25 kg/m$^2$-29.9 kg/m$^2$ | 0.162 (0.006) | 1.18 (1.16-1.19) | <.0001 | 0.106 (0.006) | 1.11 (1.10-1.13) | <.0001 | 0.109 (0.006) | 1.11 (1.10-1.13) | <.0001 |
| >30 kg/m$^2$ | 0.206 (0.016) | 1.23 (1.19-1.27) | <.0001 | 0.130 (0.016) | 1.14 (1.10-1.18) | <.0001 | 0.133 (0.016) | 1.14 (1.11-1.18) | <.0001 |
| **Fasting Blood Glucose/ T2DM** | | | | | | | | | |
| < 100 mg/dL | **Reference** | **Reference** | | **Reference** | **Reference** | | **Reference** | **Reference** | |
| >100 mg/dL-125 mg/dL | 0.082 (0.006) | 1.09 (1.07-1.11) | <.0001 | 0.011 (0.006) | 1.01 (0.99-1.02) | 0.0764 | 0.012 (0.006) | 1.01 (0.999- | 0.0722 |
| >126 mg/dL or Rx | 0.128 (0.008) | 1.14 (1.12-1.16) | <.0001 | -0.027 (0.009) | 0.97 (0.96-0.99) | 0.0021 | -0.026 (0.009) | 0.97 (0.96-0.99) | 0.0029 |
| **Total Cholesterol** | | | | | | | | | |
| < 200 mg/dL | **Reference** | **Reference** | | **Reference** | **Reference** | | **Reference** | **Reference** | |
| 200 mg/dL -239 mg/dL | 0.131 (0.006) | 1.14 (1.13-1.15) | <.0001 | 0.019 (0.006) | 1.02 (1.01-1.03) | 0.0020 | 0.021 (0.006) | 1.02 (1.01-1.03) | 0.0006 |
| > 240 mg/dL | 0.213 (0.009) | 1.24 (1.22-1.26) | <.0001 | 0.007 (0.009) | 1.01 (0.99-1.02) | 0.4315 | 0.010 (0.009) | 1.01 (0.99-1.03) | 0.2677 |
| **Blood Pressure/HTN** | | | | | | | | | |
| SBP < 120 and DBP < 80 | **Reference** | **Reference** | | **Reference** | **Reference** | | **Reference** | **Reference** | |
| SBP 120-139 or DBP 80-89 | 0.100 (0.006) | 1.11 (1.09-1.12) | <.0001 | 0.019 (0.006) | 1.02 (1.01-1.03) | 0.0020 | 0.019 (0.006) | 1.02 (1.01-1.03) | 0.0014 |
| SBP 140-159 or DBP 90-99 | 0.222 (0.009) | 1.25 (1.23-1.27) | <.0001 | -0.0008 (0.010) | 0.99 (0.98-1.02) | 0.9366 | -0.0007 (0.010) | 0.99 (0.98-1.02) | 0.9418 |
| SBP ≥ 160 or DBP ≥ 100 or Rx | 0.237 (0.022) | 1.27 (1.22-1.32) | <.0001 | -0.087 (0.022) | 0.92 (0.88-0.96) | <.0001 | -0.089 (0.022) | 0.92 (0.88-0.96) | <.0001 |
| **Prior diagnosed diseases** | | | | | | | | | |
| Diagnosed IHD | 0.544 (0.023) | 1.72 (1.65-1.80) | <.0001 | 0.170 (0.023) | 1.19 (1.13-1.24) | <.0001 | 0.172 (0.023) | 1.19 (1.14-1.24) | <.0001 |
| Diagnosed IVDD | 0.793 (0.009) | 2.21 (2.17-2.25) | <.0001 | 0.593 (0.009) | 1.81 (1.78-1.84) | <.0001 | 0.594 (0.009) | 1.81 (1.78-1.85) | <.0001 |
| History of Back Injury | 0.686 (0.030) | 1.99 (1.87-2.11) | <.0001 | 0.546 (0.030) | 1.73 (1.63-1.83) | <.0001 | 0.545 (0.0300) | 1.72 (1.63-1.83) | <.0001 |
| Spinal Stenosis | 1.094 (0.020) | 2.99 (2.87-3.11) | <.0001 | 0.603 (0.021) | 1.83 (1.76-1.90) | <.0001 | 0.602 (0.021) | 1.83 (1.75-1.90) | <.0001 |
| History of BMD Disorders | 0.897 (0.012) | 2.45 (2.40-2.51) | <.0001 | 0.384 (0.012) | 1.47 (1.43-1.50) | <.0001 | 0.387 (0.012) | 1.47 (1.44-1.51) | <.0001 |
| Spondylolisthesis | 0.992 (0.072) | 2.70 (2.34-3.11) | <.0001 | 0.575 (0.072) | 1.78 (1.54-2.05) | <.0001 | 0.577 (0.072) | 1.78 (1.55-2.05) | <.0001 |

∗Unadjusted/Univariate analysis., †Partially adjusted accounting for Age and Sex and each of the other variables added, ‡Fully adjusted accounting for Age, Sex, Income grade, Physical activity, Smoking status, alcohol consumption and each of the other risk factors [Fasting Blood Glucose/Diabetes, Total Cholesterol, Blood pressure/HTN, IHD, Ischemic Heart Disease; IVDD, Intervertebral Disc Degeneration; History of Back Injury, Spinal Stenosis; BMD, Bone Mineral Density Disorders, Spondylolisthesis)].

### 4.1.4 Model derivation for newly diagnosed low back pain outcome

Based on the univariate and hierarchical cluster analyses, sex, age, BMI, smoking status, alcohol consumption, income grade (insurance premium), physical activity, fasting blood glucose/diabetes mellitus status, total cholesterol, premorbid hypertension/blood pressure, disc degeneration (DD), history of back injury, bone mineral density disorders (BMD), spinal stenosis, and spondylolisthesis were included in the derivation of risk prediction model for newly developed low back pain (first onset of low back pain).

After applying the backward variable selection procedure at $\alpha$=0.15 and taking into consideration the numbers of cases for reliable variable selection ($\geq$10 cases per variable), the parsimonious model consisted of 14 variables including age, sex, income grade, alcohol consumption, smoking status, physical exercise, body mass index, total cholesterol, fasting blood glucose, hypertension and disc generation, history of back injury, bone mineral density disorders and spinal stenosis (Table 4). When compared with the univariate and multivariate analysis, the variables had similar directions of associations in the parsimonious model and comparable strength of associations.

**Table 4. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors in the parsimonious model of first onset of low back pain, and the points based scoring system**

| Covariate | *β* (SE) | HR (95% CI) | *P* Value | Points* |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | Reference | Reference | | 0 |
| Female | 0.304 (0.009) | 1.36 (1.33-1.38) | <.0001 | 30 |
| **Age** | | | | |
| <45 yrs. | Reference | Reference | | 0 |
| 45-54 yrs | 0.459 (0.009) | 1.58 (1.56-1.61) | <.0001 | 46 |
| 55-64 yrs | 0.740 (0.010) | 2.10 (2.06-2.14) | <.0001 | 74 |
| >65 yrs | 0.987 (0.012) | 2.68 (2.62-2.75) | <.0001 | 99 |
| **Income/Insurance** | | | | |
| High (>60%) | Reference | Reference | | 0 |
| Medium (30-60%) | 0.063 (0.007) | 1.07 (1.05-1.08) | <.0001 | 6 |
| Low (<30%) | 0.046 (0.010) | 1.05 (1.03-1.07) | <.0001 | 5 |
| **Physical Activity/Week** | | | | |
| High (>3 times/week) | Reference | Reference | | 0 |
| Moderate (1-2 times/week) | -0.009 (0.014) | 0.99 (0.97-1.02) | 0.4853 | -1 |
| Low (None) | 0.029 (0.013) | 1.03 (1.00-1.06) | 0.0263 | 3 |
| **Smoking Status** | | | | |
| Never | Reference | Reference | | 0 |
| Former Smoker | -0.023 (0.018) | 0.97 (0.94-1.01) | 0.2093 | -2 |
| Current Smoker | -0.019 (0.010) | 0.98 (0.96-1.00) | 0.0578 | -2 |
| **Alcohol** | | | | |
| Rarely (<2 time) | Reference | Reference | | 0 |
| Moderate drinker (2–3 | -0.044 (0.008) | 0.96 (0.94-0.97) | <.0001 | -4 |
| Heavy drinker ( ≥ 4 times) | -0.014 (0.013) | 0.99 (0.96-1.01) | 0.2727 | -1 |
| **Body Mass Index** | | | | |
| < 18.5 kg/$m^2$ | -0.213 (0.016) | 0.81 (0.78-0.84) | <.0001 | -21 |
| 18.5 kg/$m^2$-24.9 kg/$m^2$ | Reference | Reference | | 0 |
| 25 kg/$m^2$-29.9 kg/$m^2$ | 0.114 (0.008) | 1.12 (1.10-1.14) | <.0001 | 11 |
| >30 kg/$m^2$ | 0.135 (0.020) | 1.14 (1.10-1.19) | <.0001 | 14 |
| **Total Cholesterol** | | | | |
| <200 mg/dL | Reference | Reference | | 0 |

| Covariate | *β* (SE) | HR (95% CI) | *P* Value | Points* |
|---|---|---|---|---|
| 200 mg/dL -239 mg/dL | 0.003 (0.008) | 1.00 (0.99-1.02) | 0.7089 | 0 |
| >240 mg/dL | 0.029 (0.011) | 0.97 (0.95-0.99) | 0.0067 | 3 |
| **Blood Pressure/HTN** | | | | |
| SBP < 120 and DBP < 80 | Reference | Reference | | 0 |
| SBP 120-139 or DBP 80-89 | -0.004 (0.008) | 0.99 (0.98-1.01) | 0.5538 | 0 |
| SBP 140-159 or DBP 90-99 | 0.041 (0.012) | 0.96 (0.94-0.98) | 0.0006 | 4 |
| SBP ≥160/DBP ≥100 or Rx | -0.137 (0.028) | 0.87 (0.83-0.92) | <.0001 | -14 |
| **Fasting Blood Glucose** | | | | |
| < 100 mg/dL | Reference | Reference | | 0 |
| 100 mg/dL-125 mg/dL | 0.006 (0.009) | 1.01 (0.99-1.02) | 0.4655 | 1 |
| ≥126 mg/dL or Rx | -0.036 (0.011) | 0.97 (0.94-0.99) | 0.0008 | -4 |
| **Diagnosed IVDD** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.533 (0.012) | 1.71 (1.67-1.75) | <.0001 | 53 |
| **Spinal Stenosis** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.215 (0.028) | 1.24 (1.17-1.31) | <.0001 | 22 |
| **History of Back Injury** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.240 (0.038) | 1.27 (1.18-1.37) | <.0001 | 24 |
| **History of BMD Disorder** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.249 (0.016) | 1.28 (1.24-1.32) | <.0001 | 25 |

*****The risk points were calculated by multiplying the estimated coefficients by 100 and rounding to the next integer.

### 4.1.5 Model validation for prediction equation of first onset low back pain

The Harrell's C-statistic was 0.805 (95% CI, 0.799-0.811) and 0.804 (95% CI, 0.796-0.812), with brier score statistics of 0.282 and 0.283 for the derivation and validation cohorts, respectively. Using the optimal threshold determined by Youden's index to define high risk individuals, the specificity in the derivation and validation cohorts was 63.9% (95% CI, 63.7% to 64.2%) and 63.9% (95% CI, 63.6%

to 64.2%) whereas the sensitivity was 70.8% (95% CI, 70.5% to 71.1%) and 70.6% (95% CI, 70.2% to 71.0%), respectively. The calibration based on Hosmer Lemeshow test was ($\chi^2$=7.233, $p$=0.5986) and ($\chi^2$=7.970, $p$=0.6127) in the derivation and validation cohorts, respectively (Table 5). Hosmer Lemeshow test $\chi^2$ values exceeding 20 indicate a significant lack of calibration [449]. Figure 1 shows the calibration and discrimination performance of the prediction model for newly developed low back pain (first onset). Calibration plot was obtained by comparisons between observed and predicted probabilities across the deciles of predicted risk. The prediction model for first onset of low back pain was well calibrate calibrated both in derivation and validation cohorts (Table 5 and Figures 1-2). In addition, comparing the Hazard Ratios between the lowest risk stratum and the highest risk stratum shows that the highest risk group was 537 times more likely to develop low back pain than the lowest risk group (Table 5). Furthermore, the model performed well in separation of individual in the lower risk groups from the intermediate groups based on the graphical displays (Figure 3).

**Table 5. Model validation and performance evaluation based on discrimination and calibration in derivation and validation cohorts of newly diagnosed low back pain equation**

| Performance Evaluation Statistic | Derivation Cohort | Validation cohort |
|---|---|---|
| Brier Score† | 0.282 | 0.283 |
| Nam and D'Agostino test‡ | $\chi^2$=7.233, p=0.5986 | $\chi^2$=7.970, p=0.6127 |
| Harrell's C-statistic (95% CI) # | 0.805 (0.799-0.811) | 0.804 (0.796-0.812) |
| Sensitivity (95% CI) | 70.8% (70.5% to 71.1%) | 70.6% (70.2% to 71.0%) |
| Specificity (95% CI) | 63.9% (63.7% to 64.2%) | 63.9% (63.6% to 64.2%) |
| Positive Likelihood Ratio (95% CI) | 1.96 (1.95 to 1.98) | 1.96 (1.94 to 1.98) |
| Negative Likelihood Ratio (95% CI) | 0.46 (0.45 to 0.46) | 0.46 (0.45 to 0.47) |
| Positive Predictive Value (95% CI) | 47.4% (47.3% to 47.6%) | 47.5% (47.2% to 47.7%) |
| Negative Predictive Value (95% CI) | 82.7% (82.5% to 82.8%) | 82.5% (82.3% to 82.7%) |
| Accuracy (95% CI) | 66.1% (65.9% to 66.3%) | 66.0% (65.8% to 66.3%) |
| **Risk Strata Comparisons** | **Derivation Cohort [HR (95% CI), *P* Value)]** | **Validation cohort [HR (95% CI), P Value)]** |
| Good | Reference | Reference |
| Good Vs Fairly Good | 1.29 (1.24-1.35), *p<.0001* | 1.28 (1.21-1.36), *p<.0001* |
| Good Vs Fairly Poor | 1.28 (1.23-1.34), *p<.0001* | 1.23 (1.16-1.30), *p<.0001* |
| Good Vs Poor | 15.76 (15.11-16.45), *p<.0001* | 15.23 (14.4-16.2), *p<.0001* |
| Good Vs Very Poor | 529.67 (503.22 -557.51), *p<.0001* | 537.3(500.2-577.2), *p<.0001* |

**Abbreviation: CI=confidence interval.**

†Measures both discrimination and calibration; lower values indicate higher accuracy, ‡A modification of Hosmer Lemeshow test (Nam and D'Agostino test) suited for survival data; measure of calibration that is specific to censored survival data (lower $\chi^2$ and higher p values) indicate better calibration, #A measure of discrimination for which higher values indicate better discrimination. The Youden's J statistic was 0.467 for both cohorts corresponding to risk probability of 0.768. This probability was the cutoff value used to define high risk individuals in the calculation of Sensitivity, Specificity, Positive Likelihood Ratio (LR+), Negative Likelihood Ratio (LR-), Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy presented in table 5. The risk strata are based on the Prognostic Index from the parsimonious prediction equation.

**Figure 1. Discrimination and calibration plots in the derivation cohort for the prediction model of newly developed low back pain. (A) Discrimination. (B) Calibration**

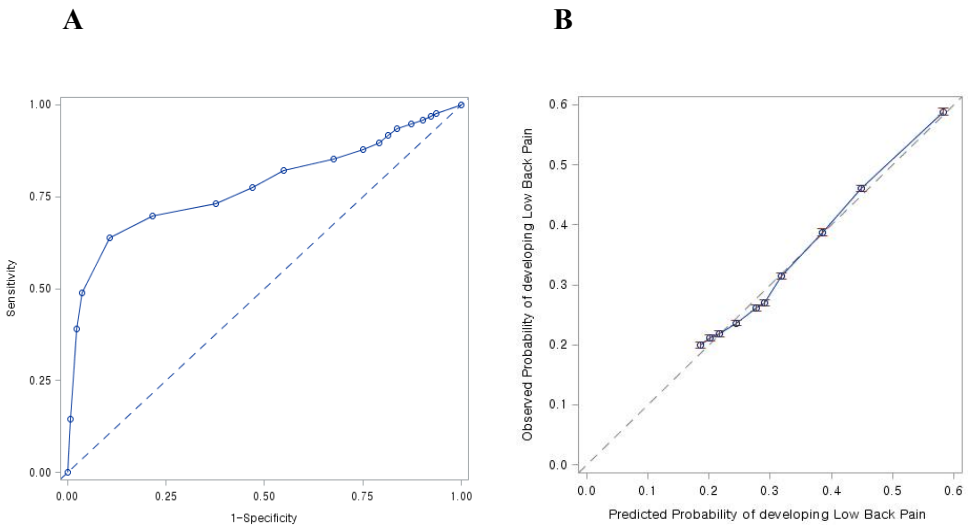



**Figure 2. Discrimination and calibration plots in the validation cohort for the prediction model of newly developed low back pain. (A) Discrimination. (B) Calibration**

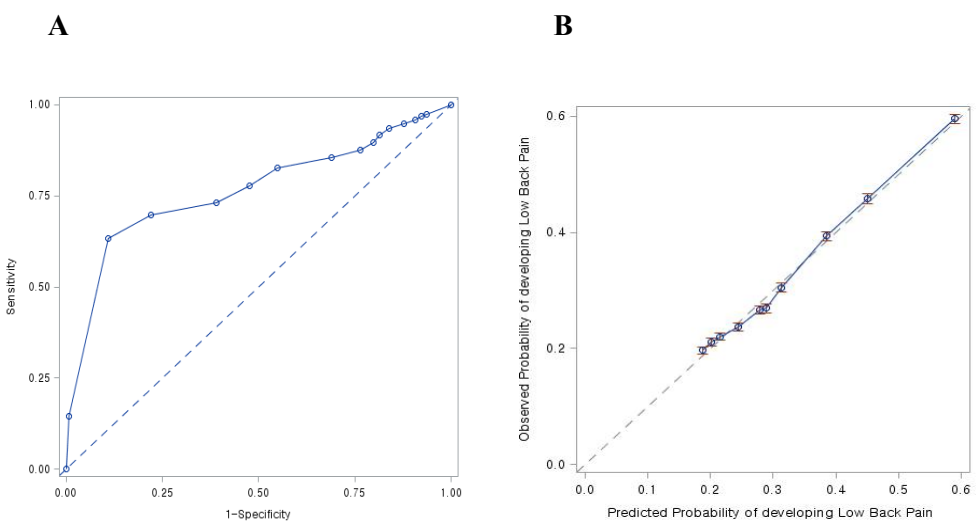
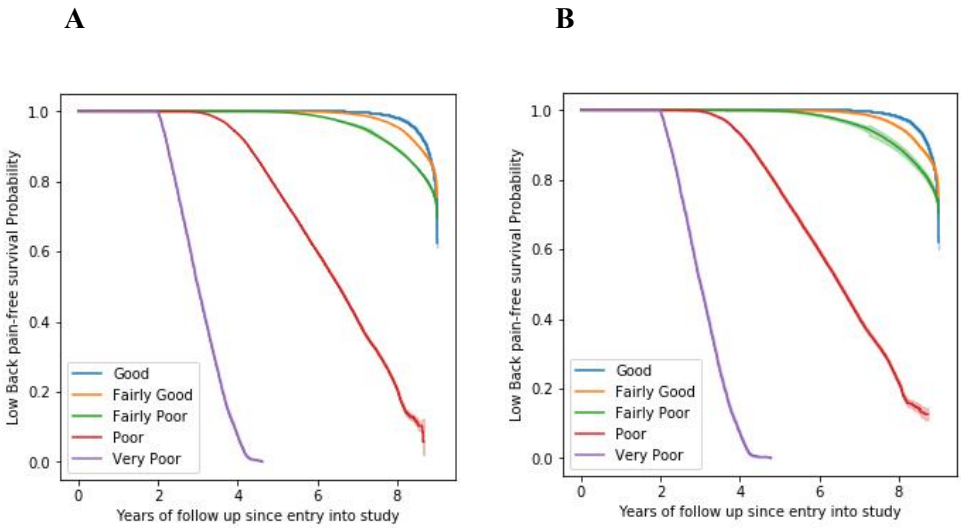


**Figure 3. Kaplan-Meier curves for low back pain-free survival in 5 risk groups in the derivation and validation cohorts based on the Prognostic Index. (A) Derivation. (B) Validation**




### 4.1.6 Model discrimination at different thresholds of predicted risk

In this study, sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values and accuracy for a range of potential cutoff points to define high-risk individuals was calculated. Table 6 shows the sensitivity, specificity, and positive and negative predictive values, positive and negative likelihood ratios, and accuracy for newly diagnosed (first onset) low back pain equation for various risk probability thresholds based on subjects in the derivation and validation cohorts. The risk probability threshold for the top 3% at highest risk of low back pain in the next 8 years was 0.974, for the top 5% was 0.955, for the top 10% was 0.911, for the top 25% was 0.817, and for the top 50% was 0.761. With a risk probability threshold of 0.911 over 8 years to identify the 10% of

participants with the highest risk of developing low back pain, the sensitivity for identifying low back pain was 27.6% (95% CI, 27.2%-28.0%), specificity 98.1% (95% CI, 98.0%-98.2%), positive predictive value (PPV) of 86.8% (95% CI, 86.2%-87.3%), negative predictive value (NPV) of 74.7% (95% CI, 74.6%-74.8%), and accuracy value of 75.9% (95% CI, 75.7%-76.1%). The corresponding thresholds for risk of developing low back pain over 8 years and the model's discrimination based on the thresholds are presented in table 6 for both the derivation and validation cohorts. Table 5 shows the sensitivity, specificity, PPV, NPV and accuracy based on the optimal cutoff determined by Youden's J statistic for the prediction equation of newly diagnosed low back pain.

**Table 6. Sensitivity, specificity, likelihood ratios, predictive values, and accuracy for low back pain at different thresholds of predicted risk of developing low back pain over 8 years.**

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values for low back pain at different thresholds of predicted risk of low back pain over 8 years in derivation cohort (Newly diagnosed or first onset of low back pain).**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥0.994 | 199,210 | 90,549 | 1,250 | 1,692 | 1.83 (1.75-1.92) | 99.4 (99.3-99.4) | 2.94 (2.74-3.16) | 0.99 (0.99-0.99) | 57.5 (55.7-59.3) | 68.8 (68.7-68.8) | 68.6 (68.5-68.8) |
| 97% | ≥0.974 | 198,761 | 85,180 | 1,587 | 7,173 | 7.77 (7.60-7.94) | 99.2 (99.2-99.3) | 9.81 (9.29-10.4) | 0.93 (0.93-0.93) | 81.9 (81.1-82.7) | 70.0 (70.0-70.0) | 70.4 (70.2-70.5) |
| 95% | ≥0.955 | 198,268 | 79,855 | 2,143 | 12,435 | 13.5 (13.3-13.7) | 98.9 (98.9-99.0) | 12.6(12.0-13.2) | 0.87 (0.87-0.88) | 85.3 (84.7-85.9) | 71.3 (71.2-71.3) | 72.0 (71.8-72.2) |
| 90% | ≥0.911 | 196,514 | 66,914 | 3,915 | 25,358 | 27.5 (27.2-27.8) | 98.1 (98.0-98.1) | 14.1 (13.6-14.5) | 0.74 (0.74-0.74) | 86.6 (86.2-87.0) | 74.6 (74.5-74.7) | 75.8 (75.7-76.0) |
| 75% | ≥0.817 | 179,650 | 39,904 | 20,771 | 52,376 | 56.8 (56.4-57.1) | 89.6(89.5-89.8) | 5.48 (5.40-5.55) | 0.48 (0.48-0.49) | 71.6 (71.3-71.9) | 81.8 (81.7-81.9) | 79.3 (79.1-79.4) |
| 50% | ≥0.761 | 120,755 | 25,650 | 79,692 | 66,604 | 72.2 (71.9-72.5) | 60.2 (60.0-60.5) | 1.82 (1.80-1.83) | 0.46 (0.46-0.47) | 45.5 (45.4-45.7) | 82.5 (82.3-82.6) | 64.0 (63.8-64.2) |
| 25% | ≥0.686 | 59,257 | 13,781 | 141,182 | 78,481 | 85.1 (84.8-85.3) | 29.6 (29.4-29.8) | 1.21 (1.20-1.21) | 0.5 (0.50-0.51) | 35.7 (35.6-35.8) | 81.1 (80.9-81.4) | 47.1 (46.9-47.2) |
| 10% | ≥0.568 | 24,371 | 4,863 | 176,210 | 87,257 | 94.7 (94.6-94.9) | 12.2 (12.0-12.3) | 1.08 (1.08-1.08) | 0.43 (0.42-0.45) | 33.1 (33.1-33.2) | 83.4 (83.0-83.8) | 38.1 (38.0-38.3) |
| 5% | ≥0.495 | 12,341 | 2,316 | 188,198 | 89,846 | 97.5 (97.4-97.6) | 6.15 (6.05-6.26) | 1.04 (1.04-1.04) | 0.41 (0.39-0.43) | 32.3 (32.3-32.4) | 84.2 (83.6-84.8) | 34.9 (34.7-35.1) |

**Sensitivity, specificity, positive and negative likelihood Ratio, positive and negative predictive values for low back pain at different thresholds of predicted risk of low back pain over 8 years in validation cohort (Newly diagnosed or first onset of low back pain).**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥0.994 | 99,451 | 45,120 | 585 | 856 | 1.86 (1.74-1.99) | 99.4 (99.4-99.5) | 3.18 (2.87-3.53) | 0.99 (0.99-0.99) | 59.4 (56.9-61.9) | 68.8 (68.8-68.8) | 68.7 (68.5-68.9) |
| 97% | ≥0.974 | 99,275 | 42,333 | 873 | 3,531 | 7.70 (7.46-7.95) | 99.1 (99.1-99.2) | 8.83 (8.21-9.50) | 0.93 (0.93-0.93) | 80.2 (79.0.-81.2) | 70.1(70.1-70.2) | 70.4 70.2-70.6) |
| 95% | ≥0.955 | 99,004 | 39,652 | 1,081 | 6,275 | 13.7 (13.4-14.0) | 98.9 (98.9-99.0) | 12.7 (11.9-13.5) | 0.87 (0.87-0.88) | 85.3 (84.5-86.1) | 71.4 (71.3-71.5) | 72.1 (71.9-72.3) |
| 90% | ≥0.911 | 98,136 | 33,277 | 1,931 | 12,668 | 27.6 (27.2-28.0) | 98.1 (98.0-98.2) | 14.3 (13.6-15.0) | 0.74 (0.73-0.74) | 86.8 (86.2-87.3) | 74.7 (74.6-74.8) | 75.9 (75.7-76.1) |
| 75% | ≥0.817 | 89,627 | 19,848 | 10,448 | 26,089 | 56.8 (56.3-57.3) | 89.6 (89.4-89.8) | 5.44 (5.33-5.55) | 0.48 (0.48-0.49) | 71.4 (71.0-71.8) | 81.9 (81.7-82.0) | 79.3 (79.0-79.5) |
| 50% | ≥0.761 | 60,241 | 12,716 | 39,808 | 33,247 | 72.3 (71.9-72.7) | 60.2 (59.9-60.5) | 1.82 (1.80-1.84) | 0.46 (0.45-0.47) | 45.5 (45.3-45.7) | 82.6 (82.3-82.8) | 64.0 (63.8-64.3) |
| 25% | ≥0.686 | 29,827 | 6,821 | 70,230 | 39,134 | 85.2 (84.8-85.5) | 29.8 (29.5-30.1) | 1.21 (1.21-1.22) | 0.50 (0.49-0.51) | 35.8 (35.7-35.9) | 81.4 (81.0-81.8) | 47.2 (47.0-47.5) |
| 10% | ≥0.568 | 12,132 | 2,506 | 87,783 | 43,591 | 94.6 (94.4-94.8) | 12.1 (11.9-12.4) | 1.08 (1.07-1.08) | 0.45 (0.43-0.47) | 33.2 (33.1-33.3) | 82.9 (82.3-83.5) | 38.2 37.9-38.4) |
| 5% | ≥0.495 | 6,059 | 1,218 | 93,898 | 44,837 | 97.4 (97.2-97.5) | 6.06 (5.91-6.21) | 1.04 (1.03-1.04) | 0.44 (0.41-0.46) | 32.3 (32.3-32.4) | 83.3 (82.4-84.1) | 34.9 (34.6-35.1) |

Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio; ratio by which the pretest probability is altered by a positive or negative test result), negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages].The thresholds of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.1.7 Prediction equations of first onset of low back pain

Basing on the parsimonious model, individualized probability of developing low back pain (first onset) within the years of follow up (t=8), can be estimated using the following equation:

$$P(\text{First onset Low Back Pain}) = 1 - \mathrm{S_o}(t)^{\exp[(\beta_1 x_1 + \beta_2 x_2 \ldots \beta_m x_m)]},$$

Where $\mathrm{S_o}(t)$ denotes the baseline survival probability at time (t) for an individual with all covariates equivalent to zero (0), $(\beta_1 \ldots \beta_m)$ denotes the change in log hazard rate (estimated $\beta$-coefficients) and $(x_1\text{-}x_m)$ denote values of risk predictors in the model. Using the estimated coefficients ($\beta_i$s) and survival probabilities $\mathrm{S_o}(t)$, personalized probabilities of developing low back pain can be calculated.

The Youden's J statistic suggested a risk probability of ≥0.768 as the optimal cutoff point to define high-risk individuals based on the predicted probability from the prediction equation. This threshold showed a sensitivity of 70.6% (95% CI, 70.2%-71.0%), specificity of 63.9% (95% CI, 63.6%-64.2%), positive likelihood ratio (LR+) of 1.96 (95% CI, 1.94-1.98), negative likelihood ratio (LR-) of 0.46 (95% CI, 0.45-0.47), positive predictive value (PPV) of 47.5% (95% CI, 47.2%-47.7%), negative predictive value (NPV) of 82.5% (95% CI, 82.3% to 82.7%) and accuracy

of 66.0% (95% CI, 65.8%-66.3%) in prediction of the risk of developing low back pain over 8 years in the validation cohort (Table 5).

#### 4.1.8 Simplified risk score for first onset of low back pain

Table 4 presents the regression coefficients for the Cox Proportional hazards model fit to the derivation cohort. In the right-most column of the table are the points associated with the presence of a given level of a risk factor (with the reference level assigned zero points). The risk points were determined by multiplying the regression coefficient by 100 and rounding to the nearest integer. Advanced age (≥65 years old) conferred the largest number of points (99 points). Among modifiable risk factors, lower BMI (<18.5 $kg/m^2$) was the most protective factor (-21) points whereas moderate alcohol consumption (2-3 times/month) was slightly protective with (-4) risk points (Table 4). The theoretical minimum and maximum sum of the points were -42 and 276, respectively. The median score was 35, while the $25^{th}$ and $75^{th}$ percentiles were 8 and 76, respectively.

Participants in the in the derivation and validation cohorts were divided into five equally sized risk strata using quintiles of the empirical risk score. The cumulative incidence risk probabilities (CIRs) for low back pain onset in each of the risk strata in the derivation and validation cohorts are described (Table 7). In the overall cohort, there were statistically significant differences in the cumulative incidence risk probabilities across the five risk strata (p<.0001). There was a clearly defined gradation in the incidence risk of low back pain across the five risk

strata. The lowest risk stratum comprised of subjects with a very low incidence of low back pain during the eight years of follow-up. In contrast, the highest risk stratum consisted of subjects with a very high incidence of low back pain during eight years of follow-up. In the validation cohort, the eight-year incidence risk of low back pain in the lowest and highest risk strata were 25.2 ( 24.3 to 26.1) and 55.6 (54.9 to 56.2) respectively. Thus, the incidence of low back pain at eight years was more than two times greater in the highest risk stratum than in the lowest risk stratum, and the HZ ratio was 3.18 times greater (Table 7). Figure 4 presents the survival trends over 8 years for participants based on the risk score strata.

**Figure 4**. **Kaplan-Meier curves for low back pain-free survival in 5 risk groups in the derivation and validation cohorts based on the simplified points based risk score. (A) Derivation. (B) Validation**

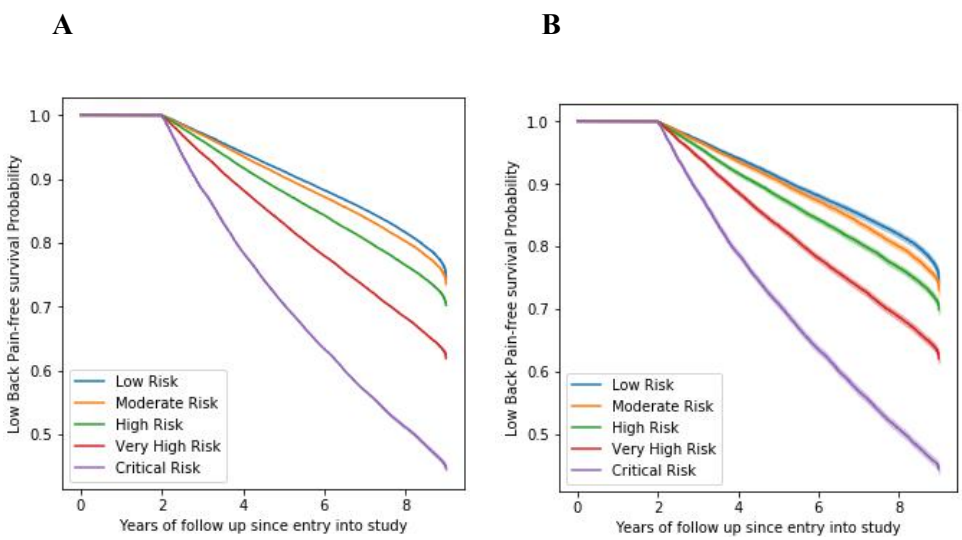


**Table 7. Risk of developing low back pain in the derivation and validation cohorts based on risk score strata**

| Risk of low back pain in the derivation cohort based on risk categories (Quintiles of the risk score). | | | | | | |
|---|---|---|---|---|---|---|
| **Risk Category** | **Risk Score Range** | **Non-Event (%)** | **Event (%)** | **Total** | **CR† (95% CI)†** | **HR (95% CI), *P* value** |
| Low Risk | <5 | 44,828 (79.34) | 11,672 (20.66) | 56,500 | 25.6 ( 25.0 to 26.3) | Reference |
| Moderate Risk | 5 to 28 | 42,705 (77.66) | 12,288 (22.34) | 54,993 | 26.4 (25.9 to 27.0) | 1.073 (1.05-1.10), *p*<.0001 |
| High Risk | 29 to 43 | 47,011 (73.30) | 17,124 (26.70) | 64,135 | 29.8 ( 29.3 to 30.2) | 1.28 (1.25 -1.31), *p* <.0001 |
| Very High Risk | 44 to 83 | 37,554 (65.12) | 20,114 (34.88) | 57,668 | 38.0 ( 37.5 to 38.5) | 1.79 (1.75-1.83), *p*<.0001 |
| Critical Risk | >83 | 28,413 (47.83) | 30,992 (52.17) | 59,405 | 55.4 (54.9 to 55.8) | 3.14 (3.07- 3.20), *p*<.0001 |
| **Risk of low back pain in the validation cohort based on risk category (Quintiles of the risk score).*** | | | | | | |
| **Risk Category** | **Risk Score Range** | **Non-Event (%)** | **Event (%)** | **Total** | **CR† (95% CI)†** | **Hazard Ratios (95% CI)** |
| Low Risk | <5 | 22,441 (79.66) | 5,731 (20.34) | 28,172 | 25.2 ( 24.3 to 26.1) | Reference |
| Moderate Risk | 5 to 28 | 21,191 (77.38) | 6,195 (22.62) | 27,386 | 26.9 (26.1 to 27.8) | 1.10 (1.06-1.14), *p*<.0001 |
| High Risk | 29 to 43 | 23,384 (73.31) | 8,515 (26.69) | 31,899 | 30.0 (29.4 to 30.8) | 1.30 (1.26-1.34), *p*<.0001 |
| Very High Risk | 44 to 83 | 18,650 (65.49) | 9,827 (34.51) | 28,477 | 37.9 (37.2 to 38.6) | 1.78 ( 1.73-1.84), *p*<.0001 |
| Critical Risk | >83 | 14,319 (47.61) | 15,759 (52.39) | 30,078 | 55.6 (54.9 to 56.2) | 3.18 (3.09-3.28), *p*<.0001 |
| **Average 8-year survival=0.5843** | | | | | | |

†Cumulative Risk

*The Cochran–Armitage test for the overall cohort (*P*<.0001)

### 4.1.9 Validation of the simplified risk score at different risk score thresholds

Table 8 shows the sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values, and accuracy for low back pain risk score (newly diagnosed or first onset low back pain) for various risk score thresholds based on subjects in the derivation and validation cohorts. The risk score threshold for the top 3% at highest risk of low back pain in the next 8 years was 143, for the top 5% was 132, for the top 10% was 110, for the top 25% was 76, and for the top 50% was 35. With a risk score threshold of 110 over 8 years to identify the 10% of participants with the highest risk of developing low back pain, the sensitivity for identifying low back pain was 18.8% (95% CI, 18.5%-19.2%), specificity 94.0% (95% CI, 93.9%-94.2%), positive predictive value 59.3% (95% CI, 58.6%-60.1%), negative predictive value 71.5% (95% CI, 71.4%-71.6%), and accuracy value 70.3% (70.1%-70.5%). The corresponding thresholds for risk of developing low back pain over 8 years and the risk score's discrimination based on the thresholds are presented both for the derivation and validation cohorts (Table 8). The Youden's J statistic suggested a risk score of ≥56 as the optimal cutoff point to define high-risk individuals based on the simplified risk score. This threshold showed a sensitivity of 47.2% (95% CI, 46.8%-47.7%), specificity of 75.6% (95% CI, 75.4%-75.9%), positive likelihood ratio (LR+) of 1.94 (95% CI, 1.91-1.97), negative likelihood ratio (LR-) of 0.70 (95% CI, 0.69-0.70), PPV of 47.2% (95% CI, 46.9%-47.6%), NPV of 75.7% (95% CI, 75.5%-75.8%) and accuracy of 66.7%

(95% CI, 66.4%-66.9%) in prediction of the risk of developing low back pain over 8 years in the validation cohort (Table 8).

**Table 8. Sensitivity, specificity, likelihood ratios, predictive values, and accuracy for low back pain at different thresholds of low the back pain risk score over 8 years in derivation and validation cohorts (Newly diagnosed low back pain risk score)**

**Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values for low back pain at different thresholds of empirical risk score of low back pain over 8 years in derivation cohort (Newly diagnosed or first onset of low back pain)**

| Threshold (Centiles) | Risk score threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥172 | 199,582 | 90,126 | 857 | 2,136 | 2.32 (2.22-2.41) | 99.6 (99.5-99.6) | 5.41 (5.00-5.86) | 0.98 (0.98-0.98) | 71.4 (69.7-73.0) | 68.9 (68.9-68.9) | 68.9 (68.8-69.1) |
| 97% | ≥143 | 197,151 | 86,226 | 3,195 | 6,129 | 6.64 (6.48-6.80) | 98.4 (98.4-98.5) | 4.16 (3.99-4.34) | 0.95 (0.95-0.95) | 65.7 (64.8-66.7) | 69.6 (69.5-69.6) | 69.5 (69.3-69.6) |
| 95% | ≥132 | 194,657 | 82,524 | 5,711 | 9,809 | 10.6 (10.4-10.8) | 97.2 (97.1-97.2) | 3.73 (3.61-3.85) | 0.92 (0.92-0.92) | 63.2 (62.5-63.9) | 70.2 (70.2-70.3) | 69.9 (69.7-70.0) |
| 90% | ≥110 | 188,358 | 75,006 | 12,207 | 17,130 | 18.6 (18.3-18.8) | 93.9 (93.8-94.0) | 3.05 (2.99-3.12) | 0.87 (0.86-0.87) | 58.4 (57.9-58.9) | 71.5 (71.5-71.6) | 70.2 (70.0-70.4) |
| 75% | ≥76 | 163,224 | 55,127 | 37,209 | 37,141 | 40.3 (39.9-40.6) | 81.4 (81.3-81.6) | 2.17 (2.14-2.19) | 0.73 (0.73-0.74) | 50.0 (49.7-50.3) | 74.8 (74.7-74.9) | 68.5 (68.3-68.6) |
| **‡68.5%** | ≥56 | 151,468 | 48,561 | 49,117 | 43,555 | 47.3 (47.0-47.6) | 75.5 (75.3-75.7) | 1.93 (1.91-1.95) | 0.70 (0.69-0.70) | 47.0 (46.7-47.3) | 75.7 (75.6-75.8) | 66.6 (66.5-66.8) |
| 50% | ≥35 | 109,432 | 31,933 | 90,845 | 60,491 | 65.5 (65.1-65.8) | 54.6 (54.4-54.9) | 1.44 (1.43-1.45) | 0.63 (0.63-0.64) | 40.0 (39.8-40.1) | 77.4 (77.2-77.6) | 58.1 (57.9-58.2) |
| 25% | ≥8 | 54,211 | 14,222 | 146,284 | 77,984 | 84.6 (84.3-84.8) | 27.0 (26.8-27.2) | 1.16 (1.15-1.16) | 0.57 (0.56-0.58) | 34.8 (34.7-34.9) | 79.2 (78.9-79.5) | 45.2 (45.0-45.3) |
| 10% | ≥-1 | 19,423 | 4,833 | 181,080 | 87,365 | 94.8 (94.6-94.9) | 9.69 (9.56-9.82) | 1.05 (1.05-1.05) | 0.54 (0.52-0.56) | 32.5 (32.5-32.6) | 80.1 (79.6-80.6) | 36.5 (36.3-36.7) |
| 5% | ≥-4 | 10,349 | 2,447 | 190,191 | 89,714 | 97.3 (97.2-97.5) | 5.16 (5.06-5.26) | 1.03 (1.02-1.03) | 0.51 (0.49-0.54) | 32.1 (32.0-32.1) | 80.9 (80.2-81.5) | 34.2 (34.0-34.4) |

**Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values for low back pain at different thresholds of predicted risk of low back pain over 8 years in validation cohort (Newly diagnosed or first onset of low back pain)**

| Threshold (Centiles) | Risk score threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥172 | 99,655 | 44,888 | 402 | 1,067 | 2.32 (2.19-2.46) | 99.6 (99.6-99.6) | 5.78 (5.16-6.48) | 0.98 (0.98-0.98) | 72.6 (70.3-74.8) | 68.9 (68.9-69.0) | 69.0 (68.7-69.2) |
| 97% | ≥143 | 98,482 | 42,833 | 1,668 | 3,029 | 6.60 (6.38-6.84) | 98.3 (98.3-98.4) | 3.97 (3.74-4.21) | 0.95 (0.95-0.95) | 64.5 (63.1-65.8) | 69.7 (69.6-69.7) | 69.5 (69.3-69.8) |
| 95% | ≥132 | 97,177 | 40,970 | 2,951 | 4,914 | 10.7 (10.4-11.0) | 97.1 (97.0-97.2) | 3.63 (3.48-3.80) | 0.92 (0.92-0.92) | 62.5 (61.4-63.5) | 70.3 (70.3-70.4) | 69.9 (69.7-70.2) |
| 90% | ≥110 | 93,978 | 37,405 | 5,953 | 8,676 | 18.8(18.5-19.2) | 94.0 (93.9-94.2) | 3.16 (3.06-3.26) | 0.86 (0.86-0.87) | 59.3 (58.6-60.1) | 71.5 (71.4-71.6) | 70.3 (70.1-70.5) |
| 75% | ≥76 | 81,420 | 27,465 | 18,643 | 18,484 | 40.2 (39.8-40.7) | 81.4 (81.1-81.6) | 2.16 (2.12-2.20) | 0.73 (0.73-0.74) | 49.8 (49.4-50.2) | 74.8 (74.6-74.9) | 68.4 (68.2-68.7) |
| **‡68.5%** | ≥56 | 75,559 | 24,321 | 24,352 | 21,780 | 47.2 (46.8-47.7) | 75.6 (75.4-75.9) | 1.94 (1.91-1.97) | 0.70 (0.69-0.70) | 47.2 (46.9-47.6) | 75.7 (75.5-75.8) | 66.7 (66.4-66.9) |
| 50% | ≥35 | 54,790 | 15,628 | 45,429 | 30,165 | 65.9 (65.4-66.3) | 54.7 (54.4-55.0) | 1.45 (1.44-1.47) | 0.62 (0.62-0.63) | 39.9 (39.7-40.1) | 77.8 (77.6-78.1) | 58.2 (57.9-58.4) |
| 25% | ≥8 | 27,288 | 7,129 | 72,713 | 38,882 | 84.5 (84.2-84.8) | 27.3 (27.0-27.6) | 1.16 (1.16-1.17) | 0.57 (0.55-0.58) | 34.8 (34.7-35.0) | 79.3 (78.9-79.7) | 45.3-45.1-45.6) |
| 10% | ≥-1 | 9,715 | 2,373 | 90,278 | 43,646 | 94.8 (94.6-95.0) | 9.72 (9.53-9.90) | 1.05 (1.05-1.05) | 0.53 (0.51-0.55) | 32.6 (32.5-32.7) | 80.4 (79.7-81.1) | 36.6 (36.3-36.8) |
| 5% | ≥-4 | 5,034 | 1,282 | 94,922 | 44,774 | 97.2 (97.1-97.4) | 5.04 (4.90-5.17) | 1.02 (1.02-1.03) | 0.55 (0.52-0.59) | 32.1 (32.0-32.1) | 79.7 (78.7-80.7) | 34.1 (33.9-34.4) |

‡The value determined by Youden's J statistic as the optimal cut off threshold for identifying high-risk group. Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages]. The thresholds of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.1.10 Practical application of the risk score for onset of low back pain

The following example illustrates how the risks can be estimated using the simplified points system.

**Case**: A 58-year-old female with insurance premium between 30-60%, high physical activity (>3 times/week) with no history of smoking, moderate drinker (2–3 times/month), with BMI below 18.5 kg/$m^2$, total cholesterol between (200-239 mg/dL), with no history of hypertension (normal blood pressure) and diabetes (normal fasting blood glucose), no history of IVDD and spinal stenosis but with history of back injury and bone mineral density disorders.

**Table 9. Practical application of the risk score for onset low back pain**

| Risk factor (Predictor) | Value (Risk Factor Category) | Points |
|---|---|---|
| Sex | Female | 30 |
| Age | 55-64 years | 74 |
| Income/Insurance | Medium (30-60%) | 6 |
| Physical Activity | High (>3 times/week) | 0 |
| Smoking Status | Never | 0 |
| Alcohol Consumption | Moderate drinker (2–3 times) | -4 |
| Body Mass Index | < 18.5 kg/$m^2$ | -21 |
| Total Cholesterol | 200 mg/dL-239 mg/dL | 0 |
| Hypertension | SBP < 120 and DBP < 80 | 0 |
| Fasting Blood Glucose | < 100 mg/dL | 0 |
| Diagnosed IVDD | No | 0 |
| Spinal Stenosis | No | 0 |
| History of Back Injury | Yes | 24 |
| History of BMD | Yes | 25 |
| **Point total** | | **134** |
| **Estimate of Risk** | | **0.872** |

**$S_0(t) = 0.5843$**

The total score was the sum of scores for each risk factor. $S_o(t)$ was low back pain-free average survival probability at time ($t$=8 years). Based on the risk score, the probability of developing low back pain can be estimated as follows;

$$P(\text{Low Back Pain onset}) = 1 - S_o(t)^{\exp[(Score/100)]}$$

$$P(\text{Low Back Pain onset}) = 1 - (0.5843)^{\exp[(134/100)]}$$

$$= 0.872$$

The $S_0(t)$ is the baseline low back pain-free survival probability at time ($t$=8 years) for an individual with all covariates equivalent to zero, which was estimated by Cox regression analysis. The beta coefficient was set to integer by multiplying 100, thus, in an actual calculation added the sum of risk scores should be divided by 100 to give an overall risk estimate. The sum (134 risk points) shown in the hypothetical score was thus divided by 100 to give the 8-year risk.

# 4.2 Prediction of chronic low back pain

### 4.2 Prediction of chronic low back pain

In low back pain studies, chronic low back pain has been defined as pain present on at least half the days in a 12 months period in a single or multiple episodes [102], and 90 days interval has been proposed as standard period between episodes of low back pain in studies based on consultation and health records (medical utilization). In this study, chronic low back pain was defined as presence of two or a series of low back pain episodes (diagnostic codes), with each episode lasting more than 90 days as recommended [102]. In order to constitute standard episodes, multiple consecutive LBP consultations within 90 days were considered as a single episode and any subsequent claim was considered as the beginning of a subsequent episode.

#### 4.2.1 Descriptive statistics for chronic low back pain outcome

Table 10 shows baseline characteristics of participants in the derivation and validation cohorts used in development of chronic low back prediction models. At baseline, 46,723 out of 502,342 participants with history of chronic low back pain were excluded from the analysis. During a median of 8.5 years of follow-up (Range: 2.17 to 8.99), there were 60,204 (13.2%) cases of chronic low back pain among 455,619 participants in the entire cohort. There were no significant differences between the derivation and validation cohorts with respect to participants' characteristics. However, there were differences between those who developed chronic low back pain (cLBP) and those who did not (Table 10). Those

who developed chronic low back pain were more likely to have higher mean values of BMI, fasting glucose, total cholesterol, and blood pressure and were mostly female participants. The total number of person-years of follow-up was 3,612,141 years. The average follow up times were approximately 8.5 years and 4.5 years among participants without cLBP and those who developed cLBP, respectively. The details of the baseline characteristics are presented (Table 10).

**Table 10. Baseline characteristic of participants in derivation and validation cohorts of chronic low back pain outcome [Mean (SD) or n (%)]**

| Covariate | Development Cohort (n=304,068) | | | Validation Cohort (n= 151,551) | | |
|---|---|---|---|---|---|---|
| | **Without cLBP** | **With cLBP** | ***P* value** | **Without cLBP** | **With cLBP** | ***P* value** |
| | **264,028 (86.8%)** | **40,040 (13.2%)** | | **131,387 (86.7%)** | **20,164 (13.3%)** | |
| Years of follow up (Years) | 8.5 (1.1) | 4.5 (1.7) | <.0001 | 8.5 (1.1) | 4.5 (1.7) | <.0001 |
| Height (cm) | 164.2 (8.7) | 160.4 (8.9) | <.0001 | 164.3 (8.6) | 160.3 (8.9) | <.0001 |
| Weight (kgs) | 62.9 (11.1) | 61.6 (10.4) | <.0001 | 62.9 (11.1) | 61.7 (10.3) | <.0001 |
| BMI ($kg/m^{2)}$ | 23.2 (3.2) | 23.9 (3.2) | <.0001 | 23.2407 (3.2) | 23.9 (3.2) | <.0001 |
| SBP (mm Hg) | 122.2 (16.9) | 125.3 (17.5) | <.0001 | 122.3 (17.1) | 125.5 (17.7) | <.0001 |
| DBP (mm Hg) | 77.0 (11.4) | 78.3 (11.3) | <.0001 | 77.1 (11.4) | 78.4 (11.4) | <.0001 |
| Fasting Blood Glucose (mg/dL) | 92.9 (27.4) | 95.4 (28.0) | <.0001 | 93.0 (27.5) | 95.9 (28.2) | <.0001 |
| Total Cholesterol (mg/dL) | 190.3 (38.3) | 197.2 (38.6) | <.0001 | 190.4 (38.4) | 197.4 (38.6) | <.0001 |
| **Sex** | | | <.0001 | | | <.0001 |
| Male | 143,303 (54.3) | 15,925 (39.8) | | 71,521 (54.4) | 8,025 (39.8) | |
| Female | 120,725 (45.7) | 24,115 (60.2) | | 59,866 (45.6) | 12,139 (60.2) | |
| **Age** | | | <.0001 | | | <.0001 |
| <44 yrs. | 178,026 (67.4) | 15,129 (37.8) | | 88,509 (67.4) | 7,506 (37.2) | |
| 45-54 yrs | 47,041 (17.8) | 9,954 (24.9) | | 23,767 (18.0) | 4,962 (24.6) | |
| 55-64 yrs | 26,217 (9.9) | 9,144 (22.8) | | 12,830 (9.8) | 4,654 (23.1) | |
| ≥65 yrs | 12,744 (4.9) | 5,813 (14.5) | | 6,281 (4.8) | 3,042 (15.1) | |
| **Occupation/Income** | | | | | | <.0001 |
| Low (<30%) | 38,017 (14.4) | 6,447 (16.1) | | 19,001 (14.5) | 3,263 (16.2) | |
| Medium (31-60%) | 95,534 (36.2) | 14,198 (35.5) | | 47,267 (36.0) | 7,018 (34.8) | |
| High (<60%) | 130,477 (49.4) | 19,395 (48.4) | | 65,119 (49.5) | 9,883 (49.0) | |
| **Physical Activity** | | | <.0001 | | | <.0001 |
| Low (None) | 151,296 (57.3) | 24,432 (61.0) | | 74,974 (57.1) | 12,500 (62.00) | |
| Moderate (1-2 times/week) | 93,884 (35.6) | 12,607 (31.5) | | 47,016 (35.8) | 6,157 (30.5) | |
| High (≥3 times/week) | 18,848 (7.1) | 3,001 (7.5) | | 9,397 (7.1) | 1,507 (7.5) | |
| **Smoking Status** | | | <.0001 | | | <.0001 |

| Covariate | Development Cohort (n=304,068) | | | Validation Cohort (n= 151,551) | | |
|---|---|---|---|---|---|---|
| | **Without cLBP** | **With cLBP** | ***P* value** | **Without cLBP** | **With cLBP** | ***P* value** |
| | **264,028 (86.8%)** | **40,040 (13.2%)** | | **131,387 (86.7%)** | **20,164 (13.3%)** | |
| Never | 168,876 (63.9) | 30,272 (75.6) | | 83,788 (63.8) | 15,234 (75.6) | |
| Former Smoker | 12,106 (4.6) | 1,344 (3.4) | | 6,173 (4.7) | 712 (3.3) | |
| Current Smoker | 83,046 (31.5) | 8,424 (21.0) | | 41,426 (31.5) | 4,218 (20.9) | |
| **Alcohol Consumption/Week** | | | <.0001 | | | <.0001 |
| Rarely (<2 times) | 127,023 (48.1) | 24,074 (60.1) | | 63,050 (47.9) | 12,164 (60.3) | |
| Moderate drinker (2–3 times) | 110,903 (42.0) | 12,853 (32.1) | | 55,261 (42.1) | 6,432 (31.9) | |
| Heavy drinker ( ≥ 4 times) | 26,102 (9.9) | 3,113 (7.8) | | 13,076 (10.0) | 1,568 (7.8) | |
| **Body Mass Index** | | | <.0001 | | | <.0001 |
| <18.5 kg/$m^2$ | 16,059 (6.1) | 1,460 (3.7) | | 8,020 (6.1) | 704 (3.5) | |
| 18.5 kg/$m^2$-24.9 kg/$m^2$ | 173,841 (65.8) | 24,601 (61.4) | | 86496 (65.8) | 12,270 (60.9) | |
| 25 kg/$m^2$-29.9 kg/$m^2$ | 67,511 (25.6) | 12,619 (31.5) | | 33,636 (25.6) | 6,518 (32.3) | |
| >30 kg/$m^2$ | 6,617 (2.5) | 1,360 (3.4) | | 3,235 (2.5) | 672 (3.3) | |
| **Fasting Blood Glucose** | | | <.0001 | | | <.0001 |
| < 100 mg/dL | 174,484 (66.1) | 24,873 (62.1) | | 86,468 (65.8) | 12,453 (61.8) | |
| 100 mg/dL-125 mg/dL | 62,435 (23.6) | 10,301 (25.7) | | 31,332 (23.9) | 5,116 (25.3) | |
| > 126 mg/dL or Rx | 27,109 (10.3) | 4,866 (12.2) | | 13,587 (10.3) | 2,595 (12.9) | |
| **Blood Pressure/HTN** | | | <.0001 | | | <.0001 |
| SBP < 120 and DBP < 80 | 99,823 (37.8) | 12,801 (32.0) | | 49,501 (37.7) | 6,448 (32.0) | |
| SBP 120-139 or DBP 80-89 | 135,364 (51.3) | 21,456 (53.6) | | 67,136 (51.1) | 10,759 (53.4) | |
| SBP 140-159 or DBP 90-99 | 25,347 (9.6) | 5,055 (12.6) | | 12,876 (9.8) | 2,566 (12.7) | |
| SBP ≥ 160 or ≥ DBP100 or Rx | 3,494 (1.3) | 728 (1.8) | | 1,874 (1.4) | 391 (1.9) | |
| **Total cholesterol** | | | <.0001 | | | <.0001 |
| < 200 mg/dL | 162,288 (61.5) | 21,669 (54.1) | | 80,610 (61.4) | 10850 (53.8) | |
| 200 mg/dL-239 mg/dL | 74,757 (28.3) | 12,894 (32.2) | | 37,327 (28.4) | 6531 (32.4) | |
| > 240 mg/dL | 26,983 (10.2) | 5,477 (13.7) | | 13,450 (10.2) | 2783 (13.8) | |
| **Diagnosed IHD** | | | <.0001 | | | <.0001 |
| No | 261,891 (99.2) | 39,323 (98.2) | | 130,278 (99.2) | 19,781 (98.1) | |

| Covariate | Development Cohort (n=304,068) | | | Validation Cohort (n= 151,551) | | |
|---|---|---|---|---|---|---|
| | **Without cLBP** | **With cLBP** | ***P* value** | **Without cLBP** | **With cLBP** | ***P* value** |
| | **264,028 (86.8%)** | **40,040 (13.2%)** | | **131,387 (86.7%)** | **20,164 (13.3%)** | |
| Yes | 2,137 (0.8) | 717 (1.8) | | 1,109 (0.8) | 383 (1.9) | |
| **Diagnosed IVDD** | | | <.0001 | | | <.0001 |
| No | 251,125 (95.1) | 34,965 (87.3) | | 124,809 (95.0) | 17,524 (86.9) | |
| Yes | 12,903 (4.9) | 5,075 (12.7) | | 6,578 (5.0) | 2,640 (13.1) | |
| **History of Back Injuries** | | | <.0001 | | | <.0001 |
| No | 262,887 (99.57) | 39,599 (98.9) | | 130,774 (99.5) | 19,976 (99.1) | |
| Yes | 1,141 (0.43) | 441 (1.1) | | 613 (0.5) | 188 (0.9) | |
| **BMD Disorders** | | | <.0001 | | | <.0001 |
| No | 257,476 (97.5) | 36,732 (91.7) | | 128,206 (97.6) | 18512 (91.8) | |
| Yes | 6,552 (2.5) | 3,308 (8.3) | | 3,181 (2.4) | 1,652 (8.2) | |
| **Spinal Stenosis** | | | <.0001 | | | <.0001 |
| No | 262,201 (99.3) | 38,932 (97.2) | | 130, 490 (99.3) | 19, 619 (97.3) | |
| Yes | 18,27 (0.7 | 1,108 (2.8) | | 897 (0.7) | 545 (2.7) | |
| **Spondylolisthesis** | | | <.0001 | | | <.0001 |
| No | 263,895 (99.95) | 39,964 (99.8) | | 131, 315 (99.95) | 72 (99.7) | |
| Yes | 133 (0.05) | 76 (0.2) | | 72 (0.05) | 51 (0.3) | |

The student's *t*-test for continuous variables and $\chi^2$-test for categorical variables were used to examine the differences in baseline characteristics between participants in the derivation and validation cohorts stratified based on chronic low back pain outcome.

### 4.2.2 Cumulative incidence probabilities of chronic low back pain

During the follow-up period (8.5 years), the cumulative risk of chronic low pain increased from 3.2 (95% CI, 3.2-3.3) in 2004 to 13.7 (95% CI, 13.6-13.8) in 2010. The risk of chronic low back pain increased at a higher rate in the first four years of follow up period and there was increase in censoring and reduction of events from the year 2007. The details of the incidence trends and risk are presented (Table 11).

**Table 11. Follow-up times, cumulative incidence, and incidence probabilities of chronic low back pain**

| Year of follow up | Censored | Events | Total | CR* (95% CI) |
|---|---|---|---|---|
| 2004 | 3,513 | 14,567 | 18,080 | 3.2 (3.2-3.3) |
| 2005 | 2,283 | 12,767 | 15,050 | 6.0 (6.0-6.1 ) |
| 2006 | 3,474 | 10,163 | 13,637 | 8.3 (8.2-8.4) |
| 2007 | 7,649 | 8,511 | 16,160 | 10.2 (10.1-10.3) |
| 2008 | 11,427 | 6,836 | 18,263 | 11.8 (11.7-11.9) |
| 2009 | 23,173 | 5,149 | 28,322 | 13.1 (13.0-13.2 ) |
| 2010 | 343,896 | 2,211 | 346,107 | 13.7 (13.6-13.8) |
| **Totals** | **395,415** | **60,204** | **455,619** | |

*Cumulative Risk

### 4.2.3 Association between risk factors and chronic low back pain

Tables 12⇓ present the estimated coefficients and hazard ratios of covariates in the unadjusted, partially adjusted, and fully adjusted models. In this study, all variables were associated with chronic low back pain in the univariate analysis ($p< 0.05$) (Table 12). However, both alcohol consumption and smoking status showed an inverse association with cLBP in the univariate and multivariate analysis

($p<0.05$) (Table 12). In contrast, body mass index (BMI), fasting blood glucose (FBG), hypertension (HTN), and total cholesterol showed positive associations in the univariate analysis. Furthermore, premorbid conditions including ischemic heart disease (IHD), intervertebral disc degeneration (IVDD), history of back injury, spinal stenosis, bone mineral density (BMD) disorders and spondylolisthesis were positively associated with cLBP ($p<0.05$) (Table 12). Generally, the strength of the relationship between premorbid conditions and cLBP was slightly higher but comparable with that observed between premorbid condition and newly developed (first onset) low back pain (Compare Table 3 and Table 12). In this study, BMI and total cholesterol showed stable positive associations with cLBP in all analyses. The predictors strongly associated with cLBP were age, female sex, and premorbid conditions ($p<0.05$) (Table 12). In general, components of metabolic syndrome (MetS) were associated with cLBP, but the directions of associations differed in adjusted and univariate analysis (Table 12).

**Table 12. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors in the univariate, partially adjusted and fully adjusted models for chronic low back pain**

| Covariate | Unadjusted∗ | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value |
| **Sex** | | | | | | | | | |
| Female | 0.529 (0.008) | 1.70 (1.67-1.73) | <.0001 | 0.516 (0.008) | 1.68 (1.65-1.70) | <.0001 | 0.461 (0.011) | 1.59 (1.55-1.62) | <.0001 |
| **Age** | | | | | | | | | |
| <45 yrs. | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 45-54 yrs | 0.847 (0.011) | 2.33 (2.29-2.38) | <.0001 | 0.841 (0.011) | 2.32 (2.27-2.37) | <.0001 | 0.841 (0.011) | 2.32 (2.27-2.37) | <.0001 |
| 55-64 yrs | 1.314 (0.011) | 3.72 (3.64-3.80) | <.0001 | 1.316 (0.011) | 3.73 (3.65-3.81) | <.0001 | 1.304 (0.011) | 3.69 (3.61-3.77) | <.0001 |
| >65 yrs | 1.601 (0.013) | 4.96 (4.84-5.08) | <.0001 | 1.583 (0.013) | 4.87 (4.75-4.99) | <.0001 | 1.568 (0.013) | 4.80 (4.68-4.92) | <.0001 |
| **Income/Insurance** | | | | | | | | | |
| High (>60%) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Medium (30-60%) | -0.005 (0.009) | 0.99 (0.98-1.01) | 0.5960 | 0.082 (0.009) | 1.09 (1.07-1.11) | <.0001 | 0.081 (0.009) | 1.08 (1.07-1.10) | <.0001 |
| Low (<30%) | 0.123 (0.012) | 1.13 (1.11-1.16) | <.0001 | 0.069 (0.012) | 1.07 (1.05-1.10) | <.0001 | 0.067 (0.012) | 1.07 (1.05-1.10) | <.0001 |
| **Physical Activity/Week** | | | | | | | | | |
| High (>3 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate (1-2 times) | -0.171 (0.017) | 0.84 (0.82-0.87) | <.0001 | -0.049(0.017) | 0.95 (0.92-0.98) | 0.0032 | -0.048 (0.017) | 0.95 (0.92-0.99) | 0.0041 |
| Low (None) | 0.019 (0.016) | 1.02 (0.99-1.05) | 0.2172 | 0.012 (0.016) | 1.01 (0.98-1.04) | 0.4660 | 0.004 (0.016) | 1.00 (0.97-1.04) | 0.8162 |
| **Smoking Status** | | | | | | | | | |
| Never | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Former | -0.431 (0.022) | 0.65 (0.62-0.68) | <.0001 | -0.061(0.024) | 0.94 (0.90-0.99) | 0.0094 | -0.055 (0.024) | 0.95 (0.90-0.99) | 0.0200 |
| Current Smoker | -0.523 (0.010) | 0.59 (0.58-0.61) | <.0001 | -0.038(0.013) | 0.96 (0.94-0.99) | 0.0024 | -0.040 | 0.96 (0.94-0.99) | 0.0017 |
| **Alcohol** | | | | | | | | | |
| Rarely (<2 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |

| Covariate | Unadjusted* | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value |
| Moderate drinker (2–3 times) | -0.461 (0.009) | 0.63 (0.62-0.64) | <.0001 | -0.073(0.010) | 0.93 (0.91-0.95) | <.0001 | -0.071 (0.010) | 0.93 (0.91-0.95) | <.0001 |
| Heavy drinker ( ≥ 4 times) | -0.425 (0.016) | 0.65 (0.63-0.67) | <.0001 | -0.017(0.017) | 0.98 (0.95-1.02) | 0.3089 | -0.017 (0.017) | 0.98 (0.95-1.02) | 0.3012 |
| **Body Mass Index** | | | | | | | | | |
| < 18.5 kg/m$^2$ | -0.428 (0.022) | 0.65 (0.62-0.68) | <.0001 | -0.327(0.022) | 0.72 (0.69-0.75) | <.0001 | -0.334 (0.022) | 0.72 (0.69-0.75) | <.0001 |
| 18.5 kg/m$^2$-24.9 kg/m$^2$ | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 25 kg/m$^2$-29.9 kg/m$^2$ | 0.265 (0.009) | 1.30 (1.28-1.33) | <.0001 | 0.154 (0.009) | 1.17 (1.15-1.19) | <.0001 | 0.159 (0.009) | 1.17 (1.15-1.19) | <.0001 |
| ≥ 30 kg/m$^2$ | 0.342 (0.023) | 1.41 (1.35-1.47) | <.0001 | 0.194 (0.023) | 1.21 (1.16-1.27) | <.0001 | 0.197 (0.023) | 1.22 (1.16-1.27) | <.0001 |
| **Fasting Blood Glucose** | | | | | | | | | |
| <100 mg/dL | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 100 mg/dL-125 mg/dL | 0.129 (0.010) | 1.14 (1.12-1.16) | <.0001 | 0.010 (0.009) | 1.01 (0.99-1.03) | 0.2979 | 0.010 (0.009) | 1.01 (0.99-1.03) | 0.2857 |
| >126 mg/dL or Rx | 0.230 (0.013) | 1.26 (1.22-1.29) | <.0001 | -0.021(0.013) | 0.98 (0.96-1.00) | 0.1008 | -0.019 (0.013) | 0.98 (0.96-1.01) | 0.1332 |
| **Total Cholesterol** | | | | | | | | | |
| < 200 mg/dL | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 200 mg/dL-239 mg/dL | 0.240 (0.009) | 1.27 (1.25-1.29) | <.0001 | 0.047 (0.009) | 1.05 (1.03-1.07) | <.0001 | 0.051 (0.009) | 1.05 (1.03-1.07) | <.0001 |
| > 240 mg/dL | 0.391 (0.012) | 1.48 (1.44-1.52) | <.0001 | 0.052 (0.013) | 1.05 (1.03-1.08) | <.0001 | 0.056 (0.013) | 1.06 (1.03-1.08) | <.0001 |
| **Blood pressure/ HTN** | | | | | | | | | |
| SBP < 120 and DBP < 80 | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| SBP 120-139 or DBP 80-89 | 0.202 (0.009) | 1.22 (1.20-1.25) | <.0001 | 0.042 (0.009) | 1.04 (1.02-1.06) | <.0001 | 0.042 (0.009) | 1.04 (1.02-1.06) | <.0001 |
| SBP 140-159 or DBP 90-99 | 0.416 (0.014) | 1.52 (1.48-1.56) | <.0001 | 0.034 (0.014) | 1.03 (1.01-1.06) | 0.0169 | 0.033 (0.014) | 1.03 (1.01-1.06) | 0.0219 |
| SBP≥160 or ≥DBP100 or Rx | 0.472 (0.031) | 1.60 (1.51-1.70) | <.0001 | -0.048(0.031) | 0.95 (0.90-1.01) | 0.1240 | -0.054 (0.031) | 0.95 (0.89-1.01) | 0.0859 |
| **Premorbid conditions** | | | | | | | | | |
| Diagnosed IHD | 0.737 (0.030) | 2.09 (1.97-2.22) | <.0001 | 0.181 (0.031) | 1.20 (1.13-1.27) | <.0001 | 0.185 (0.031) | 1.20 (1.13-1.28) | <.0001 |
| Diagnosed IVDD | 0.945 (0.012) | 2.57 (2.51-2.64) | <.0001 | 0.645 (0.012) | 1.91 (1.86-1.95) | <.0001 | 0.646 (0.012) | 1.91 (1.86-1.96) | <.0001 |
| History of Back Injury | 0.793 (0.040) | 2.21 (2.04-2.39) | <.0001 | 0.578 (0.040) | 1.78 (1.65-1.93) | <.0001 | 0.577 (0.040) | 1.78 (1.65-1.93) | <.0001 |
| Spinal Stenosis | 1.271 (0.025) | 3.56 (3.39-3.74) | <.0001 | 0.573 (0.025) | 1.77 (1.69-1.86) | <.0001 | 0.572 (0.025) | 1.77 (1.69-1.86) | <.0001 |

| Covariate | Unadjusted∗ | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value |
| History of BMD Disorders | 1.132 (0.015) | 3.10 (3.01-3.19) | <.0001 | 0.384 (0.015) | 1.47 (1.43-1.51) | <.0001 | 0.390 (0.016) | 1.49 (1.43-1.52) | <.0001 |
| Spondylolisthesis | 1.236 (0.089) | 3.44 (2.89-4.09) | <.0001 | 0.618 (0.089) | 1.86 (1.56-2.21) | <.0001 | 0.617 (0.089) | 1.85 (1.56-2.21) | <.0001 |

∗Unadjusted/Univariate analysis;†Partially adjusted accounting for Age and Sex and each of the other variables added; ‡Fully adjusted accounting for Age, Sex, Income grade, Physical activity, Smoking status, alcohol consumption and each of the other risk factors [Fasting Blood Glucose/Diabetes, Total Cholesterol, Blood pressure/HTN, IHD, Ischemic Heart Disease; IVDD, Intervertebral Disc Degeneration; History of Back Injury, Spinal Stenosis; BMD, Bone Mineral Density Disorders, Spondylolisthesis)]. Abbreviations [BMD, Bone Mineral Density; IHD, Ischemic Heart Disease; IVDD, Intervertebral Disc Degeneration; HTN, Hypertension]

### 4.2.4 Derivation of chronic low back pain prediction equations

After screening of predictors based on the univariate and hierarchical cluster analysis, 15 variables including sex, age, smoking status, alcohol consumption, income grade (insurance premium), physical inactivity, BMI, total cholesterol, fasting blood glucose (FBG), hypertension and intervertebral disc degeneration (IVDD), history of back injury, bone mineral density(BMD) disorders, spinal stenosis, and spondylolisthesis were all included in the model derivation. After applying the backward variable selection procedure at $\alpha$=0.15, taking into consideration the number of cases for reliable variable selection (≥10 cases per variable), all 15 variables were retained in the parsimonious model (Table 13).

**Table 13. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors in the parsimonious model of chronic low back pain**

| Covariate | *β* (SE) | HR (95% CI) | *P* | Points* |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | Reference | Reference | | 0 |
| Female | 0.433 (0.014) | 1.54 (1.50-1.59) | <.0001 | 43 |
| **Age** | | | | |
| <45 yrs. | Reference | Reference | | 0 |
| 45-54 yrs | 0.753 (0.013) | 2.12 (2.07-2.18) | <.0001 | 75 |
| 55-64 yrs | 1.172 (0.014) | 3.23 (3.14-3.32) | <.0001 | 117 |
| ≥65 yrs | 1.429 (0.017) | 4.17 (4.04-4.31) | <.0001 | 143 |
| **Income/Insurance Premium** | | | | |
| High (>60%) | Reference | Reference | | 0 |
| Medium (30-60%) | 0.094 (0.011) | 1.10 (1.08-1.12) | <.0001 | 9 |
| Low (<30%) | 0.085 (0.014) | 1.09 (1.06-1.12) | <.0001 | 9 |

| Covariate | *β* (SE) | HR (95% CI) | *P* | Points* |
|---|---|---|---|---|
| **Physical Activity** | | | | |
| High (≥3 times/week) | Reference | Reference | | 0 |
| Moderate (1-2 times/week) | -0.035 (0.020) | 0.97 (0.93-1.01) | 0.0847 | -4 |
| Low (None) | 0.013 (0.019) | 1.01 (0.98-1.05) | 0.5046 | 1 |
| **Smoking Status** | | | | |
| Never | Reference | Reference | | 0 |
| Former Smoker | -0.062 (0.029) | 0.94 (0.89-0.995) | 0.0343 | -6 |
| Current Smoker | -0.041 (0.016) | 0.96 (0.93-0.99) | 0.0076 | -4 |
| **Alcohol Consumption/Month** | | | | |
| Rarely (<2 times) | Reference | Reference | | 0 |
| Moderate drinker(2-3 times) | -0.068 (0.012) | 0.93 (0.912-0.96) | <.0001 | -7 |
| Heavy drinker(>3 time) | -0.013 (0.020) | 0.99 (0.95-1.03) | 0.5155 | -1 |
| **Body Mass Index** | | | | |
| < 18.5 $kg/m^2$ | -0.295 (0.027) | 0.74 (0.71-0.79) | <.0001 | -30 |
| 18.5 $kg/m^2$-24.9 $kg/m^2$ | Reference | Reference | | 0 |
| 25 $kg/m^2$-29.9 $kg/m^2$ | 0.139 (0.011) | 1.15 (1.12-1.18) | <.0001 | 14 |
| ≥ 30 $kg/m^2$ | 0.184 (0.028) | 1.20 (1.14-1.27) | <.0001 | 18 |
| **Total Cholesterol** | | | | |
| <200μmol/l | Reference | Reference | | 0 |
| 200μmol-239μmol/l | 0.027 (0.011) | 1.03 (1.01-1.05) | 0.0179 | 3 |
| >240μmol/l | 0.016 (0.015) | 1.02 (0.99-1.05) | 0.3211 | 2 |
| **Blood Pressure/HTN** | | | | |
| SBP < 120 and DBP < 80 | Reference | Reference | | 0 |
| SBP 120-139 or DBP 80-89 | 0.016 (0.012) | 1.02 (0.99-1.04) | 0.1686 | 2 |
| SBP 140-159 or DBP 90-99 | 0.001 (0.018) | 1.00 (0.97-1.04) | 0.9554 | 0 |
| SBP ≥160 or DBP ≥ 100 or Rx | -0.090 (0.039) | 0.91 (0.85-0.99) | 0.0200 | -9 |
| **Fasting Blood Glucose** | | | | |
| < 100 mg/dL | Reference | Reference | | 0 |
| 100 mg/dL-125 mg/dL | 0.009 (0.012) | 1.01 (0.986-1.03) | 0.4324 | 1 |
| ≥126 mg/dL or Rx | -0.050 (0.016) | 0.95 (0.92-0.98) | 0.0017 | -5 |
| **Diagnosed IVDD** | | | | |

| Covariate | *β* (SE) | HR (95% CI) | *P* | Points* |
|---|---|---|---|---|
| No | Reference | Reference | | 0 |
| Yes | 0.580 (0.016) | 1.78 (1.73-1.84) | <.0001 | 58 |
| **Spinal Stenosis** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.177 (0.035) | 1.19 (1.12-1.28) | <.0001 | 18 |
| **History of Back Injury** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.315 (0.049) | 1.37 (1.25-1.51) | <.0001 | 32 |
| **BMD Disorders** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.238 (0.021) | 1.27 (1.22-1.32) | <.0001 | 24 |
| **Spondylolisthesis** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.173 (0.116) | 1.19 (0.95-1.49) | 0.1348 | 17 |

***The risk points were calculated by multiplying the estimated coefficients by 100 and rounding to the next integer.

### 4.2.5 Model validation for prediction equation of chronic low back pain risk

The Harrell's C-statistic was 0.650 (95% CI, 0.640-0.660) and 0.643 (95% CI, 0.629-0.656), with brier score of 0.127 and 0.128 for the derivation and validation cohorts, respectively (Table 14). Using the optimal threshold determined by Youden's index to define high risk individuals, the model sensitivity was 38.6% (95% CI, 38.1% to 39.0%) and 38.7% (95% CI, 38.1% to 39.4%) whereas specificity was 94.2% (95% CI, 94.1% to 94.3%) and 94.3% (95% CI, 94.2% to 94.4%), in the derivation and validation cohorts, respectively (Table 14). The calibration was (Nam and D'Agostino's $\chi^2$=7.243, $p$=0.2522 and $\chi^2$=6.853, $p$=0.4656) for the derivation and validation cohorts, respectively. The prediction

model showed moderate discrimination based on Harrell's C-Statistics, sensitivity, and specificity. Table 14 and Figures 5-7 present the model calibration and discrimination performance. There was agreement between observed risks and mean predicted risks of chronic low back pain across each decile of the predicted risk. In addition, comparing the Hazard Ratios between the lowest risk stratum and the highest risk stratum shows that the highest risk group is 46 times more likely to develop chronic low back pain than the lowest risk group (Table 14). However, the model performed poorly in separation of individual in the lower risk groups based on the graphical displays (Figure 7).

.

**Table 14. Model validation and performance evaluation of chronic low back pain risk prediction equation based on discrimination and calibration in derivation and validation cohorts**

| Performance Evaluation statistic | Derivation Cohort | Validation cohort |
|---|---|---|
| Brier Score† | 0.127 | 0.128 |
| Nam and D'Agostino test‡ | $\chi^2$=7.243,*p*=0.2522 | $\chi^2$=6.853,*p*=0.4656 |
| Harrell's C statistic (95% CI) # | 0.650 (0.640-0.660) | 0.643 (0.629-0.656) |
| Sensitivity (95% CI) | 38.6% (38.1% to 39.0%) | 38.7% (38.1% to 39.4%) |
| Specificity (95% CI) | 94.2% (94.1% to 94.3%) | 94.3% (94.2% to 94.4% |
| Positive Likelihood Ratio (95% CI) | 6.66 (6.53 to 6.79) | 6.80 (6.61 to 6.99) |
| Negative Likelihood Ratio (95% CI) | 0.65 (0.65 to 0.66) | 0.65 (0.64 to 0.66) |
| Positive Predictive Value (95% CI) | 50.2% (49.8% to 50.7%) | 51.1% (50.4% to 51.8%) |
| Negative Predictive Value (95% CI) | 91.0% (90.9% to 91.1%) | 90.9% (90.8% to 91.0%) |
| Accuracy (95% CI) | 86.9% (86.8% to 87.0%) | 86.9% (86.7% to 87.1%) |
| **Risk Strata Comparisons** | **HRs (95% CI), *P* value)** | **(HRs (95% CI), P value)** |
| Good | Reference | Reference |
| Good Vs Fairly Good | 1.12 (1.06-1.19), *p*<.0001 | 0.97(0.91-1.05),*p*=0.4804 |
| Good Vs Fairly Poor | 0.85 (0.80-0.90), *p*<.0001 | 0.78 (0.73-0.85), *p*<.0001 |
| Good Vs Poor | 1.42 (1.35-1.51), *p*<.0001 | 1.39 (1.29-1.50), *p*<.0001 |
| Good Vs Very Poor | 52.7 (49.8-55.8), *p*<.0001 | 46.0 (42.6-49.6), *p*<.0001 |

**Abbreviation: CI=Confidence Interval.**

†Measures both discrimination and calibration; lower values indicate higher accuracy, ‡A modification of Hosmer Lemeshow test suited for survival data; measure of calibration that is specific to censored survival data (lower $\chi^2$ and higher p values) indicate better calibration, #A measure of discrimination for which higher values indicate better discrimination. The Youden's J statistics was 0.330 for both cohorts corresponding to risk probability of 0.948 that was used to define high risk individuals.

**Figure 5. Discrimination and calibration plots in the derivation cohort for the risk prediction equation of chronic low back pain. (A) Discrimination. (A) Calibration**

**A** **B**

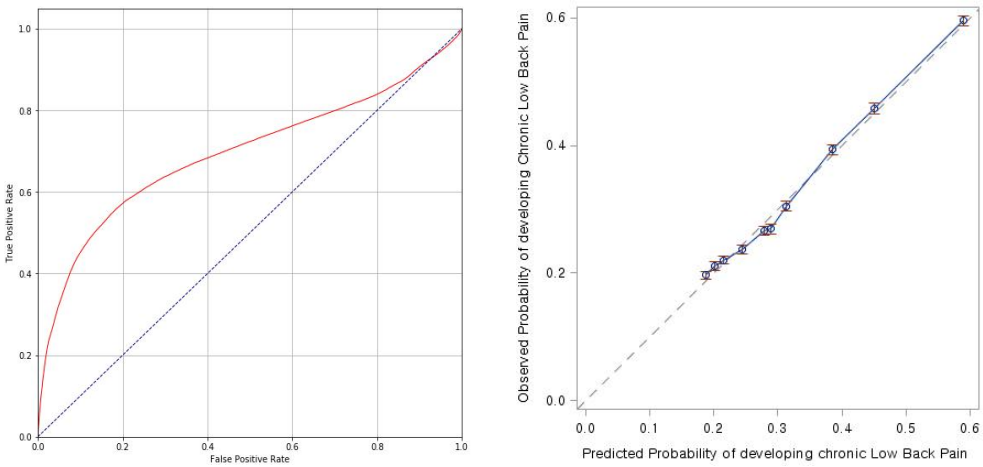



**Figure 6. Discrimination and calibration plots in the validation cohort for the risk prediction equation of chronic low back pain. (A) Discrimination. (B) Calibration**

**A** **B**

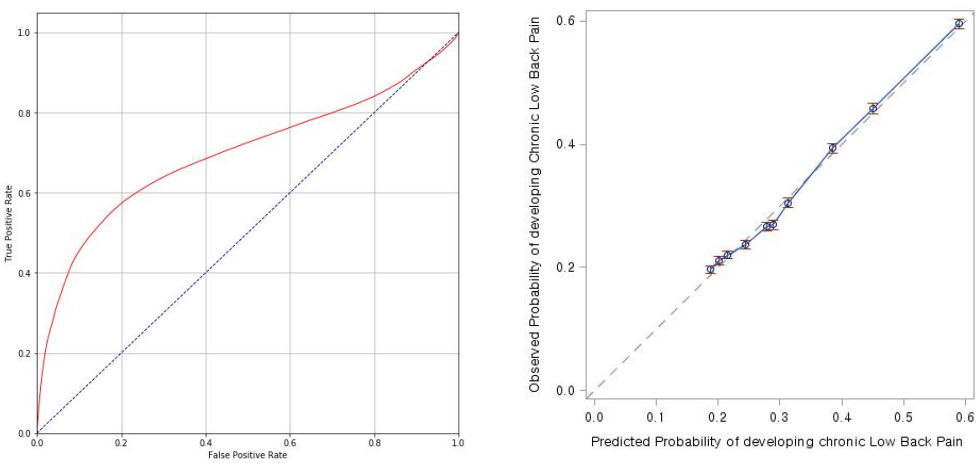
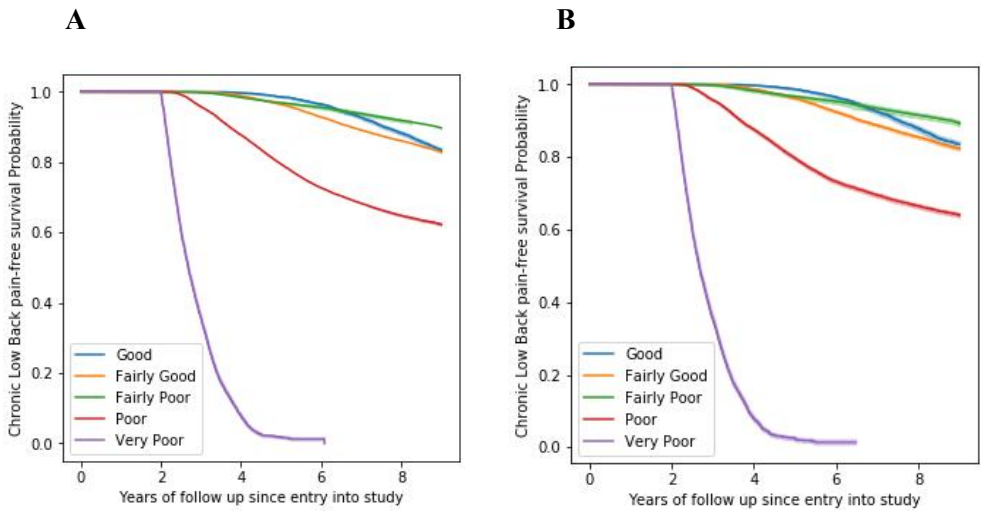


**Figure 7. Kaplan-Meier curves for chronic low back pain-free survival in 5 risk groups in the derivation and validation cohorts based on the Prognostic Index. (A) Derivation. (B) Validation**




### 4.2.6 Model discrimination at different thresholds of predicted risk

Table 15 shows the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy for chronic low back pain equation for various risk probability thresholds based on subjects in the derivation and validation cohorts. The risk probability threshold for the top 3% at highest risk of chronic low back pain in the next 8 years was 0.977, for the top 5% was 0.963, for the top 10% was 0.948, for the top 25% was 0.938, and for the top 50% was 0.906 in the both cohorts. With a risk probability threshold of 0.948 over 8 years to identify the10% of participants with the highest risk of developing chronic low back pain, the sensitivity for identifying chronic low back pain was 38.7% (95% CI, 38.0%-39.4%), specificity 94.4% (95% CI, 94.3-94.6), positive predictive value

51.5% (95% CI, 50.8%-52.2%), negative predictive value 91.0% (95% CI, 90.9%-91.0%), and accuracy value 87.0% (95% CI, 86.8%-87.2%) in the validation cohort (Table 15). The corresponding thresholds for the risk of developing chronic low back pain over 8 years and the model's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 15). Table 14 shows the results based on the optimal cut off determined by Youden's J statistic for the prediction equation of chronic low back pain

**Table 15. Sensitivity, specificity, likelihood ratios, predictive values, and accuracy for chronic low back pain prediction model at different thresholds of predicted risk**

**Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values and accuracy for chronic low back pain at different thresholds of predicted risk of chronic low back pain over 8 years in derivation cohort**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥0.994 | 262,502 | 38,509 | 1,445 | 1,612 | 4.02 (3.83-4.21) | 99.5 (99.4-99.5) | 7.34 (6.84-7.87) | 0.97(0.96-0.97) | 52.7 (51.0-54.5) | 87.2 (87.2-87.2) | 86.9 (86.7-87.0) |
| 97% | ≥0.977 | 261,413 | 33,571 | 2,457 | 6,627 | 16.5 (16.1-16.9) | 99.1 (99.0-99.1) | 17.7 (16.9-18.5) | 0.84 (0.84-0.85 | 73.0 72.1-73.8) | 88.6 (88.6-88.7) | 88.2 (88.0-88.3) |
| 95% | ≥0.963 | 259,524 | 29,411 | 4,375 | 10,758 | 26.8 (26.4-27.2) | 98.3 (98.3-98.4) | 16.2 (15.6-16.7) | 0.74 (0.74-0.75) | 71.1 (70.4-71.8) | 89.8 (89.8-89.9) | 88.9 (88.8-89.0) |
| 90% | ≥0.948 | 249,073 | 24,669 | 14,935 | 15,391 | 38.4 (37.9-38.9) | 94.3 (94.3-94.4) | 6.79 (6.66-6.93) | 0.65 (0.65-0.66) | 50.8 (50.3-51.3) | 91.0 (90.9-91.1) | 87.0 (86.7-87.1) |
| 75% | ≥0.938 | 206,205 | 21,904 | 57,721 | 18,238 | 45.4 (45.0-45.9) | 78.1 (78.0-78.3) | 2.08 (2.05-2.10) | 0.70 (0.69-0.70) | 24.0 (23.8-24.3) | 90.4 (90.3-90.5) | 73.8 (73.7-74.0) |
| 50% | ≥0.906 | 136,615 | 15,534 | 127,293 | 24,626 | 61.3 (60.8-61.8) | 51.8 (51.6-52.0) | 1.27 (1.26-1.28) | 0.75 (0.74-0.76) | 16.2 (16.1-16.3) | 89.8 (89.7-89.9) | 53.0 (52.9-53.2) |
| 25% | ≥0.859 | 66,090 | 9,824 | 197,783 | 30,371 | 75.6 (75.1-76.0) | 25.1 (24.9-25.2) | 1.01 (1.00-1.01) | 0.98 (0.96-0.99) | 13.3 (13.2-13.4) | 87.1 (86.9-87.2) | 31.7 (31.6-31.9) |
| 10% | ≥0.768 | 26,812 | 3,657 | 237,062 | 36,537 | 90.9 (90.6-91.2) | 10.2 (10.1-10.3) | 1.01 (1.01-1.02) | 0.90 (0.87-0.93) | 13.4 (13.3-13.4) | 88.0 (87.7-88.3) | 20.8 (20.7-21.0) |
| 5% | ≥0.695 | 13,769 | 1,539 | 250,104 | 38,656 | 96.2 (96.0-96.4) | 5.22 (5.13-5.30) | 1.01 (1.01-1.02) | 0.73 (0.70-0.77) | 13.4 (13.4-13.4) | 90.0 (89.5-90.4) | 17.2 (17.1-17.4) |

**Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values and accuracy for chronic low back pain at different thresholds of predicted risk of chronic low back pain over 8 years in validation cohort**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥0.994 | 130,770 | 19,278 | 698 | 805 | 4.01 (3.74-4.30) | 99.5 (99.4-99.5) | 7.55 (6.83-8.35) | 0.97 (0.96-0.97) | 53.6 (51.1-56.0) | 87.2 (87.1-87.2) | 86.8 (86.7-87.0) |
| 97% | ≥0.977 | 130,240 | 16,728 | 1,305 | 3,278 | 16.4 (15.9-16.9) | 99.0 (99.0-99.1) | 16.5 (15.5-17.6) | 0.84 (0.84-0.85) | 71.5 (70.2-72.8) | 88.6 (88.6-88.7) | 88.1 (87.9-88.3) |
| 95% | ≥0.963 | 129,291 | 14,612 | 2,225 | 5,423 | 27.1 (26.5-27.7) | 98.3 (98.2-98.4) | 16.0 (15.3-16.8) | 0.74 (0.74-0.75) | 70.9 (69.9-71.9) | 70.9 (69.9-71.9) | 88.9 (88.7-89.1) |
| 90% | ≥0.948 | 124,078 | 12,351 | 7,329 | 7,793 | 38.7 (38.0-39.4) | 94.4 (94.3-94.6) | 6.94 (6.74-7.14) | 0.65 (0.64-0.66) | 51.5 (50.8-52.2) | 91.0 (90.9-91.0) | 87.0 (86.8-87.2) |
| 75% | ≥0.938 | 102,801 | 10,831 | 28,688 | 9,231 | 46.0 (45.3-46.7) | 78.2 (78.0-78.4) | 2.11 (2.07-2.15) | 0.69 (0.68-0.70) | 24.3 (24.0-24.7) | 90.5 (90.4-90.6) | 73.9 (73.7-74.1) |
| 50% | ≥0.906 | 67,947 | 7,711 | 63,560 | 12,333 | 61.5 (60.9-62.2) | 51.7 (51.4-51.9) | 1.27 (1.26-1.29) | 0.74 (0.73-0.76) | 16.3 (16.1-16.4) | 89.8 (89.6-90.0) | 53.0 (52.7-53.2) |
| 25% | ≥0.859 | 33,128 | 4,863 | 98,414 | 15,146 | 75.7 (75.1-76.3) | 25.2 (25.0-25.4) | 1.01 (1.00-1.02) | 0.97 (0.94-0.99) | 13.3 (13.2-13.4) | 87.2 (86.9-87.5) | 31.9 (31.6-32.1) |
| 10% | ≥0.768 | 13,250 | 1,844 | 118,291 | 18,166 | 90.8 (90.4-91.2) | 10.1 (9.9-10.2) | 1.01 (1.00-1.01) | 0.91 (0.87-0.96) | 13.3 (13.3-13.4) | 87.8 (87.3-88.3) | 20.7 (20.5-20.9) |
| 5% | ≥0.695 | 6,732 | 745 | 124,810 | 19,264 | 96.3 (96.0-96.5) | 5.12 (5.00-5.24) | 1.01 (1.01-1.02) | 0.73 (0.68-0.78) | 13.4 (13.3-13.4) | 90.0 (89.4-90.7) | 17.2 (17.0-17.3) |

Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages].The thresholds of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.2.7 Prediction equations of chronic low back pain

Basing on the parsimonious model, individualized probability of developing chronic low back pain within the years of follow up (t=8) can be estimated using the following equation:

$$P(\text{chronic low back pain}) = 1 - \mathrm{S_o}(t)^{\exp[(\beta_1 x_1 + \beta_2 x_2 \ldots \beta_m x_m)]},$$

Where $\mathrm{S_o}(t)$ denotes the baseline survival probability at time (t) for an individual with all covariates equivalent to zero (0), $(\beta_1 \ldots . \beta_m)$ denotes the change in log hazard rate (estimated $\beta$-coefficients) and $(x_1 \ldots x_m)$ denote values of risk predictors in the model. Using the estimated coefficients ($\beta_i$) and baseline survival probabilities $\mathrm{S_o}(t)$, personalized probabilities of developing chronic low back pain can be calculated**.** The Youden's J statistic suggested a risk probability of ≥0.948 as the optimal cutoff point to define high-risk individuals based on the prediction equation. This threshold showed a sensitivity of 38.7% (95% CI, 38.1%-39.4%), specificity of 94.3% (95% CI, 94.2%-94.4%), positive likelihood ratio (LR+) of 6.80 (95% CI, 6.61-6.99), negative likelihood ratio (LR-) of 0.65 (95% CI, 0.64-0.66), positive predictive value (PPV) of 51.1% (95% CI, 50.4%-51.8%), negative predictive value (NPV) of 90.9% (95% CI, 90.8%-91.0%) and accuracy of 86.9% (95% CI, 86.7%-87.1%) in prediction of the risk of developing chronic low back pain over 8 years in the validation cohort (Table 14).

### 4.2.8 Simplified risk score for prediction of chronic low back pain

Table 13 present the regression coefficients for the Cox Proportional hazard model fit to the derivation cohort (parsimonious risk equation). In the right-most column of the table are the points associated with the presence of a given level of a risk factor (with the reference level assigned zero points). The points were determined by multiplying the regression coefficient by 100 and rounding to the nearest integer. Advanced age (≥65 years old) conferred the largest number of risk points (143 points). Among modifiable risk factors, low BMI (-30 points), moderate alcohol consumption (-7 points) and moderate physical exercise (-4 points) conferred protection (Table 13). Among premorbidities, IVDD conferred the largest number of points (58 points).

Participants were divided into five equally sized risk strata using quintiles of the empirical risk score. The cumulative incidence risk (CIRs) probabilities for chronic low back pain in each of the risk strata in the derivation and validation cohorts are presented (Table 16). In the overall sample, there were statistically significant differences in the cumulative incidence risk probabilities across the five risk strata based on the Cochran–Armitage test for trend ($p$<.0001). There was a clearly defined gradation in chronic low back pain risk across the five risk strata. The lowest risk stratum comprised of subjects with very low chronic low back pain cases during the years of follow-up. In contrast, the highest risk stratum consisted of subjects with a very high chronic low back pain risk during eight years of follow-up. The eight-year cumulative incidence risk of chronic low back pain in the

lowest and highest risk strata in the derivation cohort were 6.2 (95% CI, 6.0 to 6.4) and 30.1 (95% CI, 29.7 to 30.5), respectively. Thus, the CIR of chronic low back pain at eight years was approximately 5 times greater in the highest risk stratum than in the lowest risk stratum, and the HZ ratio was 5.7 times greater (Table 16). Figure 8 presents the survival trends over 8 years for participants based on the risk score strata,

**Figure 8**. **Kaplan-Meier curves for chronic low back pain-free survival in 5 risk groups in the derivation and validation cohorts based on the simplified points based risk score. (A) Derivation. (B) Validation**

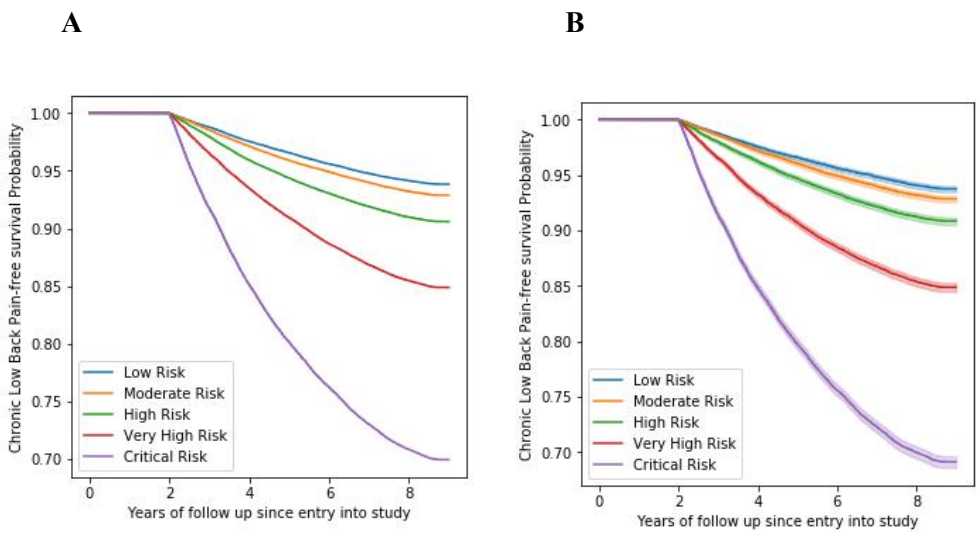


**Table 16. Risk of chronic low back pain onset in the derivation cohorts based on the risk strata**

| Risk of chronic low back pain in the derivation cohort based on the risk category (Quintiles of Risk Score) | | | | | | |
|---|---|---|---|---|---|---|
| **Risk Strata** | **Risk Score Range** | **Non-Event (%)** | **Event (%)** | **Total** | **CR* (95% CI),** | **HR (95% CI), *P* value** |
| Low Risk | <5 | 56,690 (94.2) | 3,523 (5.8) | 60,213 | 6.2 (6.0 to 6.4) | Reference |
| Moderate Risk | 5 to 41 | 56,769 (93.2) | 4,167 (6.8) | 60,936 | 7.1 ( 6.9 to 7.3) | 1.16 (1.11-1.22), p <.0001 |
| High Risk | 42 to 62 | 54,438 (90.8) | 5,506 (9.2) | 59,944 | 9.4 (9.2 to 9.6) | 1.56 (1.50-1.63), p <.0001 |
| Very High Risk | 63 to 127 | 52,990 (85.3) | 9,096 (14.7) | 62,086 | 15.1 (14.8 to 15.4) | 2.59 (2.49 to 2.69), p <.0001 |
| Critical Risk | >127 | 43,141 (70.8) | 17,748 (29.2) | 60,889 | 30.1 (29.7 to 30.5) | 5.71 (5.50 to 5.91), p <.0001 |
| **Risk of chronic low back pain in the validation cohort based on the risk category (Quintiles of Risk Score)** | | | | | | |
| **Risk Strata** | **Risk Score Range** | **Non-Event (%)** | **Event (%)** | **Total** | **CR* (95% CI),** | **Hazard Ratios (95% CI)** |
| Low Risk | <5 | 28341 (94.1) | 1780 (5.9) | 30121 | 6.3 (6.0 to 6.5) | Reference |
| Moderate Risk | 5 to 41 | 28055 (93.1) | 2066 (6.9) | 30121 | 7.1 (6.9 to 7.4) | 1.15 (1.08-1.23), p<.0001 |
| High Risk | 42 to 62 | 27121 (91.1) | 2658 (8.9) | 29779 | 9.1 (8.8 to 9.5) | 1.50 (1.41-1.59), p <.0001 |
| Very High Risk | 63 to 127 | 26601 (85.3) | 4575 (14.7) | 31176 | 15.1 ( 14.7 to | 2.57 (2.43 to 2.71), p<.0001 |
| Critical Risk | >127 | 21269 (70.07) | 9085 (29.93) | 30354 | 30.9 (30.4 to 31.4) | 5.83 (5.54 to 6.13), p<.0001 |
| **Average 8-year survival=0.8623** | | | | | | |

***CR=Cumulative Risk**

‡Cochran–Armitage test for trend (for overall cohort), *p*<.0001

### 4.2.9 Validation of the simplified risk score at different risk score thresholds

The theoretical or observed minimum and maximum sum of the points were -54 and 345, respectively. The median score was 49, while the 25$^{th}$ and 75$^{th}$ percentiles were 9 and 116, respectively. Table 17 shows the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy for chronic low back pain at various risk score thresholds based on subjects in the derivation and validation cohorts. The risk score threshold for the top 3% at highest risk of chronic low back pain in the next 8 years was 201, for the top 5% was 188, for the top 10% was 163, for the top 25% was 116, and for the top 50% was 49 in both cohorts. With a risk score threshold of 163 over 8 years to identify the 10% of participants with the highest risk of developing chronic low back pain, the sensitivity for identifying chronic low back pain was 27.0% (95% CI, 26.4%-27.6%), specificity 92.6% (95% CI, 92.4%-92.7%), positive predictive value 35.7 (95% CI, 35.0%-36.4%), negative predictive value 89.2% (95% CI, 89.2%-89.3%), and accuracy value 83.9% (83.7%-84.1%) in the validation cohort. The corresponding thresholds for risk of developing chronic low back pain over 8 years and the risk score's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 17). The Youden's J statistic suggested a risk score of ≥90 as the optimal cutoff point to define high-risk individuals based on the simplified risk score. This threshold showed a sensitivity of 58.0% (95% CI, 57.3%-58.7%), specificity of 74.2% (95% CI, 74.0%-74.5%),

positive likelihood ratio (LR+) of 2.25 (95% CI, 2.22-2.28), negative likelihood ratio (LR-) of 0.57 (95% CI, 0.56-0.58), positive predictive value (PPV) of 25.5% (95% CI, 25.3%-25.8%), negative predictive value (NPV) of 92.1% (95% CI, 91.9%-92.2%) and accuracy of 72.1% (95% CI, 71.8%-72.3%) in prediction of the risk of developing chronic low back pain over 8 years in the validation cohort (Table 17).

**Table 17. Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values for chronic low back pain at different thresholds of the risk score of chronic low back pain over 8 years in derivation and validation cohorts.**

| Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values and accuracy for chronic low back pain at different thresholds of predicted risk of chronic low back pain over 8 years in derivation cohort | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Threshold (Centiles)** | **Risk score threshold** | **True negative (count)** | **False negative (count)** | **False positive (count)** | **True positive (count)** | **Sensitivity (%)** | **Specificity (%)** | **Positive Likelihood Ratio** | **Negative Likelihood Ratio** | **Positive predictive value (%)** | **Negative predictive value (%)** | **Accuracy (%)** |
| 99% | ≥233 | 262,294 | 38,695 | 1,649 | 1,430 | 3.56 (3.38-3.75) | 99.4 (99.3-99.4) | 5.70 (5.32-6.12) | 0.97 (0.97-0.97) | 46.4 (44.7-48.2) | 87.1 (87.1-87.2) | 86.7 (86.6-86.9) |
| 97% | ≥201 | 258,450 | 36,301 | 5,406 | 3,911 | 9.73 (9.44-10.0) | 98.0 (97.9-98.0) | 4.75 (4.56-4.94) | 0.92 (0.92-0.92) | 42.0 (41.0-43.0) | 87.7 (87.7-87.7) | 86.3 (86.2-86.4) |
| 95% | ≥188 | 254,266 | 34,092 | 9,505 | 6,205 | 15.4 (15.1-15.8) | 96.4 (96.3-96.5) | 4.27 (4.15-4.40) | 0.88 (0.87-0.88) | 39.5 (38.8-40.2) | 88.2 (88.1-88.2) | 85.7 (85.5-85.8) |
| 90% | ≥163 | 244,189 | 29,348 | 19,768 | 10,763 | 26.8 (26.4-27.3) | 92.5 (92.4-92.6) | 3.58 (3.51-3.66) | 0.79 (0.79-0.80) | 35.3 (34.8-35.7) | 89.3 (89.2-89.3) | 83.9 (83.7-84.0) |
| 75% | ≥116 | 207,623 | 19,305 | 56,277 | 20,863 | 51.9 (51.5-52.4) | 78.7 (78.5-78.8) | 2.44 (2.41-2.46) | 0.61 (0.60-0.62) | 27.1 (26.8-27.3) | 91.5 (91.4-91.6) | 75.1 (75.0-75.3) |
| ‡**70%** | ≥90 | 195,845 | 16,888 | 68,063 | 23,272 | 58.0 (57.5-58.4) | 74.2 (74.0-74.4) | 2.25 (2.22-2.27) | 0.57 (0.56-0.57) | 25.5 (25.3-25.7) | 92.1 (92.0-92.2) | 72.1 (71.9-72.2) |
| 50% | ≥49 | 139,701 | 10,136 | 124,189 | 30,042 | 74.8 (74.3-75.2) | 52.9 (52.8-53.1) | 1.59 (1.58-1.60) | 0.48 (0.47-0.48) | 19.5 (19.4-19.6) | 93.2 (93.1-93.3) | 55.8 (55.7-56.0) |
| 25% | ≥9 | 69,746 | 4,459 | 194,120 | 35,743 | 88.9 (88.6-89.2) | 26.4 (26.3-26.6) | 1.21 (1.20-1.21) | 0.42 (0.41-0.43) | 15.6 (15.5-5.6) | 94.0 (93.8-94.2) | 34.7 (34.5-34.9) |
| 10% | ≥-4 | 25,219 | 1,384 | 238,716 | 38,749 | 96.6 (96.4-96.7) | 9.56 (9.44-9.67) | 1.07 (1.07-1.07) | 0.36 (0.34-0.38) | 14.0 (13.9-14.0) | 94.8 (94.5-95.1) | 21.0 (20.9-21.2) |
| 5% | ≥-9 | 12,514 | 697 | 251,364 | 39,493 | 98.3 (98.1-98.4) | 4.74 (4.66-4.82) | 1.03 (1.03-1.03) | 0.37 (0.34-0.39) | 13.6 (13.6-13.6) | 94.7 (94.3-95.1) | 17.1 (17.0-17.2) |
| **Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values and accuracy for chronic low back pain at different thresholds of predicted risk of chronic low back pain over 8 years in validation cohort** | | | | | | | | | | | | |
| **Threshold (Centiles)** | **Risk score threshold** | **True negative (count)** | **False negative (count)** | **False positive (count)** | **True positive (count)** | **Sensitivity (%)** | **Specificity (%)** | **Positive Likelihood Ratio** | **Negative Likelihood Ratio** | **Positive predictive value (%)** | **Negative predictive value (%)** | **Accuracy (%)** |
| 99% | ≥233 | 130,680 | 19,364 | 792 | 715 | 3.56 (3.31-3.83) | 99.4 (99.4-99.4) | 5.91 (5.35-6.53) | 0.97 (0.97-0.97) | 47.5 (45.0-49.9) | 87.1 (87.1-87.1) | 86.7 (86.5-86.9) |
| 97% | ≥201 | 128,791 | 18,065 | 2,768 | 1,927 | 9.64 (9.23-10.1) | 97.9 (97.8-98.0) | 4.58 (4.33 - | 0.92 (0.92-0.93) | 41.0 (39.7-42.4) | 87.7 (87.7-87.8) | 86.3 (86.1-86.4) |
| 95% | ≥188 | 126,763 | 16,835 | 4,881 | 3,072 | 15.4 (14.9-15.9) | 96.3 (96.2-96.4) | 4.16 (3.99-4.34) | 0.88 (0.87-0.88) | 38.6 (37.6-39.6) | 88.3(88.2- 88.3) | 85.7 (85.5-85.9) |
| 90% | ≥163 | 121,677 | 14,667 | 9,781 | 5,426 | 27.0 (26.4-27.6) | 92.6 (92.4-92.7) | 3.63 (3.52-3.74) | 0.79 (0.78-0.80) | 35.7 (35.0-36.4) | 89.2 (89.2-89.3) | 83.9 (83.7-84.1) |
| 75% | ≥116 | 103,559 | 9,517 | 27,956 | 10,519 | 52.5 (51.8-53.2) | 78.7 (78.5-79.0) | 2.47 (2.43-2.51) | 0.60 (0.59-0.61) | 27.3 (27.0-27.7) | 91.6 (91.5-91.7) | 75.3 (75.1-75.5) |
| ‡**70%** | ≥90 | 97,599 | 8,420 | 33,908 | 11,624 | 58.0 (57.3-58.7) | 74.2 (74.0-74.5) | 2.25 (2.22-2.28) | 0.57 (0.56-0.58) | 25.5 (25.3-25.8 | 92.1 (91.9-92.2) | 72.1 (71.8-72.3) |
| 50% | ≥49 | 69,438 | 5,067 | 62,087 | 14,959 | 74.7 (74.1-75.3) | 52.8 (52.5-53.1) | 1.58 (1.57-1.60) | 0.48 (0.47-0.49) | 19.4 (19.3-19.6) | 93.2 (93.0-93.4) | 55.7 (55.4-55.9) |
| 25% | ≥9 | 34,955 | 2,202 | 96,594 | 17,800 | 89.0 (88.6-89.4) | 26.6 (26.3-26.8) | 1.21 (1.20-1.22) | 0.41 (0.40-0.43) | 15.6 (15.5-15.6) | 94.1 (93.8-94.3) | 34.8 (34.6-35.1) |
| 10% | ≥-4 | 12,369 | 762 | 119,111 | 19,309 | 96.2 (95.9-96.5) | 9.41 (9.25-9.57) | 1.06 (1.06-1.07) | 0.40 (0.38-0.43) | 14.0 (13.9-14.0) | 94.2 (93.8-94.6) | 20.9 (20.7-21.1) |
| 5% | ≥-9 | 6,146 | 331 | 125,391 | 19,683 | 98.4 (98.2-98.5) | 4.67 (4.56-4.79) | 1.03 (1.03-1.03) | 0.35 (0.32-0.39) | 13.6 (13.5-13.6) | 94.9 (94.3-95.4) | 17.0 (16.9-17.2) |

Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects

with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages].The thresholds of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.2.10 Practical application of the risk score for chronic low back pain

The following hypothetical example illustrates how chronic low back pain risks can be estimated using the simplified points based system.

**Case**: A 49-year-old male with high insurance premium (>60%), moderate physical activity (1-2 times/week), with no history of smoking, moderate alcohol consumption (2-3 times/month), with BMI (>25 $kg/m^2$-29.9 $kg/m^2$), total cholesterol between 200 mg/dL and 239 mg/dL, who is prehypertensive (SBP 120-139 or DBP 80-89), no history of diabetes (FBG <100mg/dl), with history of IVDD and back injury but no history of spinal stenosis, bone mineral density disorders and spondylolisthesis.

**Table 18. Table of calculated score for a hypothetical example for the risk score of chronic low back pain**

| Risk factor (Predictor) | Value (Risk Factor Category) | Risk Points |
|---|---|---|
| Sex | Male | 0 |
| Age | 45-54 yrs | 75 |
| Income/Insurance Premium | High (>60%) | 0 |
| Physical Activity | Moderate (1-2 times/week) | -4 |
| Smoking Status | Never | 0 |
| Alcohol Consumption | Moderate drinker (2-3 | -7 |
| Body Mass Index | > 25 $kg/m^2$-29.9 $kg/m^2$ | 14 |
| Total Cholesterol | 200 mg/dL -239 mg/dL | 3 |
| Hypertension Status | SBP 120-139 or DBP 80-89 | 2 |
| Diabetes status/FBG | < 100 mg/dL | 0 |
| Diagnosed IVDD | Yes | 58 |
| Spinal Stenosis | No | 0 |
| History of Back Injury | Yes | 32 |
| History of BMD Disorders | No | 0 |
| Spondylolisthesis | No | 0 |

| Risk factor (Predictor) | Value (Risk Factor Category) | Risk Points |
|---|---|---|
| **Total points** | | **173** |
| **Estimate of risk** | | **0.566** |

**$S_0(t) = 0.8623$**

Based on the risk score, the probability of developing chronic low back pain can be estimated as follows;

$$P(\text{chronic low back pain}) = 1 - S_o(t)^{\exp[(Score/100)]}$$

$$P(\text{chronic low back pain}) = 1 - (0.8623)^{\exp[(173/100)]}$$

$$= 0.566$$

The $S_0(t)$ is the baseline survival probability at time ($t$=8 years) for an individual with all covariates equivalent to zero, which was estimated by Cox regression analysis. The beta coefficient was set to integer by multiplying 100, thus, in an actual calculation, the sum of risk scores should be divided by 100 to give an overall risk estimate. The sum (173 risk points) shown in the hypothetical score was thus divided by 100 to give the 8-year risk.

# 4.3 Prediction of recurrent low back pain (5-year)

### 4.3 Prediction of five (5-year) low back pain recurrence risk

Previous studies have used arbitrary cut-off points to define outcomes of low back pain [450], because there exists no consensus regarding outcome definitions and identification of individuals who recover and those who do not recover from an episode of LBP. In this study, a consecutive cohort of low back pain patients was constructed to derive prediction models for 5-year low back pain recurrence risk. In low back pain studies, a cohort of consecutive cases may include patients who have been receiving care for back pain over a long period in addition to patients who are receiving care for the first time [102]. Recurrent low back pain has been previously defined as pain present on less than half the days in 12 months period occurring in multiple episodes over the year [102]. In this study, the outcome of interest was time to first recurrence of low back pain within 5 years. Time to recurrence was defined as time between the index date of low back pain diagnosis and the time of first recurrence (subsequent medical utilization). An episode was considered as a recurrence only if 90 days had elapsed since index date of diagnosis.

#### 4.3.1 Baseline characteristics of the low back pain consecutive cohort

Table 19 presents the baseline characteristics of the consecutive cohort of low back pain patients. The total number of participants in the consecutive cohort of LPB patients was 170,729 (33.9%) of the eligible participants in the entire cohort in this study (N=502,342). The 170,729 participants in the consecutive cohort were randomly assigned to the derivation (2/3) and validation cohorts (1/3) as recommended [378].

During a median follow-up of 1.7 years (Range: 0.0 to 5.0), there were 71,160 (62.5%) and 35,767 (62.9%) cases of recurrent low back pain among 113,895 and 56,834 participants in the derivation and validation cohorts, respectively. There were no significant differences between the derivation and validation cohorts with respect to descriptive statistics (Table 19). However, there were significant differences between those who experienced subsequent episodes of low back pain and those who never experienced recurrence. Those who experienced low back pain recurrence had higher mean values of SBP, DBP, FBG, BMI and total cholesterol ($p<0.05$) (Table 19). The average follow up times were approximately 3.1 years and 1.7 years among those with no recurrence and those with recurrence, respectively. The details of the baseline characteristics of the consecutive cohort are presented (Table 19).The differences in average time of follow up between the two groups may represent the difference observed in cumulative risk within the first year following the first episode and subsequent years of follow up (Table 20).

**Table 19. Baseline characteristic of the consecutive cohort of patients for 5-year low back pain recurrence [Mean (SD) or n (%)]**

| Covariate | Development Cohort (n=113,895) | | | Validation Cohort (n=56,834) | | |
|---|---|---|---|---|---|---|
| | Without Recurrence | With Recurrence | *P* value | Without Recurrence | With Recurrence | *P* value |
| | 42,735 (37.5%) | 71,160 (62.5%) | | 21,067 (37.1%) | 35,767 (62.9%) | |
| Years of follow up (Years) | 3.1 (1.8) | 1.7 (1.5) | <.0001 | 3.1 (1.8) | 1.7 (1.5) | <.0001 |
| Height (cm) | 163.2 (8.8) | 159.4 (9.1) | <.0001 | 163.2 (8.8) | 159.4 (9.0) | <.0001 |
| Weight (kgs) | 62.5 (10.9) | 61.0(10.3) | <.0001 | 62.5 (10.9) | 60.9 (10.3) | <.0001 |
| BMI ($kg/m^{2)}$ | 23.4 (3.2) | 24.0 (3.2) | <.0001 | 23.4 (3.2) | 23.9 (3.2) | <.0001 |
| SBP (mm Hg) | 122.5 (17.1) | 126.1 (17.8) | <.0001 | 122.2 (17.1) | 126.1 (17.8) | <.0001 |
| DBP (mm Hg) | 77.1 (11.4) | 78.5 (11.4) | <.0001 | 76.9 (11.4) | 78.5 (11.4) | <.0001 |
| Fasting Blood Glucose (mg/dL) | 93.4 (27.5) | 96.4 (28.3) | <.0001 | 93.2 (27.4) | 96.2 (28.1) | <.0001 |
| Total Cholesterol (mg/dL) | 191.2 (38.3) | 198.6 (38.9) | <.0001 | 191.4 (38.4) | 198.6 (38.8) | <.0001 |
| Number of consultation (Days) | 1.3 (3.4) | 1.6 (1.9) | <.0001 | 1.3 (2.4) | 1.6 (2.0) | <.0001 |
| Length of prescription (Days) | 10.9 (21.1) | 5.5 (9.9) | <.0001 | 10.9 (21.0) | 5.5 (9.6) | <.0001 |
| Length of hospitalization (Days) | 1.9 (5.8) | 1.9 (3.0) | 0.1434 | 1.8230 (4.9) | 1.9 (2.9) | 0.0076 |
| **Sex** | | | <.0001 | | | <.0001 |
| Male | 20,820 (48.7) | 26,287 (36.9) | | 102,68 (48.7) | 13,061 (36.5) | |
| Female | 21,915 (51.3) | 44873 (63.1) | | 10,799 (51.3) | 22,706 (63.5) | |
| **Age** | | | <.0001 | | | <.0001 |
| <44 yrs. | 26,365 (61.7) | 23136 (32.5) | | 12,912 (6139) | 11607 (32.4) | |
| 45-54 yrs | 8,501 (19.9) | 16,681 (23.5) | | 4,252 (20.2) | 8423 (23.6) | |
| 55-64 yrs | 5,161 (12.1) | 17,519 (24.6) | | 2,535 (12.0) | 8675 (24.3) | |
| ≥ 65 yrs | 2,708 (6.3) | 13,824 (19.4) | | 1,368 (6.5) | 7062 (19.74) | |
| **Income/Insurance Premium** | | | <.0001 | | | 0.0041 |
| Low (<30%) | 6,180 (14.5) | 11,180 (15.7) | | 3,141 (14.9) | 5,697 (15.9) | |
| Medium (31-60%) | 15,530 (36.3) | 25,119 (35.3) | | 7,557 (35.9) | 12,576 (35.2) | |
| High (>60%) | 2,1025 (49.2) | 34,861 (49.0) | | 10,369 (49.2) | 17,494 (48.9) | |
| **Physical Activity/ Week** | | | <.0001 | | | <.0001 |

| Covariate | Development Cohort (n=113,895) | | | Validation Cohort (n=56,834) | | |
|---|---|---|---|---|---|---|
| | **Without Recurrence** | **With Recurrence** | ***P* value** | **Without Recurrence** | **With Recurrence** | ***P* value** |
| | **42,735 (37.5%)** | **71,160 (62.5%)** | | **21,067 (37.1%)** | **35,767 (62.9%)** | |
| Low (None) | 25,149 (58.8) | 44,720 (62.8) | | 12,267 (58.2) | 22,467 (62.8) | |
| Moderate (1-2 times) | 14,570 (34.1) | 21,175 (29.8) | | 7,345 (34.9) | 10,610 (29.7) | |
| High (≥ 3 times) | 3,016 (7.1) | 5,265 (7.4) | | 1,455 (6.9) | 2,690 (7.5) | |
| **Smoking Status** | | | <.0001 | | | <.0001 |
| Never | 28,983 (67.8) | 55,148 (77.5) | | 14,396 (68.3) | 27,742 (77.6) | |
| Former Smoker | 1,888 (4.4) | 2,282 (3.2) | | 885 (4.2) | 1,138 (3.2) | |
| Current Smoker | 11,864 (27.8) | 13730 (19.3) | | 5,786 (27.5) | 6,887 (19.2) | |
| **Alcohol drink/Month** | | | <.0001 | | | <.0001 |
| Rarely (< 2 times) | 22,054 (51.6) | 44,625 (62.7) | | 10,976 (52.1) | 22,386 (62.6) | |
| Moderate drinker (2–3 times) | 16,780 (39.3) | 21,319 (30.0) | | 8,155 (38.7) | 10,799 (30.2) | |
| Heavy drinker ( ≥ 4 times) | 3,901 (9.1) | 5,216 (7.3) | | 1,936 (9.2) | 2,582 (7.2) | |
| **Body Mass Index** | | | <.0001 | | | <.0001 |
| < 18.5 $kg/m^2$ | 2,327 (5.5) | 2,527 (3.6) | | 1,111 (5.2) | 1,261 (3.5) | |
| 18.5 $kg/m^2$-24.9 $kg/m^2$ | 27,785 (65.0) | 43,239 (60.8) | | 13,749 (65.3) | 21,909 (61.3) | |
| 25 $kg/m^2$-29.9 $kg/m^2$ | 11,446 (26.8) | 22,927 (32.2) | | 5,662 (26.9) | 21,909 (31.8) | |
| ≥ 30 $kg/m^2$ | 1,177 (2.7) | 2,467 (3.5) | | 545 (2.6) | 1,213 (3.4) | |
| **Fasting Blood Glucose** | | | <.0001 | | | <.0001 |
| < 100mg/dL | 27933 (65.4) | 43,588 (61.3) | | 13,815 (65.6) | 21,980 (61.5) | |
| 100 mg/dL-125 mg/dL | 10316 (24.1) | 18,443 (25.9) | | 5,108 (24.2) | 9,230 (25.8) | |
| ≥ 126 mg/dL or Rx | 4486 (10.5) | 9,129 (12.8) | | 2,144 (10.2) | 4,557 (12.7) | |
| **Blood pressure/HTN** | | | <.0001 | | | <.0001 |
| SBP < 120 and DBP < 80 | 16,061 (37.6) | 21,724 (30.5) | | 80,62 (38.3) | 10,999 (30.7) | |
| SBP 120-139 or DBP 80-89 | 21,870 (51.2) | 38,477 (54.1) | | 10,699 (50.8) | 19,266 (53.9) | |
| SBP 140-159 or DBP 90-99 | 4,220 (9.9) | 9,489 (13.3) | | 10,699 (9.6) | 4,795 (13.4) | |
| SBP ≥ 160 or DBP ≥ 100 or Rx | 584 (1.3) | 1,470 (2.1) | | 287 (1.3) | 707 (2.0) | |
| **Total cholesterol** | | | <.0001 | | | <.0001 |
| < 200 mg/dL | 25,949 (60.7) | 37,396 (52.5) | | 12,658 (60.1) | 18,869 (52.8) | |

| Covariate | Development Cohort (n=113,895) | | | Validation Cohort (n=56,834) | | |
|---|---|---|---|---|---|---|
| | **Without Recurrence** | **With Recurrence** | ***P* value** | **Without Recurrence** | **With Recurrence** | ***P* value** |
| | **42,735 (37.5%)** | **71,160 (62.5%)** | | **21,067 (37.1%)** | **35,767 (62.9%)** | |
| 200 mg/dL /l-239 mg/dL | 12252 (28.7) | 23,327 (32.8) | | 6,119 (29.0) | 11,712 (32.7) | |
| > 240 mg/dL | 4534 (10.6) | 23,327 (14.7) | | 2,290 (10.9) | 5,186 (14.5) | |
| **Diagnosed IHD** | | | <.0001 | | | 2.13 |
| No | 42,252 (98.9) | 69,618 (97.8) | | 20,847 (99.0) | 35,005 (97.9) | |
| Yes | 483 (1.1) | 69,618 (2.2) | | 220 (1.0) | 762 (2.1) | |
| **Diagnosed IVDD** | | | <.0001 | | | <.0001 |
| No | 39,208 (91.7) | 56,565 (79.5) | | 19,374 (92.0) | 28,371 (79.3) | |
| Yes | 3,527 (8.3) | 14,595 (20.5) | | 1,693 (8.0) | 73,96 (20.7) | |
| **History of Back Injuries** | | | <.0001 | | | <.0001 |
| No | 42,434 (99.30) | 69,990 (98.4) | | 20,907 (99.2) | 35,169 (98.3) | |
| Yes | 301 (0.70) | 1,170 (1.6) | | 160 (0.8) | 598 (1.7) | |
| **Mineral Density Disorders** | | | <.0001 | | | <.0001 |
| No | 41,002 (95.9) | 62,227 (87.5) | | 20,209 (95.9) | 31,186 (87.2) | |
| Yes | 1,733 (4.1) | 8,933 (12.5) | | 858 (4.1) | 4,581 (12.8) | |
| **Spinal Stenosis** | | | <.0001 | | | <.0001 |
| No | 42,187 (98.7) | 66,983 (94.1) | | 20,800 (98.7) | 33,570 (93.9) | |
| Yes | 548 (1.3) | 4,177 (5.9) | | 267 (1.3) | 2,197 (6.1) | |
| **Spondylolisthesis** | | | <.0001 | | | <.0001 |
| No | 42,696 (99.9) | 70,860 (99.6) | | 21,054 (99.9) | 35,612 (99.6) | |
| Yes | 39 (0.1) | 300 (0.4) | | 13 (0.1) | 155 (0.4) | |

The student's *t*-test for continuous variables and $\chi^2$-test for categorical variables were used to examine the differences in baseline characteristics between participants in the derivation and validation cohorts stratified based on 5-year low back pain recurrence outcome.

### 4.3.2 Cumulative incidence probabilities of 5-year low back pain recurrence

During a median follow up period of (1.7 years) in this consecutive cohort, the cumulative risk of recurrent low back pain increased from 44.8 (95% CI, 44.6-45.1) in the first year to 76.1 (95% CI, 75.9-76.4) at the end of 5-year follow up period. The greatest increase in risk probabilities and incidences was observed between the first and second year of follow up, which may due to the high recurrence risk of low back pain within a short period after first episode. The details of the incidence trends and cumulative risks are presented (Table 20).

**Table 20. Follow-up times, cumulative incidence and incidence probabilities of low back pain recurrence within 5 years**

| Length of follow up | Censored | Events | Total | CR* (95% CI) |
|---|---|---|---|---|
| 1 year | 20,594 | 71,055 | 91,649 | 44.8 (44.6-45.1) |
| 2 years | 7,037 | 12,986 | 20,023 | 54.3 (54.1-54.6) |
| 3 years | 6,810 | 8,632 | 15,442 | 61.4 (61.1-61.7) |
| 4 years | 6,842 | 5,807 | 12,649 | 67.0 (66.7-67.2) |
| 5 years | 22,519 | 8,447 | 30,966 | 76.1 (75.9-76.4) |
| **Totals** | **63,802** | **106,927** | **170,729** | |

CR* =Cumulative Risk

### 4.3.3 Association between risk factors and recurrent low back pain (5 years)

Tables 21 present the estimated coefficients and hazard ratios for covariates in the unadjusted, partially adjusted, and fully adjusted analyses. In this study, all risk factors were associated with low back pain recurrence within 5 years. However, smoking and alcohol consumption were inversely associated with low back pain both in the univariate and multivariate analyses ($p$<0.05) (Table 21). Low-income

grade (insurance premium <30%) was weakly associated with 5-year low back pain recurrence whereas physical activity showed unclear association in the univariate analysis. Hypertension (blood pressure), BMI, FBG and total cholesterol showed positive association in all analyses, although the associations were weaker in fully adjusted model. In general, metabolic syndrome (MetS) variables were associated with 5-year low back pain recurrence ($p<0.05$) (Table 21).

In this study, premorbid intervertebral disc degeneration (IVDD), spondylolisthesis, history of back injury, spinal stenosis, and bone mineral density disorders (BMD) were positively associated with 5-year low back pain recurrence in all analyses (Table 21) ($p<0.05$). In addition, this study examined how previous low back pain medication influences risk of LBP recurrence or prognosis. The variables assessed included total number of days of prescription (length or duration of medication), length or duration of hospital admission and frequency of consultation (number of previous LBP consultations). In the all analyses, total days of prescription, total number of days admitted (hospitalization) and number of previous consultations were positively and stably associated with LBP recurrence in all analyses (Table 21) ($p<0.05$).

**Table 21. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors in the univariate, partially adjusted and fully adjusted models for 5-year low back pain recurrence**

| Covariate | Unadjusted∗ | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value |
| **Sex** | | | | | | | | | |
| Female | 0.242 (0.006) | 1.27 (1.26-1.29) | <.0001 | 0.198 (0.006) | 1.22(1.20-1.23) | <.0001 | 0.171 (0.009) | 1.19 (1.17- | <.0001 |
| **Age** | | | | | | | | | |
| <45 yrs. | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 45-54 yrs | 0.447 (0.008) | 1.56 (1.54-1.59) | <.0001 | 0.433 (0.008) | 1.54 (1.52-1.57) | <.0001 | 0.432 (0.008) | 1.54 (1.52-1.57) | <.0001 |
| 55-64 yrs | 0.723 (0.008) | 2.06 (2.03-2.09) | <.0001 | 0.711 (0.008) | 2.04 (2.00-2.07) | <.0001 | 0.705 (0.008) | 2.02 (1.99-2.06) | <.0001 |
| ≥65 yrs | 0.931 (0.009) | 2.54 (2.49-2.58) | <.0001 | 0.917 (0.009) | 2.50 (2.46-2.54) | <.0001 | 0.909 (0.009) | 2.48 (2.44-2.53) | <.0001 |
| **Income/Insurance Premium** | | | | | | | | | |
| High (>60%) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Medium (31-60%) | 0.081 (0.009) | 1.08 (1.07-1.10) | <.0001 | 0.056 (0.009) | 1.06 (1.04-1.08) | <.0001 | 0.054 (0.009) | 1.06 (1.04-1.07) | <.0001 |
| High (<30%) | -1.99E-6 (0.007) | 1.00 (0.99-1.01) | 0.9998 | 0.051 (0.007) | 1.05 (1.04-1.07) | <.0001 | 0.050 (0.007) | 1.05 (1.04-1.07) | <.0001 |
| **Physical Activity/week** | | | | | | | | | |
| High (≥3 times/week) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate (1-2 times) | -0.116 (0.013) | 0.89 (0.87-0.91) | <.0001 | -0.035 (0.013) | 0.97 (0.94-0.99) | 0.0053 | -0.035 | 0.97 (0.94-0.99) | 0.0058 |
| Low (None) | 0.008 (0.012) | 1.01 (0.99-1.03) | 0.4855 | 0.003 (0.012) | 1.00 (0.98-1.03) | 0.8326 | -0.003 | 0.99 (0.97-1.02) | 0.8076 |
| **Smoking Status** | | | | | | | | | |
| Never | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Former | -0.228 (0.017) | 0.80 (0.77-0.82) | <.0001 | -0.041 (0.018) | 0.96 (0.93-0.99) | 0.0264 | -0.038 | 0.96 (0.93-0.99) | 0.0391 |
| Current Smoker | -0.261 (0.008) | 0.77 (0.76-0.78) | <.0001 | -0.015 (0.010) | 0.99 (0.97-1.00) | 0.1320 | -0.017 | 0.98 (0.97-1.00) | 0.0907 |
| **Alcohol** | | | | | | | | | |
| Rarely (<2 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate drinker (2–3 times) | -0.242 (0.007) | 0.79 (0.78-0.80) | <.0001 | -0.033 (0.007) | 0.97 (0.95-0.98) | <.0001 | -0.032 | 0.97 (0.96-0.98) | <.0001 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Heavy drinker ( ≥ 4 times) | -0.213 (0.012) | 0.81 (0.79-0.83) | <.0001 | -0.015 (0.013) | 0.99 (0.96-1.01) | 0.2393 | -0.016 | 0.98 (0.96-1.01) | 0.2029 |
| **Body Mass Index** | | | | | | | | | |
| < 18.5 kg/$m^2$ | -0.185 (0.017) | 0.83 (0.80-0.86) | <.0001 | -0.126 (0.017) | 0.88 (0.85-0.91) | <.0001 | -0.131 | 0.88 (0.85-0.91) | <.0001 |
| 18.5 kg/$m^2$-24.9 kg/$m^2$ | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 25 kg/$m^2$-29.9 kg/$m^2$ | 0.126 (0.007) | 1.13 (1.12-1.15) | <.0001 | 0.059 (0.007) | 1.06 (1.05-1.08) | <.0001 | 0.062 (0.007) | 1.06 (1.05-1.08) | <.0001 |
| >30 kg/$m^2$ | 0.158 (0.017) | 1.17 (1.13-1.21) | <.0001 | 0.070 (0.017) | 1.07 (1.04-1.11) | <.0001 | 0.072 (0.017) | 1.07 (1.04-1.11) | <.0001 |
| **Fasting Blood Glucose** | | | | | | | | | |
| <100 mg/dL | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 100 mg/dL-125 mg/dL | 0.079 (0.007) | 1.08 (1.07-1.10) | <.0001 | 0.009 (0.007) | 1.01 (0.99-1.02) | 0.2218 | 0.009 (0.007) | 1.01 (0.99-1.02) | 0.2037 |
| ≥126 mg/dL or Rx | 0.144 (0.009) | 1.15 (1.15-1.18) | <.0001 | -0.002 (0.009) | 0.99 (0.98-1.02) | 0.8601 | -0.0004 | 1.00 (0.98-1.02) | 0.9636 |
| **Total Cholesterol** | | | | | | | | | |
| < 200 mg/dL | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 200 mg/dL-239 mg/dL | 0.139 (0.007) | 1.1 (1.13-1.16) | <.0001 | 0.030 (0.007) | 1.03 (1.02-1.05) | <.0001 | 0.033 (0.007) | 1.03 (1.02-1.05) | <.0001 |
| ≥240 mg/dL | 0.233 (0.009) | 1.26 (1.24-1.29) | <.0001 | 0.046 (0.009) | 1.05 (1.03-1.07) | <.0001 | 0.049 (0.009) | 1.05 (1.03-1.07) | <.0001 |
| **Blood Pressure/HTN** | | | | | | | | | |
| SBP < 120 and DBP < 80 | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| SBP 120-139 or DBP 80-89 | 0.160 (0.007) | 1.17 (1.16-1.19) | <.0001 | 0.038 (0.007) | 1.04 (1.03-1.05) | <.0001 | 0.038 (0.007) | 1.04 (1.02-1.05) | <.0001 |
| SBP 140-159 or DBP 90-99 | 0.295 (0.010) | 1.34 (1.32-1.37) | <.0001 | 0.045 (0.010) | 1.05 (1.03-1.07) | <.0001 | 0.043 (0.010) | 1.04 (1.02-1.07) | <.0001 |
| SBP ≥ 60 or DBP ≥ 100 or Rx | 0.336 (0.022) | 1.40 (1.40-1.46) | <.0001 | 0.026 (0.022) | 1.03 (0.98-1.07) | 0.2506 | 0.021 (0.022) | 1.02 (0.98-1.07) | 0.3439 |
| **Prior diagnosed diseases** | | | | | | | | | |
| Diagnosed IHD | 0.315 (0.021) | 1.37 (1.31-1.43) | <.0001 | 0.043 (0.021) | 1.04 (1.00-1.09) | 0.0412 | 0.045 (0.021) | 1.05 (1.00-1.09) | 0.0332 |
| Diagnosed IVDD | 0.426 (0.008) | 1.53 (1.51-1.55) | <.0001 | 0.304 (0.008) | 1.36 (1.34-1.38) | <.0001 | 0.305 (0.008) | 1.36 (1.34-1.38) | <.0001 |
| History of Back Injury | 0.345 (0.024) | 1.41 (1.35-1.48) | <.0001 | 0.268 (0.024) | 1.31 (1.25-1.37) | <.0001 | 0.267 (0.024) | 1.31 (1.25-1.37) | <.0001 |
| Spinal Stenosis | 0.646 (0.013) | 1.91 (1.86-1.96) | <.0001 | 0.337 (0.013) | 1.40 (1.37-1.44) | <.0001 | 0.337 (0.013) | 1.40 (1.37-1.44) | <.0001 |
| BMD Disorders | 0.539 (0.009) | 1.71 (1.68-1.75) | <.0001 | 0.217 (0.010) | 1.24 (1.22-1.27) | <.0001 | 0.219 (0.010) | 1.25 (1.22-1.27) | <.0001 |
| Spondylolisthesis | 0.678 (0.047) | 1.97 (1.80-2.16) | <.0001 | 0.427 (0.047) | 1.53 (1.40-1.68) | <.0001 | 0.428 (0.047) | 1.53 (1.40-1.68) | <.0001 |
| **Total days of Consultation** | | | | | | | | | |
| 1 day | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 2-3 days | 0.809 (0.008) | 2.25 (2.21-2.28) | <.0001 | 0.716 (0.008) | 2.05 (2.01-2.08) | <.0001 | 0.715 (0.008) | 2.05 (2.01-2.08) | <.0001 |
| ≥4 days | 0.842 (0.012) | 2.32 (2.27-2.37) | <.0001 | 0.683 (0.012) | 1.98 (1.93-2.03) | <.0001 | 0.682 (0.012) | 1.98 (1.93-2.02) | <.0001 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Length of Prescription** | | | | | | | | | |
| ≥8 days | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 1-7 days | 0.165 (0.009) | 1.18 (1.16-1.20) | <.0001 | 0.318 (0.009) | 1.38 (1.35-1.40) | <.0001 | 0.317 (0.009) | 1.37 (1.35-1.39) | <.0001 |
| None | 0.331 (0.010) | 1.39 (1.37-1.42) | <.0001 | 0.401 (0.010) | 1.49 (1.47-1.52) | <.0001 | 0.400 (0.010) | 1.49 (1.46-1.50) | <.0001 |
| **Length of Hospitalisation** | | | | | | | | | |
| 1 day | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 2-4 days | 0.794 (0.008) | 2.21 (2.18-2.25) | <.0001 | 0.698 (0.008) | 2.01 (1.98-2.04) | <.0001 | 0.698 (0.008) | 2.01 (1.98-2.04) | <.0001 |
| ≥5 days | 0.550 (0.012) | 1.73 (1.69-1.78) | <.0001 | 0.387 (0.012) | 1.47 (1.44-1.51) | <.0001 | 0.385 (0.012) | 1.47 (1.43-1.51) | <.0001 |

∗Unadjusted/Univariate analysis;†Partially adjusted accounting for Age and Sex and each of the other variables added; ‡Fully adjusted accounting for Age, Sex, Income grade, Physical activity, Smoking status, alcohol consumption and each of the other risk factors [Fasting Blood Glucose/Diabetes, Total Cholesterol, Blood pressure/HTN, IHD, Ischemic Heart Disease; IVDD, Intervertebral Disc Degeneration; History of Back Injury, Spinal Stenosis; BMD, Bone Mineral Density Disorders, Spondylolisthesis)].

### 4.3.4 Derivation of prediction equations for 5-year low back pain recurrence

In this study, sex, age, BMI, smoking status, alcohol consumption, income grade (insurance premium), physical activity, fasting blood glucose, total cholesterol, blood pressure, premorbid disc degeneration, history of back injury, history of bone mineral density disorders, spinal stenosis, spondylolisthesis and total number of days of prescription (length of prescription) were included in the derivation of 5-year low back pain recurrence risk prediction equations.

After applying the backward variable selection procedure at $\alpha$=0.15 and taking into consideration the numbers of cases for reliable variable selection (≥10 cases per variable), the risk predictors that were retained in the parsimonious model consisted of 15 variables including age, sex, income grade, physical activity, smoking status, alcohol consumption, body mass index, blood pressure, total cholesterol, and disc generation, history of back injury, bone mineral density disorders, spinal stenosis, spondylolisthesis and total days of prescription ($p$<0.15) (Table 22).

**Table 22. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors in the parsimonious equation of low back pain recurrence within 5 years**

| Covariate | *β* (SE) | HR (95% CI) | *P* Value | Points |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | Reference | Reference | | 0 |
| Female | 0.135 (0.011) | 1.14 (1.12-1.17) | <.0001 | 14 |
| **Age** | | | | |
| <45 yrs. | Reference | Reference | | 0 |

| Covariate | *β* (SE) | HR (95% CI) | *P* Value | Points |
|---|---|---|---|---|
| 45-54 yrs | 0.406 (0.011) | 1.50 (1.47-1.53) | <.0001 | 41 |
| 55-64 yrs | 0.655 (0.011) | 1.93 (1.89-1.97) | <.0001 | 66 |
| ≥65 yrs | 0.856 (0.012) | 2.35 (2.30-2.41) | | 86 |
| **Income/Insurance Premium** | | | | |
| High (>60%) | Reference | Reference | | 0 |
| Medium (30-60%) | 0.055 (0.008) | 1.06 (1.04-1.07) | <.0001 | 6 |
| Low (<30%) | 0.067 (0.011) | 1.07 (1.05-1.09) | <.0001 | 7 |
| **Physical Activity/Week** | | | | |
| High (≥ 3 times/week) | Reference | Reference | | 0 |
| Moderate (1-2 times/Week) | -0.021 (0.015) | 0.98 (0.95-1.01) | 0.5130 | -2 |
| Low (None) | 0.010 (0.015) | 1.01 (0.98-1.04) | 0.1689 | 1 |
| **Smoking Status** | | | | |
| Never | Reference | Reference | | 0 |
| Former | -0.043 (0.022) | 0.96 (0.92-1.00) | 0.0561 | -4 |
| Current Smoker | -0.025 (0.012) | 0.98 (0.95-0.99) | 0.0355 | -3 |
| **Alcohol Consumption/Month** | | | | |
| Rarely (<2 times) | Reference | | | 0 |
| Moderate drinker (2–3 times) | -0.034 (0.009) | 0.97 (0.95-0.98) | 0.0002 | -3 |
| Heavy drinker ( ≥ 4 times) | -0.019 (0.016) | 0.98 (0.95-1.01) | 0.2368 | -2 |
| **Body Mass Index** | | | | |
| < 18.5 kg/$m^2$ | -0.134 (0.021) | 0.87 (0.84-0.91) | <.0001 | -13 |
| 18.5 kg/$m^2$-24.9 kg/$m^2$ | Reference | Reference | | 0 |
| 25 kg/$m^2$-29.9 kg/$m^2$ | 0.061 (0.008) | 1.06 (1.05-1.08) | <.0001 | 6 |
| ≥30 kg/$m^2$ | 0.045 (0.021) | 1.05 (1.00-1.09) | 0.0322 | 5 |
| **Blood Pressure (HTN)** | | | | |
| SBP < 120 and DBP < 80 | Reference | Reference | | 0 |
| SBP 120-139 or DBP 80-89 | 0.029 (0.009) | 1.03 (1.01-1.05) | 0.0010 | 3 |
| SBP 140-159 or DBP 90-99 | 0.031 (0.013) | 1.03 (1.01-1.06) | 0.0176 | 3 |
| SBP ≥160 or DBP ≥ 100 or Rx | 0.009 (0.027) | 1.01 (0.96-1.07) | 0.7332 | 1 |
| **Total Cholesterol** | | | | |
| <200 mg/dL | Reference | Reference | | 0 |
| 200 mg/dL-239 mg/dL | 0.030 (0.009) | 1.03 (1.01-1.05) | 0.0005 | 3 |
| >240 mg/dL | 0.042 (0.011) | 1.04 (1.02-1.07) | 0.0002 | 4 |
| **Diagnosed IVDD** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.256 (0.010) | 1.29 (1.27-1.32) | <.0001 | 26 |
| **History of Back Injury** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.114 (0.030) | 1.12 (1.06-1.19) | 0.0001 | 11 |
| **Spinal Stenosis** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.152 (0.019) | 1.17 (1.12-1.21) | <.0001 | 15 |
| **BMD Disorders** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.116 (0.014) | 1.12 (1.09-1.15) | <.0001 | 12 |
| **Spondylolisthesis** | | | | |
| No | Reference | Reference | | 0 |

| Covariate | $\beta$ (SE) | HR (95% CI) | *P* Value | Points |
|---|---|---|---|---|
| Yes | 0.187 (0.058) | 1.21 (1.08-1.35) | 0.0013 | 19 |
| **Days of Prescription** | | | | |
| ≥8 days | Reference | Reference | | 0 |
| 1-7 days | 0.317 (0.011) | 1.37 (1.34-1.40) | <.0001 | 32 |
| None | 0.398 (0.012) | 1.49 (1.46-1.52) | <.0001 | 40 |

*****The risk points were calculated by multiplying the estimated coefficients by 100 and rounding to the next integer.

### 4.3.5 Model validation for 5-year low back pain recurrence prediction equation

The Harrell's C-statistic was 0.856 (95% CI, 0.849-0.862) and 0.857 (95% CI, 0.847-0.866), and brier score of 0.388 and 0.388 for the derivation and validation cohorts, respectively. Using the optimal threshold determined by Youden's index to define high risk individuals, the sensitivity in the derivation and validation cohorts was 62.8% (95% CI, 62.4% to 63.2%) and 62.7% (95% CI, 62.2% to 63.2%), whereas the specificity was 57.5% (95% CI, 57.1% to 58.0%) and 57.7% (95% CI, 57.0% to 58.4%), respectively. The calibration was (Nam and D'Agostino's, $\chi^2$=4.213, $p$=0.182 and $\chi^2$=4.172, $p$=0.3090) for the derivation and validation cohorts, respectively (Table 23). This model showed excellent discrimination and calibration based on Harrell's C-statistics. Table 23 and Figures 9-11 shows the calibration and discrimination performance. There was agreement between the observed risks and mean predicted risks of 5-year low back pain recurrence across each decile of the predicted risk showing good calibration. In addition, comparing the HRs between the lowest risk stratum and the highest risk stratum shows that the model's highest risk group was 2684 times more likely to

experience low back pain recurrence within 5 years than the lowest risk group, and the model performed well in separation of individual in the lower and intermediate risk groups (Table 23 and Figure 11).

**Table 23. Model validation and performance evaluation based on discrimination and calibration in derivation and validation cohorts (low back pain recurrence within 5 years)**

| **Performance Evaluation statistic** | **Derivation Cohort** | **Validation cohort** |
|---|---|---|
| Brier Score† | 0.388 | 0.389 |
| Nam and D'Agostino test‡ | $\chi^2$=4.213, *P*=0.182 | $\chi^2$=4.172, *P*=0.3090 |
| Harrell's C statistic (95% CI) # | 0.856 (0.849-0.862) | 0.857 (0.847-0.866) |
| Sensitivity (95% CI) | 62.8% (62.4% to 63.2%) | 62.7% (62.2% to 63.2%) |
| Specificity (95% CI) | 57.5% (57.1% to 58.0%) | 57.7% (57.0% to 58.4%) |
| Positive Likelihood Ratio (95% CI) | 1.48 (1.46 to 1.50) | 1.48 (1.45 to 1.51) |
| Negative Likelihood Ratio (95% CI) | 0.65 (0.64 to 0.65) | 0.65 (0.64 to 0.66) |
| Positive Predictive Value (95% CI) | 71.2% (70.9% to 71.4%) | 71.4% (71.0% to 71.8%) |
| Negative Predictive Value (95% CI) | 48.1% (47.8% to 48.4%) | 47.8% (47.4% to 48.3%) |
| Accuracy (95% CI) | 60.8% (60.5% to 61.1%) | 60.8% (60.4% to 61.2%) |
| **Risk Strata Comparisons** | **Hazard Ratio, *P* value** | **Hazard Ratio, *P* value** |
| Good | Reference | Reference |
| Good Vs Fairly Good | 1.13 (1.08-1.17), *p*<.0001 | 1.11(1.05-1.17), *p*=0.0004 |
| Good Vs Fairly Poor | 3.38 (3.25-3.50), *p*<.0001 | 3.44 (3.26-3.63), *p*<.0001 |
| Good Vs Poor | 55.6 (53.2-58.0), *p*<.0001 | 56.0 (52.7-59.6), *p*<.0001 |
| Good Vs Very Poor | 3032.3(2793.9-3291.1),*p*<.0001 | 2684.9(2397.9-3006.2),*p*<.0001 |

**Abbreviation: CI=confidence interval.**

†Measures both discrimination and calibration; lower values indicate higher accuracy, ‡A modification of Hosmer Lemeshow test suited for survival data; measure of calibration that is specific to censored survival data (lower $\chi^2$ and higher p values) indicate better calibration, #A measure of discrimination for which higher values indicate better discrimination.The Youden's J statistics was 0.203 for both cohorts corresponding to risk probability of 0.567.

**Figure 9. Discrimination and calibration plots in the derivation cohort for the prediction equation of 5-year low back pain recurrence. (A) Discrimination. (B) Calibration**

**A** **B**

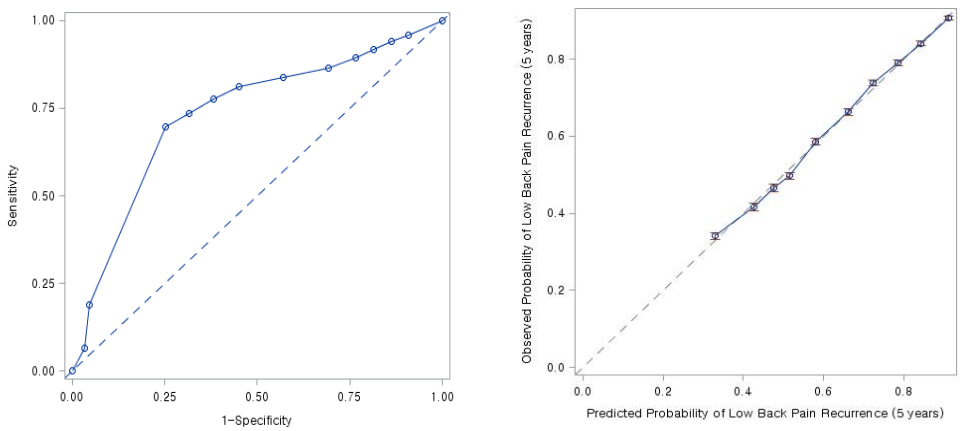



**Figure 10. Discrimination and calibration plots in the validation cohort for the prediction equation of 5-year low back pain recurrence. (A) Discrimination. (B) Calibration**

**A** **B**

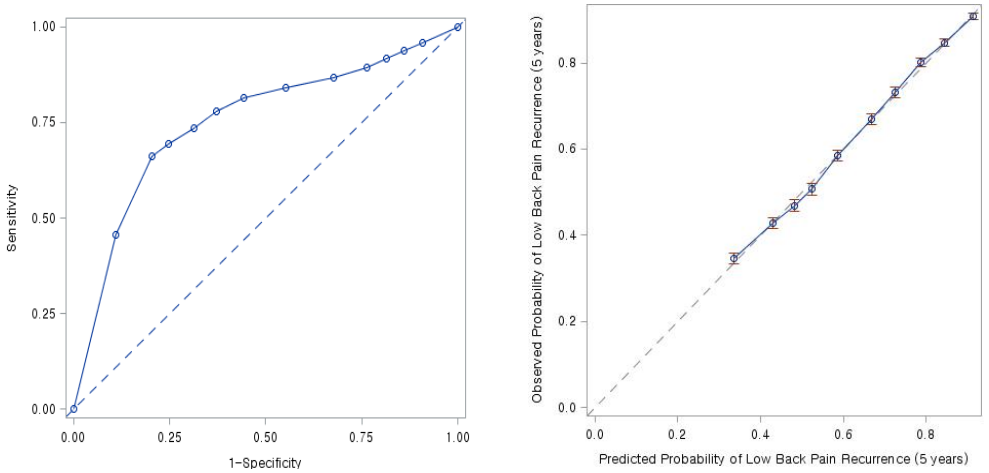
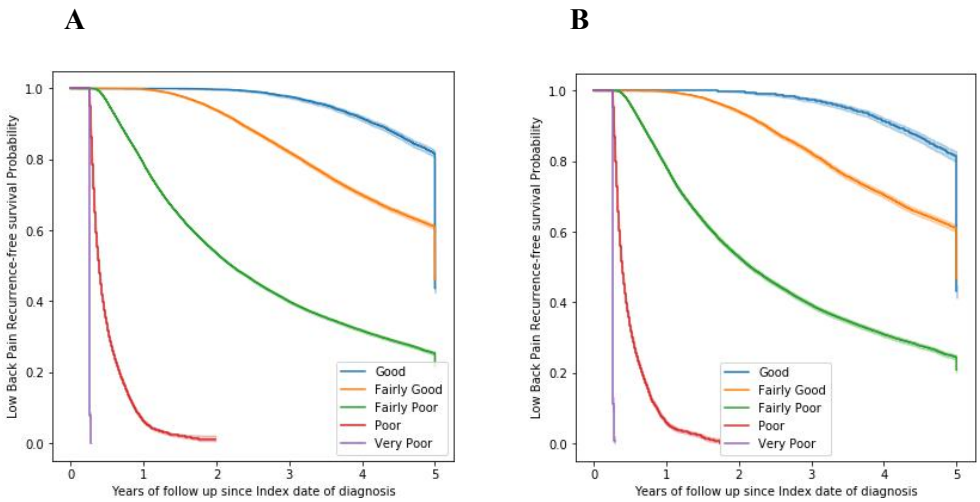


**Figure 11. Kaplan-Meier curves for 5-year low back pain recurrence-free survival in 5 risk groups in the derivation and validation cohorts based on the Prognostic Index. (A) Derivation. (B) Validation**




### 4.3.6 Model discrimination at different thresholds of predicted risk

Table 24 shows the sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values, and accuracy for 5-year low back pain recurrence equation at various risk probability thresholds based on subjects in the derivation and validation cohorts. The risk probability threshold for the top 3% at highest risk of low back pain recurrence in the next 5 years was 0.989, for the top 5% was 0.979, for the top 10% was 0.933, for the top 25% was 0.807, and for the top 50% was 0.607 in both cohorts. With a risk probability threshold of 0.933 over 5 years to identify the 10% of participants with the highest risk of low back pain recurrence, the sensitivity for identifying 5-year low back pain recurrence was 9.91% (95% CI, 9.60%-10.22%), specificity 89.6% (95% CI,

89.2%-90.0%), positive predictive value 61.5% (95% CI, 60.3%-62.7%), negative predictive value 37.4% (95% CI, 37.2%-37.5%), and accuracy value 39.8% (95% CI, 39.4%-40.2%) in the validation cohort. The corresponding thresholds for risk of experiencing low back pain recurrence over 5 years and the model's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 24). Table 23 shows the results based on the optimal cut off determined by Youden's J statistic for the 5-year low back pain recurrence prediction equation

**Table 24. Sensitivity, specificity, likelihood ratios, predictive values, and accuracy at different thresholds of predicted risk of low back pain recurrence over 5 years in derivation cohort and validation cohorts**

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values and accuracy for low back pain recurrence at different thresholds of predicted risk of low back pain recurrence over 5 years in derivation cohort**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | 1.000 | 39,011 | 71,304 | 3,580 | 0 | 0.00 (0.00-0.00) | 91.6 (91.3-91.9) | 0.00 | 1.09 (1.09-1.09) | 0 | 35.4 (35.3-35.4) | 34.3 (34.0-34.5) |
| 97% | ≥0.989 | 38,955 | 70,334 | 3,679 | 927 | 1.30 (1.22-1.39) | 91.4 (91.1-91.6) | 0.15 (0.14-0.16) | 1.08 (1.08-1.08) | 20.1 (19.0-21.3) | 35.6 (35.6-35.7) | 35.0 (34.7-35.3) |
| 95% | ≥0.979 | 38,867 | 69,303 | 3,745 | 1,980 | 2.78 (2.66-2.90) | 91.2 (90.9-91.5) | 0.32 (0.30-0.33) | 1.07 (1.06-1.07) | 34.6 (33.4-35.8) | 35.9 (35.9-36.0) | 35.9 (35.6-36.1) |
| 90% | ≥0.933 | 38,308 | 64,244 | 4,194 | 7,149 | 10.0 (9.79-10.2) | 90.1 (89.8-90.4) | 1.01 (0.98-1.05) | 1.00 (0.99-1.00) | 63.0 (62.2-63.9) | 37.4 (37.3-37.5) | 39.9 (39.6-40.2) |
| 75% | ≥0.807 | 35,139 | 50,268 | 7,501 | 20,987 | 29.5 (29.1-29.8) | 82.4 (82.0-82.8) | 1.67 (1.64-1.71) | 0.86 (0.85-0.86) | 73.7 (73.2-74.1) | 41.1 (41.0-41.3) | 49.3 (49.0-49.6) |
| 50% | ≥0.607 | 26,652 | 30,284 | 15,983 | 40,976 | 57.5 (57.1-57.9) | 62.5(62.1-63.0) | 1.53 (1.51-1.56) | 0.68 (0.67-0.69) | 71.9 (71.7-72.2) | 46.8 (46.5-47.1) | 59.4 (59.1-59.7) |
| 25% | ≥0.408 | 14,173 | 14,306 | 28,345 | 57,071 | 80.0 (79.7-80.3) | 33.3 (32.9-33.8) | 1.20 (1.19-1.21) | 0.60 (0.59-0.61) | 66.8 (66.7-67.0) | 49.8 (49.3-50.3) | 62.6 (62.3-62.8) |
| 10% | ≥0.263 | 5,305 | 6,055 | 37,248 | 65,287 | 91.5 (91.3-91.7) | 12.5 (12.2-12.8) | 1.05 (1.04-1.05) | 0.68 (0.66-0.70) | 63.7 (63.6-63.8) | 46.7 (45.8-47.6) | 62.0 (61.7-62.3) |
| 5% | ≥0.183 | 2,577 | 3,086 | 40,013 | 68,219 | 95.7 (95.5-95.8) | 6.05(5.83-6.28) | 1.02 (1.02-1.02) | 0.72 (0.68-0.75) | 63.0 (63.0-63.1) | 45.5 (44.3-46.8 ) | 62.2 (61.9-62.4) |

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values for low back pain recurrence at different thresholds of predicted risk of low back pain recurrence over 5 years in validation cohort**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | 1.000 | 19,435 | 35,623 | 1,776 | 0 | 0.00 (0.00-0.01) | 91.6( 91.3-92.0) | 0.00 | 1.09 (1.09-1.10) | 0 | 35.3 (35.2-35.4) | 34.2 (33.8-34.6) |
| 97% | ≥0.989 | 19,409 | 35,200 | 1,759 | 466 | 1.31 (1.19-1.43) | 91.7 (91.3-92.1) | 0.16 (0.14-0.17) | 1.08 (1.07-1.08) | 20.9 (19.3-22.7) | 35.5 (35.4-35.6) | 35.0 (34.6-35.4) |
| 95% | ≥0.979 | 19,379 | 34,643 | 1,811 | 1,001 | 2.81 (2.64-2.99) | 91.5 (91.1-91.8) | 0.33 (0.30-0.35) | 1.06 (1.06-1.07) | 35.6 (33.9-37.3) | 35.9 (35.8-36.0) | 35.9 (35.5-36.3) |
| 90% | ≥0.933 | 19,092 | 32,013 | 2,208 | 3,521 | 9.91 (9.60-10.2) | 89.6 (89.2-90.0) | 0.96 (0.91-1.01) | 1.01 (1.00-1.01) | 61.5 (60.3-62.7) | 37.4 (37.2-37.5) | 39.8 (39.4-40.2) |
| 75% | ≥0.807 | 17,543 | 25,097 | 3,619 | 10,575 | 29.7 (29.2-30.1) | 82.9 (82.4-83.4) | 1.73 (1.68-1.79) | 0.85 (0.84-0.86) | 74.5 (73.9-75.1) | 41.1 (40.9-41.4) | 49.5 (49.1-49.9) |
| 50% | ≥0.607 | 13,246 | 15,184 | 7,921 | 20,483 | 57.4 (56.9-57.9) | 62.6 (61.9-63.2) | 1.53 (1.50-1.56) | 0.68 (0.67-0.69) | 72.1 (71.7-72.5) | 46.6 (46.2-47.0) | 59.4 (58.9-59.8) |
| 25% | ≥0.408 | 7,117 | 7,087 | 14,167 | 28,463 | 80.1 (79.7-80.5) | 33.4 (32.8-34.1) | 1.20 (1.19-1.22) | 0.60 (0.58-0.61) | 66.8 (66.5-67.0) | 50.1 (49.4-50.8) | 62.6 (62.2-63.0) |
| 10% | ≥0.263 | 2,704 | 3,011 | 18,545 | 32,574 | 91.5 (91.2-91.8) | 12.7 (12.3-13.2) | 1.05 (1.04-1.06) | 0.66 (0.63-0.70) | 63.7 (63.6-63.9) | 47.3 (46.1-48.5) | 62.1 (61.7-62.5) |
| 5% | ≥0.183 | 1,316 | 1,560 | 19,896 | 34,062 | 95.6 (95.4-95.8) | 6.20 (5.88-6.54) | 1.02 (1.02-1.02) | 0.71 (0.66-0.76) | 63.1 (63.0-63.2) | 45.8 (44.0-47.5) | 62.3 (61.9-62.7) |

Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages].The threshold of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.3.7 Prediction equation of low back pain recurrence within 5 years

With reference to the derived model, individualized probability of experiencing low back pain recurrence within the years of follow up (t=5) can be estimated using the following equation:

$$P(\text{Low back pain recurrence}) = 1 - S_o(t)^{\exp[(\beta_1 x_1 + \beta_2 x_2 \ldots \beta_m x_m)]},$$

Where $S_o(t)$ denotes the baseline survival probability at time (t) for an individual with all covariates equivalent to zero (0), $(\beta_1 \ldots . \beta_m)$ denotes the change in log hazard rate (estimated $\beta$-coefficients) and $(x_1 \ldots x_m)$ denote values of risk predictors in the model. Using the estimated coefficients ($\beta_i$s) and survival probabilities $S_o(t)$, personalized probabilities of experiencing low back pain recurrence within 5 years can be calculated.

The Youden's J statistic suggested a risk probability of ≥0.567 as the optimal cut-off point to define high-risk individuals based on the derived prediction equation. This threshold showed a sensitivity of 62.7% (95% CI, 62.2%-63.2%), specificity of 57.7% (95% CI, 57.0%-58.4%), positive likelihood ratio (LR+) of 1.48 (95% CI, 1.45-1.51), negative likelihood ratio (LR-) of 0.65 (95% CI, 0.64-0.66), positive predictive value (PPV) of 71.4% (95% CI, 71.0%-71.8%), negative predictive value (NPV) of 47.8% (95% CI, 47.4%-48.3%) and accuracy of 60.8% (95% CI, 60.4%-61.2%) in

prediction of risk of low back pain recurrence over 5 years in the validation cohort (Table 24).

### 4.3.8 Simplified risk score for low back pain recurrence within 5 years

Table 22 present the regression coefficients for the Cox Proportional hazard model fit to the derivation cohort. In the right-most column of the table are the points associated with the presence of a given level of a risk factor (with the reference level assigned zero points). The points were determined by multiplying the regression coefficient by 100 and rounding to the nearest integer. Advanced age (≥65 years old) conferred the largest number of points (86 points). Among modifiable risk factors, lower BMI was protective (-13 points) (Table 22).

Participants in the overall sample were divided into five equally sized risk strata using the quintiles of the empirical risk score and Cochran–Armitage test for trend was used to test for difference in risk among strata. Table 25 presents the cumulative incidence risk (CIRs) probabilities for 5-year low back pain recurrence in each of the risk strata in the derivation and validation cohorts. There were statistically significant differences in the cumulative incidence risk probabilities across the five risk strata based on the Cochran–Armitage test for trend ($p<.0001$). There was a clearly defined gradation in the risk of low back pain recurrence across the five risk strata. The lowest risk stratum comprised of subjects with very low cases of low back pain recurrence during the 5-year follow-up period. In contrast, the highest risk stratum comprised of subjects with very high cases of low back

pain recurrence during the 5-year follow-up period. The five-year cumulative incidence risk of low back pain recurrence in the lowest and highest risk strata in the derivation cohort were 53.8 (95% CI, 53.0 to 54.7) and 93.3 (95% CI, 93.0 to 93.7), respectively. Thus, the incidence probability of low back pain recurrence was greater in the highest risk stratum than in the lowest risk stratum, and the hazard ratio (HR) was 3.2 times greater. Figure 12 presents the survival trends over 5 years for participants based on the risk score strata.

**Figure 12. Kaplan-Meier curves for 5-year low back pain recurrence-free survival in five risk groups in the derivation and validation cohorts based on the simplified points based risk score. (A) Derivation. (B) Validation**

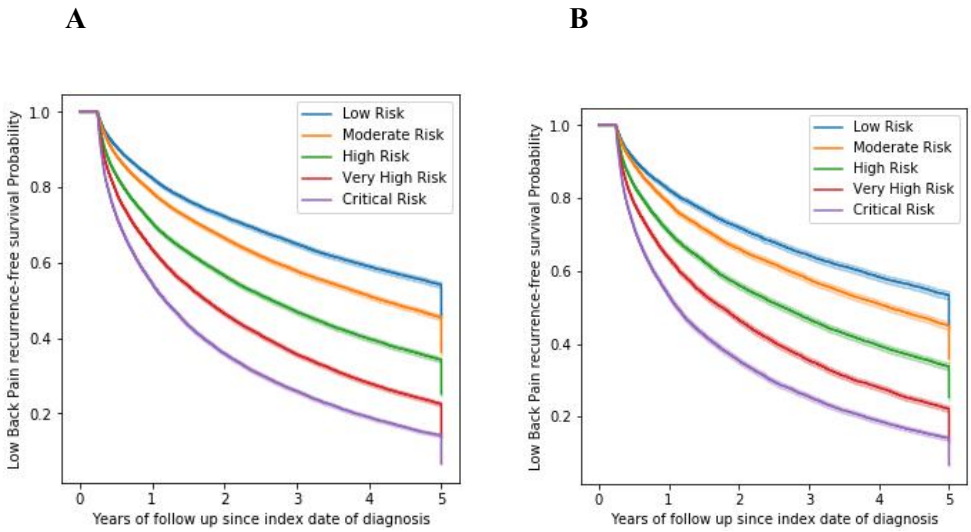


**Table 25. Risk of 5-year low back pain recurrence in the derivation and validation cohorts based on the risk score strata**

| Risk of low back pain in the derivation cohort based on the risk category | | | | | | |
|---|---|---|---|---|---|---|
| **Risk Strata** | **Risk Score Range** | **Non-Event (%)** | **Event (%)** | **Total** | **CR* (95% CI)** | **HR (95% CI), *P* value** |
| Low Risk | <44 | 13,782 (61.5) | 8,625 (38.5) | 22,407 | 53.8 (53.0 to 54.7) | Reference |
| Moderate Risk | 44 to 61 | 11,913 (51.6) | 11,196 (48.4) | 23,109 | 63.8 (63.0 to 64.6 ) | 1.28 (1.25 to 1.32), *p*<.0001 |
| High Risk | 62 to 95 | 8,712 (38.1) | 14,150 (61.9) | 22,862 | 74.8 (74.1 to 75.5) | 1.76 (1.72 to 1.81), *p*<.0001 |
| Very High Risk | 96 to 124 | 5,417 (23.9) | 17,254 (76.1) | 22,671 | 86.0 (85.5 to 86.5) | 2.41(2.35 to 2.48), *p*<.0001 |
| Critical Risk | >124 | 2,911 (12.7) | 19,935 (87.3) | 22,846 | 93.3 (93.0 to 93.7) | 3.20 (3.12 to 3.29), *p*<.0001 |
| **Risk of low back pain in the validation cohort based on the risk category** | | | | | | |
| **Risk Strata** | **Risk Score Range** | **Non-Event (%)** | **Event (%)** | **Total** | **CR* (95% CI)** | **Hazard Ratios (95% CI)** |
| Low Risk | <44 | 6,786 (60.8) | 4,367 (39.2) | 11,153 | 54.7 (53.5 to 56.0) | Reference |
| Moderate Risk | 44 to 61 | 5,812 (51.0) | 5,578 (49.0) | 11,390 | 64.1 (63.0 to 65.2) | 1.26 (1.21 to 1.31), *p*<.0001 |
| High Risk | 62 to 95 | 4,305 (38.0) | 7,026 (62.0) | 113,31 | 74.6 (73.7to 75.6) | 1.73 (1.69 to 1.80), *p*<.0001 |
| Very High Risk | 96 to 124 | 2,691 (23.6) | 8,698 (76.4) | 11,389 | 86.4 (85.7to 87.2) | 2.38 (2.30 to 2.47), *p*<.0001 |
| Critical Risk | >124 | 1,473 (12.7) | 10,098 (87.3) | 11,571 | 93.2(92.7 to 93.7) | 3.18 (3.07 to 3.29), *p*<.0001 |
| **Average 5-years low back pain recurrence survival probability= 0.3284** | | | | | | |

*CIR=Cumulative Risk

†Cochran–Armitage test for trend (for overall cohort), *p*<.0001

### 4.3.9 Validation of the simplified risk score at different risk score thresholds

The theoretical minimum and maximum sum of the points were -21 and 228, respectively. The median score was 80, while the 25$^{th}$ and 75$^{th}$ percentiles were 47 and 117, respectively. Table 26 shows the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy for low back pain recurrence at various risk score thresholds based on subjects in the derivation and validation cohorts. The risk score threshold for the top 3% at highest risk of low back pain recurrence in the next 5 years was 165, for the top 5% was 155, for the top 10% was 142, for the top 25% was 117, and for the top 50% was 80 in both cohorts.

With a risk score threshold of 142 over 5 years to identify the 10% of participants with the highest risk of low back pain recurrence the sensitivity for identifying 5-year low back pain recurrence was 15.2% (95% CI, 14.9%-15.6%), specificity 97.3% (95% CI, 97.0-97.5%), positive predictive value 90.3% (95% CI, 89.6%-91.0%), negative predictive value 40.6% (95% CI, 40.5%-40.8%), and accuracy value 45.9% (95% CI, 45.5%-46.3%) in the validation cohort (Table 26). The corresponding thresholds for risk of experiencing low back pain recurrence over 5 years and the risk score's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 26). The Youden's J statistic suggested a risk score of ≥81 as the optimal cutoff point to define high-risk individuals based on the simplified risk score. This threshold

showed a sensitivity of 62.3% (95% CI, 61.8%-62.9%), specificity of 72.1% (95% CI, 71.5%-72.8%), positive likelihood ratio (LR+) of 2.24 (95% CI, 2.19-2.29), negative likelihood ratio (LR-) of 0.52 (95% CI, 0.51-0.53), positive predictive value (PPV) of 79.0% (95% CI, 78.6%-79.3%), negative predictive value (NPV) of 53.3% (95% CI, 52.9%-53.7%) and accuracy of 66.0% (95% CI, 65.6%-66.4%) in prediction of the risk of low back pain recurrence over 5 years in the validation cohort (Table 26).

**Table 26. Sensitivity, specificity, likelihood ratios, predictive values, and accuracy at different thresholds of 5-year low back pain recurrence risk score in derivation and validation cohorts**

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values for low back pain at different thresholds of the 5-year low back pain recurrence risk score in derivation cohort**

| Threshold (Centiles) | Risk Score Threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥181 | 42,509 | 70,216 | 61 | 1,109 | 1.55 (1.47-1.65) | 99.9 (99.8-99.9) | 10.9 (8.39-14.0) | 0.99 (0.98-0.99) | 94.8 (93.4-95.9) | 37.7 (37.7-37.7) | 38.3 (38.0-38.6) |
| 97% | ≥165 | 42,347 | 68,064 | 213 | 3,271 | 4.59 (4.43-4.74) | 99.5 (99.4-99.6) | 9.16 (7.98-10.5) | 0.96 (0.96-0.96) | 93.9 (93.0-94.6) | 38.4 (38.3-38.4) | 40.1 (39.8-40.3) |
| 95% | ≥155 | 42,100 | 65,903 | 459 | 5,433 | 7.62 (7.42-7.81) | 98.9 (98.8-99.0) | 7.06 (6.42-7.76) | 0.93 (0.93-0.94) | 92.2 (91.5-92.9) | 39.0 (38.9-39.0) | 41.7 (41.5-42.0) |
| 90% | ≥142 | 41,437 | 60,575 | 1,128 | 10,755 | 15.1 (14.8-15.3) | 97.4 (97.2-97.5) | 5.69 (5.36-6.04) | 0.87 (0.87-0.88) | 90.5 (90.0-91.0) | 40.6 (40.5-40.7) | 45.8 (45.5-46.1) |
| 75% | ≥117 | 38,559 | 46,604 | 4,062 | 24,670 | 34.6 (34.3-35.0) | 90.5 (90.2-90.8) | 3.63 (3.52-3.75) | 0.72 (0.72-0.73) | 85.9 (85.5-86.2) | 45.3 (45.1-45.4) | 55.5 (55.2-55.8) |
| **‡50.6%** | ≥81 | 30,636 | 26,937 | 11,936 | 44,386 | 62.2 (61.9-62.6) | 72.0 (71.5-72.4) | 2.22 (2.18-2.26) | 0.52 (0.52-0.53) | 78.8 (78.5-79.1) | 53.2 (52.9-53.5) | 65.9 (65.6-66.1) |
| 50% | ≥80 | 30,384 | 26,484 | 12,209 | 44,818 | 62.9 (62.5-63.2) | 71.3 (70.9-71.8) | 2.19 (2.16-2.23) | 0.52 (0.51-0.53) | 78.6 (78.3-78.9) | 53.4 (53.2-53.7) | 66.0 (65.8-66.3) |
| 25% | ≥47 | 15,610 | 10,413 | 26,860 | 61,012 | 85.4 (85.2-85.7) | 36.8 (36.3-37.2) | 1.35 (1.34-1.36) | 0.40 (0.39-0.41) | 69.4 (69.3-69.6) | 60.0 (59.5-60.5) | 67.3 (67.0-67.6) |
| 10% | ≥34 | 7,000 | 3,840 | 35,585 | 67,470 | 94.6 (94.5-94.8) | 16.4 (16.1-16.8) | 1.13 (1.13-1.14) | 0.33 (0.32-0.34) | 65.5 (65.4-65.6) | 64.6 (63.7-65.4) | 65.4 (65.1-65.7) |
| 5% | ≥27 | 3,909 | 1,729 | 38,653 | 69,604 | 97.6 (97.5-97.7) | 9.18 (8.91-9.46) | 1.07 (1.07-1.08) | 0.26 (0.25-0.28) | 64.3 (64.2-64.4) | 69.3 (68.1-70.5) | 64.5 (64.3-64.8) |

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values for low back pain at different thresholds of the risk score of low back pain recurrence over 5 years in validation cohort**

| Threshold (Centiles) | Risk Score Threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥181 | 21,206 | 35,046 | 26 | 556 | 1.56 (1.44-1.70) | 99.9 (99.8-99.9) | 12.8 (8.61-18.9) | 0.99 (0.98-0.99) | 95.5 (93.5-96.9) | 37.7 (37.7-37.7) | 38.3 (37.9-38.7) |
| 97% | ≥165 | 21,126 | 33,975 | 116 | 1,617 | 4.54 (4.33-4.76) | 99.5 (99.4-99.6) | 8.32 (6.90-10.0) | 0.96 (0.96-0.96) | 93.3 (92.0-94.4) | 38.3 (38.3-38.4) | 40.0 (39.6-40.4) |
| 95% | ≥155 | 21,004 | 32,931 | 239 | 2,660 | 7.47 (7.20-7.75) | 98.9 (98.7-99.0) | 6.64 (5.83-7.57) | 0.94 (0.93-0.94) | 91.8 (90.7-92.7) | 38.9 (38.9-39.0) | 41.6 (41.2-42.0) |
| 90% | ≥142 | 20,656 | 30,177 | 581 | 5,420 | 15.2 (14.9-15.6) | 97.3 (97.0-97.5) | 5.57 (5.12-6.05) | 0.87 (0.87-0.88) | 90.3 (89.6-91.0) | 40.6 (40.5-40.8) | 45.9 (45.5-46.3) |
| 75% | ≥117 | 19,213 | 23,301 | 1,968 | 12,352 | 34.7 (34.2-35.1) | 90.7 (90.3-91.1) | 3.73 (3.57-3.90) | 0.72 (0.71-0.73) | 86.3 (85.7-86.8) | 45.2 (45.0-45.4) | 55.5 (55.1-56.0) |
| **‡50.6%** | ≥81 | 15,316 | 13,407 | 5,914 | 22,197 | 62.3 (61.8-62.9) | 72.1 (71.5-72.8) | 2.24 (2.19-2.29) | 0.52 (0.51-0.53) | 79.0 (78.6-79.3) | 53.3 (52.9-53.7) | 66.0 (65.6-66.4) |
| 50% | ≥80 | 15,156 | 13,228 | 6,053 | 22,397 | 62.9 (62.4-63.4) | 71.5 (70.9-72.1) | 2.20 (2.15-2.25) | 0.52 (0.51-0.53) | 78.7 (78.3-79.1) | 53.4 (53.0-53.8) | 66.1 (65.7-66.5) |
| 25% | ≥47 | 7,867 | 5,081 | 13,465 | 30,421 | 85.7 (85.3-86.1) | 36.9 (36.2-37.5) | 1.36 (1.34-1.37) | 0.39 (0.38-0.40) | 69.3 (69.1-69.6) | 60.8 (60.0-61.5) | 67.4 (67.0-67.8) |
| 10% | ≥34 | 3,509 | 1,926 | 17,708 | 33,691 | 94.6 (94.4-94.8) | 16.5 (16.0-17.1) | 1.13 (1.13-1.14) | 0.33 (0.31-0.34) | 65.6 (65.4-65.7) | 64.6 (63.3-65.8) | 65.5 (65.1-65.8) |
| 5% | ≥27 | 1,983 | 879 | 19,257 | 34,715 | 97.5 (97.4-97.7) | 9.34 (8.95-9.74) | 1.08 (1.07-1.08) | 0.26 (0.24-0.29) | 64.3 (64.2-64.4) | 69.3 (67.6-70.9) | 64.6 (64.2-65.0) |

Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages]. The threshold of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.3.10 Practical application of risk score for 5-year low back pain recurrence

The following example illustrates how the 5-year low back pain recurrence risk can be estimated using the simplified points based system.

**Case**: A 50-year-old female with insurance premium below 30%, who moderately exercises (1-2 times/week), with normal BMI (>18.5 kg/m$^2$-24.9 kg/m$^2$), normal total cholesterol (<200 mg/dL), prehypertensive (SBP 120-139 or DBP 80-89), with no history of IVDD, back injury, spinal stenosis and spondylolisthesis but with history of bone mineral density disorders and who receives low back pain treatment for more than 8 days during the first onset on low back pain.

**Table 27. Table of calculated 5-year low back pain recurrence risk score for a hypothetical example of a risk profile**

| Risk factor | Value (Risk Factor Category) | Points |
|---|---|---|
| Sex | Female | 14 |
| Age | 45-54 yrs | 41 |
| Income/Insurance Premium | Low (<30%) | 7 |
| Physical Activity | Moderate (1-2 times/week) | -2 |
| Body Mass Index | >18.5 kg/m$^2$-24.9 kg/m$^2$ | 0 |
| Total Cholesterol | <200 mg/dL | 0 |
| Hypertension status | SBP 120-139 or DBP 80-89 | 3 |
| Diagnosed IVDD | No | 0 |
| History of Back Injury | No | 0 |
| Spinal stenosis | No | 0 |
| Spondylolisthesis | No | 0 |
| Bone Mineral Density | Yes | 12 |
| Days of Prescription | ≥ 8 days | 0 |
| **Total Points** | | **68** |
| **Estimate of Risk** | | **0.889** |

***$S_o(t)$ = 0.3284**

The probability of 5-year low back pain recurrence can be estimated as follows;

$$P(\text{Low Back Pain recurrence}) = 1 - \mathrm{S_o}(t)^{\exp[(Score/100)]}$$

$$P(\text{Low Back Pain recurrence}) = 1 - (0.3284)^{\exp[(68/100)]}$$

$$= 0.889$$

The $S_0(t)$ is the baseline survival probability at time ($t$=5 years) for an individual with all covariates equivalent to zero, which was estimated by Cox regression analysis. The beta coefficient was set to integer by multiplying 100, thus, in the actual calculation, the sum of risk scores was divided by 100 to give an overall risk estimate. The sum (68 risk points) shown in the hypothetical score was thus divided by 100 to give the 8-year risk.

# 4.4 Prediction of low back pain recurrence within twelve (12) months

### 4.4 Prediction of low back pain recurrence within twelve (12) months

In this study, a consecutive cohort of low back pain patients was analysed. Previous studies have defined transient low back pain as an episode in which pain is present on no more than 90 days and does not recur over a 12 months period [102]. Studies have reported varying rates of recurrence within 12 months following the first low back pain episode. This study aimed to assess predictors associated with 12-months prognosis. Recurrence was defined as a new episode of care seeking between the third and the twelfth month from the previous index date of diagnosis (medical utilisation). A new episode was defined based on a standard definition of at least three months (90 days) from the previous episode.

#### 4.4.1 Baseline characteristics of the consecutive cohort of patients (12 months)

In this study, data from 170,729 (33.9%) of the full cohort (N=502,342) was analysed. The participants were allocated to the derivation (2/3) and validation cohorts (1/3) as recommended [378]. During a follow up period of 12 months, 49,462 (29.0%) participants experienced recurrent episodes. The details of the baseline characteristics are presented (Table 28). There were no significant differences between the derivation and validation cohorts with respect to descriptive statistics. However, those who experienced a recurrence within 12 months had high mean values of SBP, DBP, total cholesterol, FBG, and BMI (Table 28).

**Table 28. Baseline characteristic of participants in derivation and validation cohorts for low back pain recurrence within 12 months [Mean (SD) or n (%)]**

| Covariate | Derivation Cohort (n=113,895) | | | Validation Cohort (n=56,834) | | |
|---|---|---|---|---|---|---|
| | **Without Recurrence** | **With Recurrence** | **P value** | **Without Recurrence** | **With Recurrence** | **P value** |
| | **81,043 (71.2%)** | **32,852 (28.8%)** | | **40,224 (70.8%)** | **16,610 (29.2%)** | |
| Months | 11.2 (2.4) | 6.1 (2.7) | <.0001 | 11.2 (2.6) | 6.2 (2.7) | <.0001 |
| Height (cm) | 161.7 (9.0) | 158.8 (9.2) | <.0001 | 161.6 (9.0) | 158.8 (9.1) | <.0001 |
| Weight (kgs) | 62.0 (10.7) | 60.6 (10.4) | <.0001 | 61.9 (10.6) | 60.6 (10.2) | <.0001 |
| BMI ($kg/m^{2)}$ | 23.7 (3.2) | 24.0 (3.2) | <.0001 | 23.6 (3.2) | 24.0 (3.2) | <.0001 |
| SBP (mm Hg) | 123.8 (17.4) | 126.9 (17.9) | <.0001 | 123.7 (17.4) | 127.0 (17.9) | <.0001 |
| DBP (mm Hg) | 77.6 (11.4) | 78.9 (11.3) | <.0001 | 77.6 (11.4) | 78.8 (11.4) | <.0001 |
| Fasting Glucose (mg/dL) | 94.6 (27.9) | 97.0 (28.4) | <.0001 | 94.3 (27.6) | 97.1 (28.5) | <.0001 |
| Total Cholesterol (mg/dL) | 194.4 (38.7) | 199.6 (39.0) | <.0001 | 194.4 (38.5) | 199.7 (39.2) | <.0001 |
| Number of consultations (Days) | 1.4 (2.7) | 1.8 (2.1) | <.0001 | 1.4 (2.1) | 1.8 (2.2) | <.0001 |
| Length of prescription (Days) | 8.1 (16.7) | 6.4 (10.9) | <.0001 | 8.1 (16.7) | 6.2 (10.4) | <.0001 |
| Length of hospitalization (Days) | 1.8 (4.6) | 2.1 (3.2) | <.0001 | 1.8 (4.0) | 2.1 (3.1) | <.0001 |
| **Sex** | | | <.0001 | | | <.0001 |
| Male | 35,307 (43.6) | 11,800 (35.9) | | 17,476 (43.5) | 5,853 (35.2) | |
| Female | 45,736 (56.4) | 21,052 (64.1) | | 22,748 (56.5) | 10,757 (64.8) | |
| **Age** | | | <.0001 | | | <.0001 |
| <44 yrs. | 40,163 (49.5) | 9,338 (28.4) | | 19,822 (49.3) | 4,697 (28.3) | |
| 45-54 yrs | 17,909 (22.1) | 7,273 (22.1) | | 8,973 (22.3) | 3,702 (22.3) | |
| 55-64 yrs | 14,092 (17.4) | 8,588 (26.2) | | 6,945 (17.3) | 4,265 (25.7) | |
| ≥ 65 yrs | 8,879 (11.0) | 7,653 (23.3) | | 4,484 (11.1) | 3,946 (23.7) | |
| **Income/Insurance Premium** | | | <.0001 | | | <.0001 |
| Low (<30%) | 11,972 (14.8) | 5,388 (16.4) | | 6,080 (15.1) | 2,758 (16.6) | |
| Medium (30-60%) | 29,082 (35.9) | 11,567 (35.2) | | 14,282 (35.5) | 5,851 (35.2) | |
| High (>60%) | 39,989 (49.3) | 15,897 (48.4) | | 19,862 (49.4) | 8,001 (48.2) | |

| Covariate | Derivation Cohort (n=113,895) | | | Validation Cohort (n=56,834) | | |
|---|---|---|---|---|---|---|
| | **Without Recurrence** | **With Recurrence** | **P value** | **Without Recurrence** | **With Recurrence** | **P value** |
| | **81,043 (71.2%)** | **32,852 (28.8%)** | | **40,224 (70.8%)** | **16,610 (29.2%)** | |
| **Physical Activity** | | | <.0001 | | | <.0001 |
| Low (None) | 48,942 (60.4) | 20,927 (63.7) | | 24,121 (60.0) | 10,613 (63.9) | |
| Moderate(1-2 times/week) | 26,214 (32.3) | 9,531 (29.0) | | 13,209 (32.8) | 4,746 (28.6) | |
| High (>3 times/week) | 5,887 (7.3) | 2,394 (7.3) | | 2,894 (7.2) | 1,251 (7.5) | |
| **Smoking Status** | | | <.0001 | | | <.0001 |
| Never | 58,373 (72.0) | 25,758 (78.4) | | 29,066 (72.3) | 13,072 (78.7) | |
| Former Smoker | 3,167 (3.9) | 1,003 (3.1) | | 1,513 (3.8) | 510 (3.1) | |
| Current Smoker | 19,503 (24.1) | 6,091 (18.5) | | 9,645 (23.9) | 3,028 (18.2) | |
| **Alcohol Consumption/Week** | | | <.0001 | | | <.0001 |
| Rarely (< 2 times) | 45,627 (56.3) | 21052 (64.1) | | 22,712 (56.5) | 10,650 (64.1) | |
| Moderate drinker (2–3 times) | 28,630 (35.3) | 9469 (28.8) | | 14,148 (35.2) | 4,806 (28.9) | |
| Heavy drinker ( ≥ 4 times) | 6,786 (8.4) | 2331 (7.1) | | 3,364 (8.3) | 1,154 (7.0) | |
| **Body Mass Index** | | | <.0001 | | | <.0001 |
| < 18.5 kg/m2 | 3,679 (4.5) | 1,175 (3.6) | | 1,793 (4.5) | 579 (3.5) | |
| 18.5 $kg/m^2$-24.9 $kg/m^2$ | 51130 (63.1) | 19,894 (60.6) | | 25,558 (63.5) | 10,100 (60.8) | |
| 25 $kg/m^2$-29.9 $kg/m^2$ | 23752 (29.3) | 10,621 (32.3) | | 11,692 (29.1) | 5,354 (32.2) | |
| >30 $kg/m^2$ | 2,482 (3.1) | 1,162 (3.5) | | 1,181 (2.9) | 577 (3.5) | |
| **Fasting Blood Glucose** | | | <.0001 | | | <.0001 |
| < 100 mg/dL | 51,671 (63.8) | 19,850 (60.4) | | 25,790 (64.1) | 10,005 (60.2) | |
| 100 mg/dl-125 mg/dL | 20,107 (24.8) | 86,52 (26.3) | | 9,968 (24.8) | 4,370 (26.3) | |
| ≥ 126 mg/dL or Rx | 9,265 (11.4) | 4,350 (13.3) | | 4,466 (11.1) | 2,235 (13.5) | |
| **Blood Pressure/HTN** | | | <.0001 | | | <.0001 |
| SBP <120 and DBP < 80 | 28,257 (34.9) | 9,528 (29.0) | | 14,204 (35.3) | 4,857 (29.2) | |
| SBP 120−139 or DBP 80-89 | 42,464 (52.4) | 17,883 (54.4) | | 20,919 (52.0) | 9,046 (54.5) | |
| SBP 140−159 or DBP 90-99 | 8,986 (11.1) | 4,723 (14.4) | | 4,474 (11.1) | 2,340 (14.1) | |
| SBP ≥ 160 or≥DBP100 or Rx | 1,336 (1.6) | 718 (2.2) | | 627 (1.6) | 367 (2.2) | |
| **Total cholesterol** | | | <.0001 | | | <.0001 |

| Covariate | Derivation Cohort (n=113,895) | | | Validation Cohort (n=56,834) | | |
|---|---|---|---|---|---|---|
| | **Without Recurrence** | **With Recurrence** | **P value** | **Without Recurrence** | **With Recurrence** | **P value** |
| | **81,043 (71.2%)** | **32,852 (28.8%)** | | **40,224 (70.8%)** | **16,610 (29.2%)** | |
| < 200 mg/dL | 46,341 (57.2) | 17,004 (51.8) | | 22,963 (57.1) | 8,564 (51.6) | |
| 200 mg/dL-239 mg/dL | 24,722 (30.5) | 10,857 (33.0) | | 12,345 (30.7) | 5,486 (33.0) | |
| > 240 mg/dL | 9,980 (12.3) | 4,991 (15.2) | | 4,916 (12.2) | 2,560 (15.4) | |
| **Diagnosed IHD** | | | <.0001 | | | <.0001 |
| No | 79,802 (98.5) | 32,068 (97.6) | | 39,628 (98.5) | 16,224 (97.7) | |
| Yes | 1,241 (1.5) | 784 (2.4) | | 596 (1.5) | 386 (2.3) | |
| **Diagnosed IVDD** | | | <.0001 | | | <.0001 |
| No | 70205 (86.6) | 25568 (77.8) | | 34885 (86.7) | 12,860 (77.4) | |
| Yes | 10838 (13.4) | 7284 (22.2) | | 5339 (13.3) | 3,750 (22.6) | |
| **History of Back Injuries** | | | <.0001 | | | <.0001 |
| No | 80,141 (98.9) | 32,283 (98.3) | | 39,769 (98.9) | 16,307 (98.2) | |
| Yes | 902 (1.1) | 569 (1.7) | | 455 (1.1) | 303 (1.8) | |
| **BMD Disorders** | | | <.0001 | | | <.0001 |
| No | 75,136 (92.7) | 28,093 (85.5) | | 37,275 (92.7) | 14,120 (85.0) | |
| Yes | 5,907 (7.3) | 4,759 (85.5) | | 2,949 (7.3) | 2,490 (15.0) | |
| **Spinal Stenosis** | | | | | | |
| No | 78,654 (97.1) | 30,516 (92.9) | | 39,008 (97.0) | 15,362 (92.5) | |
| Yes | 2,389 (2.9) | 2,336 (7.1) | | 12,16 (3.0) | 1,248 (7.5) | |
| **Spondylolisthesis** | | | <.0001 | | | <.0001 |
| No | 80,871 (99.8) | 32,685 (99.5) | | 40,160 (99.8) | 16,506 (99.4) | |
| Yes | 172 (0.2) | 167 (0.5) | | 64 (0.2) | 104 (0.6) | |

The student's *t*-test for continuous variables and $\chi^2$-test for categorical variables were used to examine the differences in baseline characteristics between participants in the derivation and validation cohorts stratified based on 12-months low back pain recurrence outcome

### 4.4.2 Cumulative incidence probabilities for low back pain recurrence

During twelve months of follow up of consecutive patients, the cumulative risk of low back pain recurrence increased from 0.7 (95% CI, 0.7-0.8) to 30.5 (95% CI, 30.3-30.7) at the end of the follow up period (12 months). The cumulative incidence within this period was high, indicating high risk of recurrence within 12 months. The details of the incidence trends and cumulative risks are presented (Table 29). The standard episode definition of 90 day was used in the case definition and low back pain diagnostic records within 3 months from the index date of diagnosis were considered as a single episode.

**Table 29. Follow-up times, cumulative incidence, and incidence probabilities of low back pain recurrence within 12 months**

| Length of follow up | Censored | Events | Total | CR* (95% CI) |
|---|---|---|---|---|
| 1 Month | 3,537 | 0 | 3,537 | 0 |
| 2 Month | 879 | 0 | 879 | 0 |
| 3 Month | 981 | 1,227 | 2,208 | 0.7 (0.7-0.8) |
| 4 Month | 929 | 13,907 | 14,836 | 9.2 (9.0-9.3) |
| 5 Month | 859 | 7,647 | 8,506 | 13.8 (13.7-14.0) |
| 6 Month | 820 | 5,582 | 6,402 | 17.3 (17.1-17.4) |
| 7 Month | 856 | 4,644 | 5,500 | 20.1 (19.9-20.3) |
| 8 Month | 795 | 3,874 | 4,669 | 22.5 (22.3-22.7) |
| 9 Month | 838 | 3,488 | 4,326 | 24.7 (24.5-24.9) |
| 10 Month | 770 | 3,242 | 4,012 | 26.8 (26.6-27.0) |
| 11 Month | 669 | 2,903 | 3,572 | 28.6 (28.4-28.8) |
| 12 Month | 109,334 | 2,948 | 112,282 | 30.5 (30.3-30.7) |
| **Totals** | **121,267** | **49,462** | **170,729** | |

*CR=Cumulative Risk

### 4.4.3 Association between risk factors and low back pain recurrence (12 months)

Tables 30 present the estimated coefficients and hazard ratios for covariates in the unadjusted, partially adjusted, and fully adjusted analyses. In this study, female sex, age, income grade (insurance premium), BMI, FBG or medical utilisation due to diabetes, total cholesterol, blood pressure/HTN, premorbid disc degeneration, spondylolisthesis, history of back injury, spinal stenosis and BMD were positively associated with recurrent of low back pain within 12 months ($p$<0.05) (Table 30). In contrast, smoking and alcohol consumption were inversely associated with low back pain recurrence within 12 months. In addition, total days of prescription (Duration of medication), total days of medical consultation (number of previous low back pain consultations) and total days of admission (hospitalization) were associated with low back pain recurrence within 12 months, although total days of consultation showed an inverse association in the fully adjusted models ($p$<0.05) (Table 30). Total number of consultation visits and duration of hospitalization were positively associated with LBP recurrence within 12 months in unadjusted and partially adjusted models. One of the remarkable findings in both 5-year and 12-months recurrence outcomes was a stable positive association between low back pain recurrence and blood pressure in all analyses ($p$<0.05) (Table 21 and Table 30, respectively), which was different from the previous analyses of first onset and chronic low back pain (Table 3 and Table 12, respectively).

**Table 30. Hazard Ratios (95% confidence interval) and β-coefficients for risk predictors in the univariate, partially adjusted and fully adjusted models for low back pain recurrence within 12 months**

| Covariate | Unadjusted∗ | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | *β* (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value |
| **Sex** | | | | | | | | | |
| Female | 0.251 (0.009) | 1.29 (1.26-1.31) | <.0001 | 0.193 (0.009) | 1.21 (1.19-1.25) | <.0001 | 0.165 (0.013) | 1.18 (1.15-1.21) | <.0001 |
| **Age** | | | | | | | | | |
| <45 yrs. | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 45-54 yrs | 0.450 (0.013) | 1.57 (1.53-1.61) | <.0001 | 0.434 (0.013) | 1.54 (1.51-1.58) | <.0001 | 0.434 (0.013) | 1.54 (1.51-1.58) | <.0001 |
| 55-64 yrs | 0.771 (0.012) | 2.16 (2.11-2.22) | <.0001 | 0.757 (0.012) | 2.13 (2.08-2.18) | <.0001 | 0.751 (0.012) | 2.12 (2.07-2.17) | <.0001 |
| ≥ 65 yrs | 1.039 (0.013) | 2.83 (2.76-2.90) | <.0001 | 1.022 (0.013) | 2.78 (2.71-2.85) | <.0001 | 1.015 (0.013) | 2.76 (2.69-2.83) | <.0001 |
| **Income/Insurance** | | | | | | | | | |
| High (>60%) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Medium (31-60%) | 0.008 (0.010) | 1.01 (0.99-1.03) | 0.4003 | 0.064 (0.010) | 1.07 (1.05-1.09) | <.0001 | 0.062 (0.010) | 1.06 (1.04-1.09) | <.0001 |
| Low (<30%) | 0.109 (0.013) | 1.12 (1.09-1.14) | <.0001 | 0.081 (0.013) | 1.09 (1.06-1.11) | <.0001 | 0.079 (0.013) | 1.08 (1.06-1.11) | <.0001 |
| **Physical Activity/Week** | | | | | | | | | |
| High (>3 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate (1-2 times) | -0.112 (0.019) | 0.89 (0.86-0.93) | <.0001 | -0.023 (0.019) | 0.98 (0.94-1.01) | 0.2174 | -0.022 (0.019) | 0.98 (0.94-1.01) | 0.2306 |
| Low (None) | 0.031 (0.017) | 1.03 (0.99-1.07) | 0.0795 | 0.018 (0.018) | 1.02 (0.98-1.05) | 0.2972 | 0.011 (0.018) | 1.01 (0.98-1.05) | 0.5255 |
| **Smoking Status** | | | | | | | | | |
| Never | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Former | -0.245(0.026) | 0.78 (0.74-0.82) | <.0001 | -0.044 (0.027) | 0.96 (0.90-1.01) | 0.1116 | -0.040 (0.027) | 0.96 (0.91-1.01) | 0.1418 |
| Current Smoker | -0.275(0.012) | 0.76 (0.74-0.78) | <.0001 | -0.010 (0.014) | 0.99 (0.96-1.02) | 0.5007 | -0.013 (0.015) | 0.99 (0.96-1.02) | 0.3821 |

| Covariate | Unadjusted* | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | *β* (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value |
| **Alcohol** | | | | | | | | | |
| Rarely (<2 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate drinker (2–3 | -0.263(0.010) | 0.77 (0.75-0.78) | <.0001 | -0.034 (0.011) | 0.96 (0.95-0.99) | 0.0020 | -0.033 (0.011) | 0.97 (0.95-0.99) | 0.01907 |
| Heavy drinker ( ≥ 4 times) | -0.233(0.018) | 0.79 (0.77-0.82) | <.0001 | -0.020 (0.019) | 0.98 (0.94-1.02) | 0.2916 | -0.023 (0.019) | 0.98 (0.94-1.02) | 0.2388 |
| **Body Mass Index** | | | | | | | | | |
| < 18.5 kg/$m^2$ | -0.150(0.025) | 0.86 (0.82-0.90) | <.0001 | -0.097 (0.025) | 0.91 (0.87-0.95) | <.0001 | -0.103 (0.025) | 0.90 (0.86-0.95) | <.0001 |
| 18.5 kg/$m^2$-24.9 kg/$m^2$ | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 25 kg/$m^2$-29.9 kg/$m^2$ | 0.111 (0.010) | 1.12 (1.10-1.14) | <.0001 | 0.044 (0.010) | 1.05 (1.03-1.07) | <.0001 | 0.047 (0.010) | 1.05 (1.03-1.07) | <.0001 |
| ≥ 30 kg/$m^2$ | 0.156 (0.025) | 1.17 (1.11-1.23) | <.0001 | 0.064 (0.025) | 1.07(1.02-1.12) | 0.0094 | 0.065 (0.025) | 1.07 (1.02-1.12) | 0.0081 |
| **Fasting Blood Glucose** | | | | | | | | | |
| < 100 mg/dL | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 100 mg/dL-125 mg/dL | 0.095 (0.011) | 1.10 (1.08-1.12) | <.000 | 0.016 (0.011) | 1.02 (0.99-1.04) | 0.1255 | 0.017 (0.011) | 1.02 (1.00-1.04) | 0.1144 |
| ≥ 126 mg/dL Or Rx | 0.174 (0.014) | 1.19 (1.16-1.22) | <.000 | 0.014 (0.013) | 1.01 (0.98-1.04) | 0.2960 | 0.016 (0.014) | 1.02 (0.99-1.04) | 0.2546 |
| **Total Cholesterol** | | | | | | | | | |
| < 200 mg/dL | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 200 mg/dL-239 mg/dL | 0.139 (0.010) | 1.15 (1.13-1.17) | <.0001 | 0.024 (0.010) | 1.02 (1.00-1.05) | 0.0173 | 0.027 (0.010) | 1.03 (1.01-1.05) | 0.0078 |
| > 240 mg/dL | 0.247 (0.013) | 1.28 (1.25-1.31) | <.0001 | 0.048 (0.013) | 1.049 (1.02- | 0.0173 | 0.052 (0.013) | 1.05 (1.03-1.08) | 0.0001 |
| **Blood Pressure/HTN** | | | | | | | | | |
| SBP < 120 and DBP < 80 | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| SBP 120-139 or DBP 80-89 | 0.187 (0.010) | 1.21 (1.18-1.23) | <.000 | 0.044 (0.011) | 1.05 (1.02-1.07) | <.0001 | 0.043 (0.011) | 1.04 (1.02-1.07) | <.0001 |
| SBP 140-159 or DBP 90-99 | 0.354 (0.015) | 1.42 (1.38-1.47) | <.000 | 0.069 (0.015) | 1.07 (1.04-1.10) | <.0001 | 0.067 (0.015) | 1.07 (1.04-1.10) | <.0001 |
| SBP ≥160 or ≥ DBP100 or Rx | 0.392 (0.032) | 1.48 (1.39-1.58) | <.000 | 0.046 (0.032) | 1.05 (0.98-1.11) | 0.1524 | 0.040 (0.032) | 1.04 (0.98-1.11) | 0.2136 |
| **Premorbid diseases** | | | | | | | | | |

| Covariate | Unadjusted∗ | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | *β* (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value | β (SE) | HR (95% CI) | *P* Value |
| Diagnosed IHD | 0.343 (0.030) | 1.41 (1.33-1.49) | <.000 | 0.053 (0.030) | 1.05 (0.99-1.12) | 0.0769 | 0.055 (0.030) | 1.06 (1.00-1.12) | 0.0637 |
| Diagnosed IVDD | 0.468 (0.011) | 1.60 (1.56-1.63) | <.0001 | 0.324 (0.011) | 1.38 (1.35-1.41) | <.0001 | 0.325 (0.011) | 1.38 (1.35-1.41) | <.0001 |
| History of Back Injury | 0.344 (0.034) | 1.41 (1.32-1.51) | <.0001 | 0.245 (0.034) | 1.28 (1.19-1.37) | <.0001 | 0.243 (0.034) | 1.28 (1.19-1.36) | <.0001 |
| Spinal Stenosis | 0.697 (0.017) | 2.01 (1.94-2.08) | <.0001 | 0.359 (0.018) | 1.43 (1.38-1.48) | <.0001 | 1.363 (0.018) | 1.43 (1.38-1.48) | <.0001 |
| History of BMD Disorders | 0.588 (0.013) | 1.80 (1.76-1.85) | <.0001 | 0.249 (0.013) | 1.28 (1.25-1.32) | <.0001 | 0.252 (0.013) | 1.29 (1.25-1.32) | <.0001 |
| Spondylolisthesis | 0.763 (0.061) | 2.14 (1.90-2.42) | <.0001 | 0.508 (0.061) | 1.66 (1.48-1.87) | <.0001 | 0.511 (0.061) | 1.67 (1.48-1.88) | <.0001 |
| **Number of Consultation** | | | | | | | | | |
| 1 day | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 2-3 days | 0.788 (0.011) | 2.20 (2.15-2.25) | <.0001 | 0.664 (0.012) | 1.94 (1.90-1.99) | <.0001 | 0.063 (0.013) | 1.07 (1.04-1.09) | <.0001 |
| ≥4 days | 0.887 (0.016) | 2.43 (2.35-2.50) | <.0001 | 0.702 (0.016) | 2.02 (1.96-2.08) | <.0001 | -0.173 (0.012) | 0.84 (0.82-0.86) | <.0001 |
| **Length of Prescription** | | | | | | | | | |
| ≥8 days | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 1-7 days | -0.173(0.012) | 0.84 (0.82-0.86) | <.0001 | -0.022 (0.012) | 0.98 (0.96-1.00) | 0.0665 | -0.023 (0.012) | 0.98 (0.95-1.00) | 0.0544 |
| None | 0.063 (0.013) | 1.07 (1.04-1.09) | <.0001 | 0.132 (0.013) | 1.14 (1.11-1.17) | <.0001 | 0.131 (0.013) | 1.14 (1.11-1.17) | <.0001 |
| **Length of Hospitalisation** | | | | | | | | | |
| 1 day | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 2-4 days | 0.785 (0.011) | 2.19 (2.15-2.24) | <.0001 | 0.656 (0.011) | 1.93 (1.89-1.97) | <.0001 | 0.655 (0.011) | 1.93 (1.88-1.97) | <.0001 |
| ≥5 days | 0.703 (0.016) | 2.02 (1.96-2.09) | <.0001 | 0.515 (0.016) | 1.67 (1.62-1.73) | <.0001 | 0.512 (0.016) | 1.67 (1.62-1.72) | <.0001 |

∗Univariate analysis. †Partially adjusted models account for age, sex and each variable added. ‡Fully adjusted models account for Age, Sex, Income grade, Physical activity, Smoking status, alcohol consumption and each of the other risk factors [*MetS (Fasting Glucose, Total Cholesterol, Blood Pressure/HTN, prior history of IHD, Ischemic Heart Disease] and (IVDD, Intervertebral Disc Degeneration;, spondylolisthesis, spinal Stenosis; BMD, Bone Mineral Density Disorders; history of back injury )].

### 4.4.4 Derivation of prediction equation for low back pain recurrence (12) months

Based on the univariate analysis and hierarchical cluster analysis, sex, age, BMI, smoking status, alcohol consumption,, income grade (insurance premium), physical inactivity, FBG or diabetes mellitus status, total cholesterol, blood pressure, disc degeneration, history of back injury, bone mineral density disorders, spinal stenosis, spondylolisthesis and total number of days of prescription were included in the derivation of a prediction model for low back pain recurrence within 12 months.

After applying the backward variable selection procedure at α=0.15 and taking into consideration the numbers of cases for reliable variable selection (≥10 cases per variable), the risk predictors that were retained in the parsimonious model consisted of thirteen variables including age, sex, income grade, physical exercise, alcohol consumption, BMI, blood pressure, disc generation, history of back injury, spinal stenosis, bone mineral density disorders, spondylolisthesis and total days of consultations ($p$<0.15) (Table 31).

**Table 31. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors in the parsimonious model of low back pain recurrence within 12 months and associated risk points**

| Covariate | *β* (SE) | HR (95% CI) | *P* Value | Points* |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | Reference | Reference | | 0 |

| Covariate | $\beta$ (SE) | HR (95% CI) | *P* Value | Points* |
|---|---|---|---|---|
| Female | 0.129 (0.013) | 1.14 (1.11-1.17) | <.0001 | 13 |
| **Age** | | | | |
| <45 yrs. | Reference | Reference | | 0 |
| 45-54 yrs | 0.354 (0.016) | 1.43 (1.38-1.47) | <.0001 | 35 |
| 55-64 yrs | 0.612 (0.016) | 1.85 (1.79-1.90) | <.0001 | 61 |
| ≥ 65 yrs | 0.819 (0.017) | 2.27 (2.19-2.35) | <.0001 | 82 |
| **Income Grade/Insurance** | | | | |
| High (>60%) | Reference | Reference | | 0 |
| Medium (30-60%) | 0.061 (0.012) | 1.06 (1.04-1.09) | <.0001 | 6 |
| Low (<30%) | 0.086 (0.016) | 1.09 (1.06-1.12) | <.0001 | 9 |
| **Physical Activity** | | | | |
| High (≥3 times/week) | Reference | Reference | | 0 |
| Moderate (1-2 times/week) | 0.0009 | 1.00 (0.96-1.05) | 0.9672 | 0 |
| Low (None) | 0.028 (0.022) | 1.03 (0.99-1.07) | 0.1903 | 3 |
| **Alcohol Consumption** | | | | |
| Rarely (< 2 times) | Reference | Reference | | 0 |
| Moderate drinker (2–3 | -0.037 | 0.96 (0.94-0.99) | 0.0066 | -4 |
| Heavy drinker ( ≥ 4 times) | -0.031 | 0.97 (0.93-1.02) | 0.1890 | -3 |
| **Body Mass Index** | | | | |
| < 18.5 kg/$m^2$ | -0.085 | 0.92 (0.87-0.98) | 0.0049 | -9 |
| 18.5 kg/$m^2$-24.9 kg/$m^2$ | Reference | Reference | | 0 |
| 25 kg/$m^2$-29.9 kg/$m^2$ | 0.033 (0.012) | 1.03 (1.01-1.06) | 0.0075 | 3 |
| ≥30 kg/$m^2$ | 0.034 (0.030) | 1.03 (0.98-1.10) | 0.2666 | 3 |
| **Blood Pressure/HTN** | | | | |
| SBP < 120 and DBP < 80 | Reference | Reference | | 0 |
| SBP 120-139 or DBP 80- | 0.025 (0.013) | 1.03 (0.99-1.05) | 0.0592 | 3 |
| SBP 140-159 or DBP 90- | 0.053 (0.019) | 1.05 (1.02-1.09) | 0.0047 | 5 |
| SBP ≥160/DBP ≥100 or | -0.022 | 0.98 (0.91-1.06) | 0.5771 | -2 |
| **Diagnosed IVDD** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.226 (0.014) | 1.25 (1.22-1.29) | <.0001 | 23 |
| **History of Back Injury** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.063 (0.043) | 1.07 (0.98-1.16) | 0.1386 | 6 |
| **Spinal Stenosis** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.132 (0.026) | 1.14 (1.09-1.20) | <.0001 | 13 |

| Covariate | *β* (SE) | HR (95% CI) | *P* Value | Points* |
|---|---|---|---|---|
| **History of BMD** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.108 (0.019) | 1.11 (1.07-1.16) | <.0001 | 11 |
| **Spondylolisthesis** | | | | |
| No | Reference | Reference | | 0 |
| Yes | 0.195 (0.078) | 1.22 (1.04-1.42) | 0.0126 | 20 |
| **Days of consultation** | | | | |
| 1 day | Reference | Reference | | 0 |
| 2-3 days | 0.631 (0.014) | 1.88 (1.83-1.93) | <.0001 | 63 |
| ≥4 days | 0.671 (0.019) | 1.96 (1.88-2.03) | <.0001 | 67 |

*The risk points were calculated by multiplying the estimated coefficients by 100 and rounding to the next integer.

### 4.4.5 Model validation for prediction equations of low back pain recurrence

The Harrell's C-statistic was 0.763 (95% CI, 0.752-0.773) and 0.759 (95% CI, 0.745-0.774), and brier score statistics of 0.259 and 0.262 for the derivation and validation cohorts, respectively. Using the optimal threshold determined by Youden's index to define high risk individuals, the sensitivity was 52.8% (95% CI, 52.3% to 53.4%) and 53.3% (95% CI, 52.5% to 54.1%) whereas specificity was 90.5% (95% CI, 90.3% to 90.7%) and 90.8% (95% CI, 90.5% to 91.1%), in the derivation and validation cohorts respectively (Table 32). The calibration was (Nam and D'Agostino's, $\chi^2$=3.938, $p$=0.2946 and $\chi^2$=3.9458, $p$=0.6044) for the derivation and validation cohorts, respectively. These prediction equations showed good discrimination and calibration. However, the sensitivity was relatively low compared to specificity. Table 32 and Figures 13-15 show the calibration and discrimination performance. The calibration plot was obtained by comparisons between observed and predicted probabilities across deciles of predicted

risk .There was agreement between the observed risks and mean predicted risks of low back pain recurrence (within 12 months) across each decile of the predicted risk, showing excellent calibration. In addition, comparing the hazard ratios (HRs) between the lowest risk stratum and the highest risk stratum shows that the model's highest risk group is 387 times more likely to experience low back pain recurrence within 12 months than the lowest risk group (Table 32). The model generally performed well in separation of individual in the lower risk groups and high-risk groups (Figure 15).

**Table 32. Model validation and performance evaluation based on discrimination and calibration in derivation and validation cohorts for low back pain recurrence within 12 months**

| Performance Evaluation statistic | Derivation Cohort | Validation cohort |
|---|---|---|
| Brier Score† | 0.259 | 0.262 |
| Nam and D'Agostino test‡ | $\chi^2$=3.938,p=0.2946 | $\chi^2$=3.9458, p=0.6044 |
| Harrell's C statistic (95% CI)# | 0.763 (0.752-0.773) | 0.759 (0.745-0.774) |
| Sensitivity (95% CI) | 52.8% (52.3% to 53.4%) | 53.3% (52.5% to 54.1%) |
| Specificity (95% CI) | 90.5% (90.3% to 90.7%) | 90.8% (90.5% to 91.1%) |
| Positive Likelihood Ratio (95% CI) | 5.59 (5.46 to 5.72) | 5.81 (5.62 to 6.01) |
| Negative Likelihood Ratio (95% CI) | 0.52 (0.51 to 0.53) | 0.51 (0.51 to 0.52) |
| Positive Predictive Value (95% CI) | 69.4% (68.9% to 69.9%) | 70.5% (69.8% to 71.2%) |
| Negative Predictive Value (95% CI) | 82.5% (82.4% to 82.7%) | 82.6% (82.3% to 82.8%) |
| Accuracy (95% CI) | 79.7% (79.4% to 79.9%) | 79.9% (79.6% to 80.2%) |
| **Risk Strata Comparisons** | **Hazard Ratio, *P* value** | **Hazard Ratio, P value** |
| Good Vs Fairly Good | 0.92 (0.86-0.98), *p*=0.0129 | 0.86 (0.79 -0.95), *p*=0.0020 |
| Good Vs Fairly Poor | 1.02 (0.95-1.08), *p*=0.6247 | 0.93 (0.86 -1.02), *p*=0.1052 |
| Good Vs Poor | 9.21 (8.65-9.81), *p*<.0001 | 8.08 (7.43-8.79), *p*<.0001 |
| Good Vs Very Poor | 451.4(412.4-494.1) *p*<.0001 | 386.6(340.8-438.5),*p*<.0001 |

**Abbreviation: CI=confidence interval.**

†Measures both discrimination and calibration; lower values indicate higher accuracy, ‡A modification of Hosmer Lemeshow test suited for survival data; measure of calibration that is specific to censored survival data (lower $\chi^2$ and higher *p* values) indicate better calibration, #A measure of discrimination for which higher values indicate better discrimination. The Youden's J statistics was 0.437 for both cohorts corresponding to risk probability of 0.839.

**Figure 13. Discrimination and calibration plots in the derivation cohort for prediction equation of low back pain recurrence within 12 months. (A) Discrimination. (B) Calibration**

**A** **B**

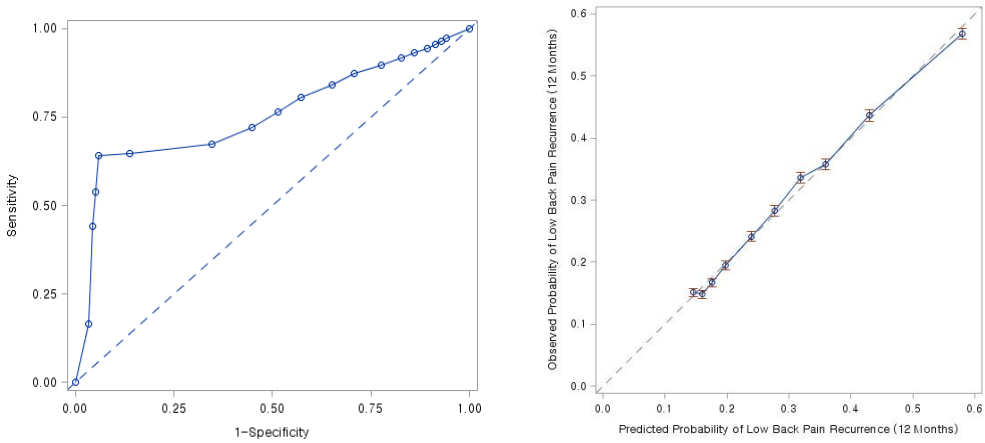



**Figure 14. Discrimination and calibration plots in the validation cohort for the prediction equation of low back pain recurrence within 12 months. (A) Discrimination. (B) Calibration**

A B

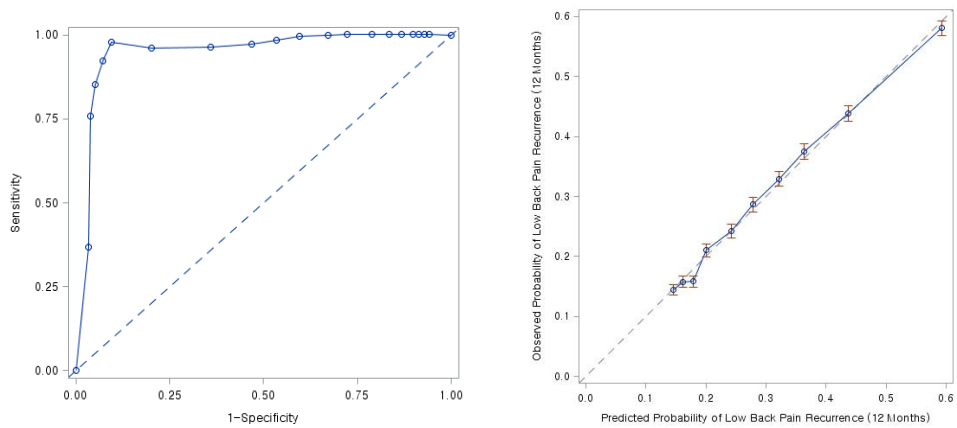
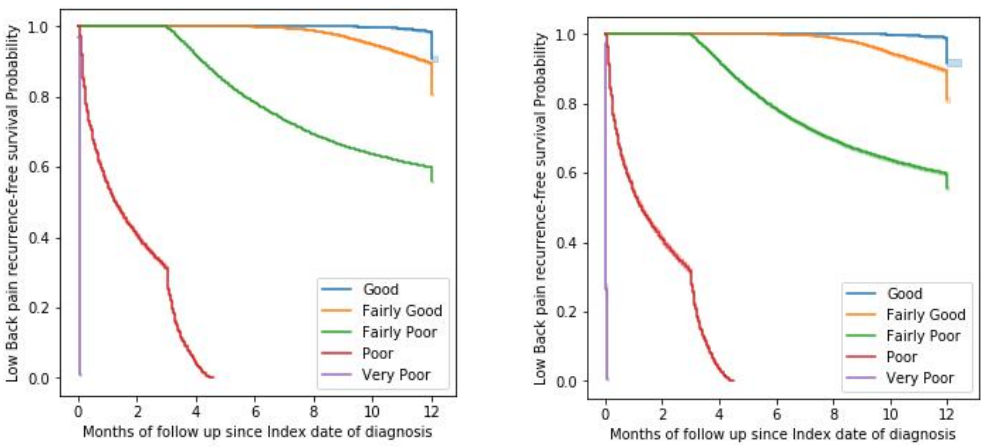


**Figure 15. Kaplan-Meier curves for 12-months low back pain recurrence -free survival in 5 risk groups in the derivation and validation cohorts based on the Prognostic Index. (A) Derivation. (B) Validation**

**A** **B**



### 4.4.6 Model discrimination at different thresholds of predicted risk

Table 33 shows the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy for low back pain recurrence equation for various risk probability thresholds based on subjects in the derivation and validation cohorts. The risk probability threshold for the top 3% at highest risk of low back pain recurrence in the next 12 months was 0.988, for the top 5% was 0.979, for the top 10% was 0.933, for the top 25% was 0.834, and for the top 50% was 0.792 in both cohorts. With a risk probability threshold of 0.933 over 12 months to identify the 10% of participants with the highest risk of low back pain recurrence, the sensitivity for identifying 12 month low back pain recurrence was 21.3% (95% CI, 20.7%-22.0%), specificity 94.5% (95% CI, 94.3%-94.7%), positive predictive value 61.0% (95% CI, 59.9%-62.2%), negative predictive value 74.8% (95% CI, 74.6%-74.9%), and accuracy value 73.4% (95% CI, 73.0%-73.7%) in the validation cohort (Table 33). The corresponding thresholds for risk of experiencing low back pain recurrence over 12 months and the model's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 33). Table 32 shows the results based on the optimal cut-off determined by Youden's J statistic for the prediction equation of low back pain recurrence in the next 12 months.

**Table 33. Sensitivity, specificity, likelihood ratios, predictive values for low back pain at different thresholds of predicted risk of low back pain recurrence over 12 months in derivation and validation cohorts**

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values and accuracy for low back pain at different thresholds of predicted risk of low back pain recurrence over 12 months in derivation cohort**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | 1.000 | 77,280 | 33,035 | 3,580 | 0 | 0.00 (0.00-0.01) | 95.6 (95.4-95.7) | 0.00 | 1.05 (1.04-1.05) | 0 | 70.1 (70.0-70.1) | 67.9 (67.6-68.1) |
| 97% | ≥0.988 | 77,213 | 32,079 | 3,690 | 913 | 2.77 (2.59-2.95) | 95.4 (95.3-95.6) | 0.61 (0.56-0.65) | 1.02 (1.02-1.02) | 19.8 (18.7-21.0) | 70.7 (70.6-70.7) | 68.6 (68.3-68.9) |
| 95% | ≥0.979 | 77,142 | 31,026 | 3,760 | 1,967 | 5.96 (5.71-6.22) | 95.4 (95.2-95.5) | 1.28 (1.22-1.35) | 0.99 (0.98-0.99) | 34.4 (33.2-35.6) | 71.3 (71.3-71.4) | 69.5 (69.2-69.7) |
| 90% | ≥0.933 | 76,558 | 25,996 | 4,269 | 7,072 | 21.4 (21.0-21.8) | 94.7(94.6-94.9) | 4.05 (3.91-4.20) | 0.83 (0.83-0.83) | 62.4 (61.5-63.2) | 74.7 (74.5-74.8) | 73.4 (73.2-73.7) |
| 75% | ≥0.834 | 70,581 | 14,922 | 10,432 | 17,960 | 54.6 (54.1-55.2) | 87.1(86.9-87.4) | 4.24 (4.16-4.33) | 0.52 (0.51-0.53) | 63.3 (62.8-63.7) | 82.6 82.4-82.7) | 77.7 (77.5-78.0) |
| 50% | ≥0.792 | 45,771 | 11,150 | 35,174 | 21,800 | 66.2 (65.7-66.7) | 56.6 (56.2-56.9) | 1.52 (1.51-1.54) | 0.60 (0.59-0.61) | 38.3 (38.0-38.5) | 80.4 (80.2-80.7) | 59.3 (59.0-59.6) |
| 25% | ≥0.684 | 23,594 | 4,887 | 57,293 | 28,121 | 85.2 (84.8-85.6) | 29.2 (28.9-29.5) | 1.20 (1.20-1.21) | 0.51 (0.49-0.52) | 32.9 (32.8-33.1) | 82.8 (82.4-83.2) | 45.4 (45.1-45.7) |
| 10% | ≥0.591 | 9,138 | 2,233 | 71,740 | 30,784 | 93.2 (93.0-93.5) | 11.3 (11.1-11.5) | 1.05 (1.05-1.06) | 0.60 (0.57-0.63) | 30.0 (30.0-30.1) | 80.4 (79.7-81.1) | 35.1 (34.8-35.3) |
| 5% | ≥0.506 | 4,596 | 1,080 | 76,278 | 31,941 | 96.7 (96.5-96.9) | 5.68 (5.52-5.84) | 1.03 (1.02-1.03) | 0.58 (0.54-0.61) | 29.5 (29.5-29.6) | 81.0 (80.0-82.0) | 32.1 (31.8-32.4) |

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values for low back pain at different thresholds of predicted risk of low back pain recurrence over 12 months in validation cohort**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | 1.000 | 38,631 | 16,427 | 1,776 | 0 | 0.00 (0.00-0.02) | 95.6 (95.4-95.8) | 0.00 | 1.05 (1.04-1.05) | 0 | 70.2 (70.1-70.2) | 68.0 (67.6-68.4) |
| 97% | ≥0.988 | 38,600 | 16,010 | 1,764 | 460 | 2.79 (2.55-3.06) | 95.6 (95.4-95.8) | 0.64 (0.58-0.71) | 1.02 (1.01-1.02) | 20.7 (19.1-22.4) | 70.7 (70.6-70.8) | 68.7 (68.3-69.1) |
| 95% | ≥0.979 | 38,546 | 15,476 | 1,819 | 993 | 6.03 (5.67-6.40) | 95.5 (95.3-95.7) | 1.34 (1.24-1.44) | 0.98 (0.98-0.99) | 35.3 (33.6-37.1) | 35.3 (33.6-37.1) | 69.6 (69.2-70.0) |
| 90% | ≥0.933 | 38,208 | 12,897 | 2,232 | 3,497 | 21.3 (20.7-22.0) | 94.5 (94.3-94.7) | 3.86 (3.68-4.06) | 0.83 (0.83-0.84) | 61.0 (59.9-62.2) | 74.8 (74.6-74.9) | 73.4 (73.0-73.7) |
| 75% | ≥0.834 | 35,196 | 7,483 | 5,058 | 9,097 | 54.9 (54.1-55.6) | 87.4 (87.1-87.8) | 4.37 (4.24-4.50) | 0.52 (0.51-0.53) | 64.3 (63.6-64.9) | 82.5 (82.2-82.7) | 77.9 (77.6-78.3) |
| 50% | ≥0.792 | 22,832 | 5,587 | 17,490 | 10,925 | 66.2(65.4-67.0) | 56.6 (56.1-57.1) | 1.53 (1.50-1.55) | 0.60 (0.58-0.61) | 38.5 (38.1-38.8) | 80.3 80.0-80.7) | 59.4 (59.0-59.8) |
| 25% | ≥0.684 | 11,780 | 2,430 | 28,600 | 14,024 | 85.2 (84.7-85.8) | 29.2 (28.7-29.6) | 1.20 (1.19-1.21) | 0.51 (0.49-0.53) | 32.9 (32.7-33.1) | 82.9 (82.3-83.5) | 45.4 (45.0-45.8) |
| 10% | ≥0.591 | 4,596 | 1,122 | 35,793 | 15,323 | 93.2 (92.8-93.6) | 11.4 (11.1-11.7) | 1.05 (1.05-1.06) | 0.60 (0.56-0.64) | 30.0 (29.9-30.1) | 80.4 (79.4-81.4) | 35.1 (34.7-35.4) |
| 5% | ≥0.506 | 2,351 | 533 | 38,042 | 15,908 | 96.8 (96.5-97.0) | 5.82 (5.59-6.05) | 1.03 (1.02-1.03) | 0.56 (0.51-0.61) | 29.5 (29.4-29.6) | 81.5 (80.1-82.9) | 32.1 (31.7-32.5) |

Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages] The threshold of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals..

### 4.4.7 Prediction equations for low back pain recurrence within 12 months.

Basing on the derived parsimonious model, individualized probability of low back recurrence within follow up time (t=12 months) for an individual with covariate values x = $(x_1,...,x_k)$ for K risk factors can be estimated using the following equation:

$$P(\text{Low Back Recurrence}) = 1 - S_o(t)^{\exp[(fx)]}, \text{ where}$$

$$f(x) = \sum_i \beta_i x_i$$

In the above equation, $S_o(t)$ is the baseline survival probability at time (t) for an individual with all covariates equivalent to zero (0), and the $\beta_i$ are the estimated coefficients from the Cox proportional hazard model in 12-month recurrence outcome. Using the estimated coefficients $\beta_i$ and survival probabilities $S_o(t)$, personalized probabilities of low back pain recurrence within 12 months can be calculated. The Youden's J statistic suggested a risk probability of ≥0.839 as the optimal cutoff point to define high-risk individuals based on the prediction equation. This threshold showed a sensitivity of 53.3% (95% CI, 52.5%-54.1%), specificity of 90.8% (95% CI, 90.5%-91.1%), positive likelihood ratio (LR+) of 5.81 (95% CI, 5.62-6.01), negative likelihood ratio (LR-) of 0.51 (95% CI, 0.51-0.52), positive predictive value (PPV) of 70.5% (95% CI, 69.8%-71.2%), negative predictive value (NPV) of 82.6% (95%

CI, 82.3%-82.8%) and accuracy of 79.9% (95% CI, 79.6%-80.2%) in prediction of the risk of low back pain recurrence over 12 months in the validation cohort (Table 32).

### 4.4.8 Simplified risk score for prediction of 12-months low back pain recurrence

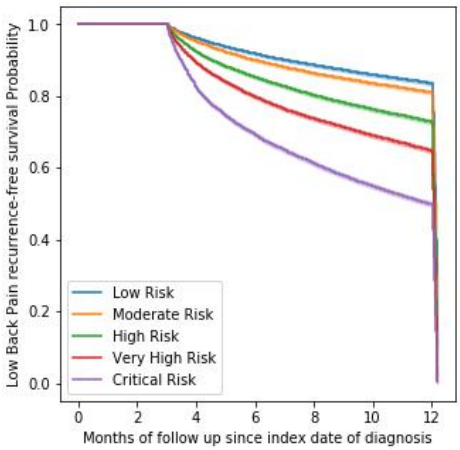
Table 31 present the regression coefficients for the Cox Proportional hazard model fit to the derivation cohort. In the right-most column of the table are the points associated with the presence of a given level of a risk factor (with the reference level assigned zero points). The points were determined by multiplying the regression coefficient by 100 and rounding to the nearest integer. Advanced age (≥65 years old) conferred the highest risk (82 points). Among modifiable risk factors, lower BMI was the most protective risk factor (-9 points) whereas moderate alcohol consumption also showed moderate protective potential (-4 points). In addition, more than 4 days of previous consultations was predictive and a significant risk factor for low back pain recurrence within 12 months (67 points) (Table 31).

Participants in the overall sample were divided into five equally sized risk strata using the quintiles of the empirical risk score and randomly assigned to the derivation (2/3) and validation cohorts (1/3), respectively. Table 34 presents the cumulative incidence probabilities for low back pain recurrence within 12-months in each of the risk strata in the derivation and validation cohorts. In the overall

sample, there were statistically significant differences in the cumulative incidence risk probabilities across the five risk strata based on the Cochran–Armitage test for trend ($p$<.0001). There was a clearly defined gradation in the risk of low back pain recurrence within 12 months across the five risk strata. The lowest risk stratum comprised subjects with the lowest low back pain recurrence during 12 months of follow-up. In contrast, the highest risk stratum consisted of subjects with a very high low back pain recurrence during 12 months of follow-up. The twelve-months cumulative incidence risk of low back pain recurrence in the lowest and highest risk strata in the derivation cohort were 78.8 (95% CI, 66.3 to 89.1) and 99.5 (95% CI, 97.7 to 100.0 ), respectively. Thus, the incidence of low back pain at 12 months was greater in the highest risk stratum than in the lowest risk stratum, and the hazard ratio (HR) was 3.90 times greater (Table 34). Figure 16 presents the survival trends over 12 months for participants based on the risk score strata.

**Figure 16. Kaplan-Meier curves for 12-months low back pain recurrence-free survival in five (5) risk groups in the derivation and validation cohorts based on the simplified points based risk score. (A) Derivation. (B) Validation**

**A** **B**


Low Back Pain recurrence-free survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Low Risk
Moderate Risk
High Risk
Very High Risk
Critical Risk
0
2
4
6
8
10
12
Months of follow up since index date of diagnosis

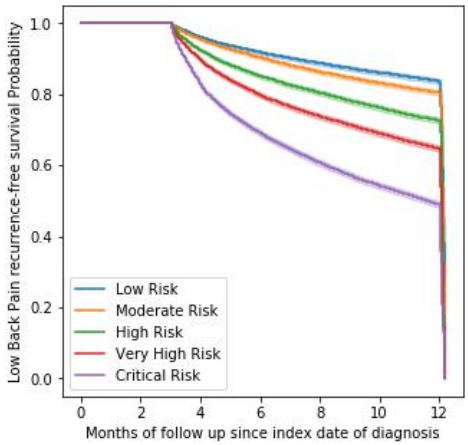

Low Back Pain recurrence-free survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Low Risk
Moderate Risk
High Risk
Very High Risk
Critical Risk
0
2
4
6
8
10
12
Months of follow up since index date of diagnosis

**Table 34. Risk of low back pain recurrence within 12 months in the derivation cohorts based on the risk score strata (quintiles)**

| Risk of low back pain recurrence within 12 months in the derivation cohort based on to risk category | | | | | | |
|---|---|---|---|---|---|---|
| **Risk Strata** | **Risk Score Range** | **Non-Event (%)** | **Event (%)** | **Total** | **CR (95% CI)** | **HR (95% CI), *P* value** |
| Low Risk | <15 | 18,792 (85.0) | 3,318 (15.0) | 22,110 | 78.8 (66.3 to 89.1) | Reference |
| Moderate Risk | 15 to 40 | 18,792 (82.1) | 4,208 (17.9) | 23,490 | 92.5 (83.7 to 97.5) | 1.18 (1.13 to 1.23), *p*<.0001 |
| High Risk | 41 to 72 | 16,672 (73.8) | 5,935 (26.2) | 22,607 | 93.5 (93.5 to 97.3) | 1.78 (1.70 to 1.85), *p*<.0001 |
| Very High Risk | 73 to 102 | 14,681 (65.3) | 7,792 (34.7) | 22,473 | 99.2 (95.9 to 99.9) | 2.44 (2.34 to 2.54), *p*<.0001 |
| Critical Risk | >102 | 11,616 (50.1) | 11,599 (49.9) | 23,215 | 99.5(97.7 to 100.0 ) | 3.90 (3.75 to 4.05), *p*<.0001 |
| **Risk of low back pain recurrence within 12 months in the validation cohort, according to risk category** | | | | | | |
| **Risk Strata** | **Risk Score Range** | **Non-Event (%)** | **Event (%)** | **Total** | **CR (95% CI)** | **Hazard Ratios (95% CI)** |
| Low Risk | <15 | 9,303 (85.0) | 1,639 (15.0) | 10,942 | 72.6 (54.9 to 87.8) | Reference |
| Moderate Risk | 15 to 40 | 9,508 (81.5) | 2,153 (18.5) | 11,661 | 94.6 (84.4 to 99.0) | 1.22 (1.14-1.30), *p*<.0001 |
| High Risk | 41 to 72 | 8,318 (73.6) | 2,992 (26.4) | 11,310 | 97.5 ( 88.9 to 99.8) | 1.80 (1.69-1.91), *p*<.0001 |
| Very High Risk | 73 to 102 | 7,321 (65.3) | 3,888 (34.7) | 11,209 | 100.0 (100.0 to 100.0) | 2.46 ( 2.32 to 2.60), *p*<.0001 |
| Critical Risk | >102 | 5,774 (49.3) | 5,938 (50.7) | 11,712 | 100.0 (100.0 to 100.0) | 4.01 (3.78 to 4.24), *p*<.0001 |
| **Average 12 months baseline survival=0.6989** | | | | | | |

CR*=Cumulative Risk

†Cochran–Armitage test for trend (for overall cohort), *P* <.0001.

### 4.4.9 Validation of the simplified risk score at different risk score thresholds

The theoretical minimum and maximum sum of the points were -13 and 240, respectively. The median score was 59, while the 25$^{th}$ and 75$^{th}$ percentiles were 19 and 93, respectively. Table 35 shows the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy for low back pain recurrence risk score for various risk score thresholds based on subjects in the derivation and validation cohorts. The risk score threshold for the top 3% at highest risk of low back pain recurrence in the next 12 months was 171, for the top 5% was 158, for the top 10% was 133, for the top 25% was 93, and for the top 50% was 59 in both cohorts. With a risk score threshold of 133 over 12 months to identify the 10% of participants with the highest risk of low back pain recurrence, the sensitivity for identifying 12 month low back pain recurrence was 19.9% (95% CI, 19.3%-20.5%), specificity 93.7% (95% CI, 93.5%-94.0%), positive predictive value 56.3% (95% CI, 55.1%-57.5%), negative predictive value 74.2 (95% CI, 74.1%-74.4%), and accuracy value 72.4% (95% CI, 72.0%-72.8%) in the validation cohort (Table 35). The corresponding thresholds for risk of experiencing low back pain recurrence over 12 months and the risk score's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 35).

The Youden's J statistic suggested a risk score of ≥68 as the optimal cut-off point to define high-risk individuals based on the simplified risk score. This threshold showed a sensitivity of 62.3% (95% CI, 61.6%-63.0%), specificity of

64.8% (95% CI, 64.3%-65.3%), positive likelihood ratio (LR+) of 1.77 (95% CI, 1.74-1.80), negative likelihood ratio (LR-) of 0.58 (95% CI, 0.57-0.59), positive predictive value (PPV) of 42.2% (95% CI, 41.8%-42.6%), negative predictive value (NPV) of 80.7% (95% CI, 80.3%-81.0%) and accuracy of 64.1% (95% CI, 63.7%-64.5%) in prediction of the risk of low back pain recurrence over 12 months in the validation cohort (Table 35).

**Table 35. Sensitivity, specificity, likelihood ratios, predictive values for low back pain at different thresholds of 12-months low back pain recurrence risk score in the derivation and validation cohorts**

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values for low back pain at different thresholds of the risk score of low back pain recurrence over 12 months in derivation cohort**

| Threshold (Centiles) | Risk score threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥191 | 80,516 | 32,193 | 384 | 802 | 2.43 (2.27-2.60) | 99.5 (99.5-99.6) | 5.12 (4.54-5.78) | 0.98 (0.98-0.98) | 67.6 (64.9-70.2) | 71.4 (71.4-71.5) | 71.4 (71.1-71.7) |
| 97% | ≥171 | 79,646 | 30,767 | 1,240 | 2,242 | 6.79 (6.52-7.07) | 98.5 (98.4-98.6) | 4.43 (4.14-4.74) | 0.95 (0.94-0.95) | 64.4 (62.8-65.9) | 72.1 (72.1-72.2) | 71.9 (71.6-72.2) |
| 95% | ≥158 | 78,646 | 29,411 | 2,270 | 3,568 | 10.8 (10.5-11.2) | 97.2 (97.1-97.3) | 3.86 (3.66-4.06) | 0.92 (0.91-0.92) | 61.1 (59.9-62.3) | 72.8 (72.7-72.9) | 72.2 (71.9-72.4) |
| 90% | ≥133 | 75,942 | 26,471 | 4,901 | 6,581 | 19.9 (19.5-20.4) | 93.9 (93.8-94.1) | 3.28 (3.17-3.40) | 0.85 (0.85-0.86) | 57.3 (56.5-58.2) | 74.2 (74.0-74.3) | 72.5 (72.2-72.7) |
| 75% | ≥93 | 65,926 | 19,258 | 15,030 | 13,681 | 41.5 (41.0-42.1) | 81.4 (81.2-81.7) | 2.24 (2.19-2.28) | 0.72 (0.71-0.72) | 47.7 (47.2-48.1) | 77.4 (77.2-77.6) | 69.9 (69.6-70.2) |
| **‡56.9%** | ≥68 | 52,270 | 12,401 | 28,749 | 20,475 | 62.3 (61.8-62.8) | 64.5 (64.2-64.9) | 1.76 (1.73-1.78) | 0.58 (0.58-0.59) | 41.6 (41.3-41.9) | 80.8 (80.6-81.1) | 63.9 (63.6-64.2) |
| 50% | ≥59 | 46,528 | 10,267 | 34,406 | 22,694 | 68.9 (68.4-69.4) | 57.5 (57.2-57.8) | 1.62 (1.60-1.64) | 0.54 (0.53-0.55) | 39.7 (39.5-40.0) | 81.9 (81.7-82.2) | 60.8 (60.5-61.1) |
| 25% | ≥19 | 23,657 | 4,250 | 57,242 | 28,746 | 87.1 (86.8-87.5) | 29.2 (28.9-29.6) | 1.23 (1.22-1.24) | 0.44 (0.43-0.45) | 33.4 (33.3-33.6) | 84.8 (84.4-85.2) | 46.0 (45.7-46.3) |
| 10% | ≥6 | 8,801 | 1,567 | 72,018 | 31,509 | 95.3 (95.0-95.5) | 10.9 (10.7-11.1) | 1.07 (1.07-1.07) | 0.44 (0.41-0.46) | 30.4 (30.4-30.5) | 84.9 (84.2-85.5) | 35.4 (35.1-35.7) |
| 5% | ≥2 | 3,467 | 574 | 77,428 | 32,426 | 98.3 (98.1-98.4) | 4.29 (4.15-4.43) | 1.03 (1.02-1.03) | 0.41 (0.37-0.44) | 29.5 (29.5-29.6) | 85.8 (84.7-86.8) | 31.5 (31.2-31.8) |

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values for low back pain at different thresholds of risk score of low back pain recurrence over 12 months in validation cohort**

| Threshold (Centiles) | Risk score threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥191 | 40,175 | 16,064 | 192 | 403 | 2.45 (2.22-2.69) | 99.5 (99.5-99.6) | 5.15 (4.34-6.10) | 0.98 (0.98-0.98) | 67.7 (63.9-71.4) | 71.4 (71.4-71.5) | 71.4 (71.0-71.8) |
| 97% | ≥171 | 39,768 | 15,335 | 613 | 1,118 | 6.80 (6.42-7.19) | 98.5 (98.4-98.6) | 4.48 (4.06-4.93) | 0.95 (0.94-0.95) | 64.6 (62.3-66.8) | 72.2 (72.1-72.3) | 71.9 (71.6-72.3) |
| 95% | ≥158 | 39,255 | 14,716 | 1,096 | 1,767 | 10.7 (10.3-11.2) | 97.3 (97.1-97.4) | 3.95 (3.67-4.25) | 0.92 (0.91-0.92) | 61.7 (60.0-63.4) | 72.7 (72.6-72.8) | 72.2 (71.8-72.6) |
| 90% | ≥133 | 37,892 | 13,148 | 2532 | 3,262 | 19.9 (19.3-20.5) | 93.7 (93.5-94.0) | 3.17 (3.02-3.33) | 0.85 (0.85-0.86) | 56.3 (55.1-57.5) | 74.2 (74.1-74.4) | 72.4 (72.0-72.8) |
| 75% | ≥93 | 32,878 | 9,650 | 7,433 | 6,873 | 41.6 (40.8-42.4) | 81.6 (81.2-81.9) | 2.26 (2.20-2.32) | 0.72 (0.71-0.73) | 48.0 (47.4-48.7) | 77.3 (77.1-77.6) | 69.9 (69.6-70.3) |
| **‡56.9%** | ≥68 | 26,081 | 6,252 | 14,167 | 10,334 | 62.3 (61.6-63.0) | 64.8 (64.3-65.3) | 1.77 (1.74-1.80) | 0.58 (0.57-0.59) | 42.2 (41.8-42.6) | 80.7 (80.3-81.0) | 64.1 (63.7-64.5) |
| 50% | ≥59 | 23,198 | 5,160 | 17,135 | 11,341 | 68.7 (68.0-69.4) | 57.5 (57.0-58.0) | 1.62 (1.59-1.64) | 0.54 (0.53-0.56) | 39.8 (39.5-40.2) | 81.8 (81.4-82.2) | 60.8 (60.4-61.2) |
| 25% | ≥19 | 11,818 | 2,128 | 28,550 | 14,338 | 87.1 (86.6-87.6) | 29.3 (28.8-29.7) | 1.23 (1.22-1.24) | 0.44 (0.42-0.46) | 33.4 (33.2-33.6) | 84.7 (84.2-85.3) | 46.0 (45.6-46.4) |
| 10% | ≥6 | 4,443 | 733 | 36,005 | 15,653 | 95.5 (95.2-95.8) | 11.0 (10.7-11.3) | 1.07 (1.07-1.08) | 0.41 (0.38-0.44) | 30.3 (30.2-30.4) | 85.8 (84.9-86.7) | 35.4 (35.0-35.8) |
| 5% | ≥2 | 1,750 | 316 | 38,622 | 16,146 | 98.1 (97.9-98.3) | 4.33 (4.14-4.54) | 1.0 (1.02-1.03) | 0.44 (0.39-0.50) | 29.5 (29.4-29.5) | 84.7 (83.1-86.2) | 31.5 (31.1-31.9) |

Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages]. The threshold of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.4.10 Practical application of the risk score for low back pain recurrence

The following example illustrates how the risk of low back pain recurrence within 12 months can be estimated using the simplified points based system.

**Case**: A 70-year-old female with an insurance premium of 30-60%, who does not exercise, moderately consumes alcohol, with normal BMI (>18.5 kg/m$^2$-24.9 kg/m$^2$), SBP 140-159 or DBP 90-99 mmHg, with no history of IVDD, no spinal stenosis, no history of back injury and no history of spondylolisthesis, but with history of bone mineral density disorders and with more than 4 times of previous low back pain consultations (medical utilisation due to low back pain) (Table 36).

**Table 36. Table of calculated 12-months low back pain recurrence risk score for a hypothetical example of a risk profile**

| Risk Factor (Predictor) | Value (Risk Factor Category) | Risk Points |
|---|---|---|
| Female | Female | 13 |
| Age | >65 yrs | 82 |
| Income/Insurance | Medium (30-60%) | 6 |
| Physical activity | None | 3 |
| Alcohol consumption | Moderate drinker (2–3 | -4 |
| Body Mass Index | >18.5 kg/m$^2$-24.9 kg/m$^2$ | 0 |
| Hypertension status | SBP 140-159 or DBP 90-99 | 5 |
| Diagnosed IVDD | No | 0 |
| History of Back Injury | No | 0 |
| Spinal Stenosis | No | 0 |
| History of BMD disorders | Yes | 11 |
| Spondylolisthesis | No | 0 |
| Days of consultation | ≥ 4 days | 67 |
| **Total Points** | | **183** |
| **Estimate of Risk** | | **0.893** |

***$S_o$ (t) = 0.6989**

Based on the above hypothetical risk profile, the probability of low back pain recurrence within 12 months can be estimated as follows;

$$P(\text{Low Back Pain recurrence}) = 1 - S_o(t)^{\exp[(Score/100)]}$$
$$P(\text{Low Back Pain recurrence}) = 1 - (0.6989)^{\exp[(183/100)]}$$
$$= 0.893$$

The $S_0(t)$ is the baseline survival probability at time (t=12 months) for an individual with all covariates equivalent to zero, which was estimated by Cox regression analysis. The beta coefficients were converted to integer risk points by multiplying with 100. Thus, in the actual calculation, the sum of risk score (183 risk points) was divided by 100 to give an overall 12-months risk estimate.

# 4.5. Modelling low back pain recurrence using Prentice, Williams and Peterson Gap Time models

### 4.5 Modelling low back pain using Prentice, Williams and Peterson models

Previous studies have defined an episode of care for low back pain as a consultation or series of consultations for low back pain, preceded and followed by at least three months without consultation for low back pain [106]. In modelling recurrent events, considerations should be made for the intrinsic correlation between episodes occurring in the same subject [451]. The original Cox proportional hazard model is only appropriate for modelling time to the first event [452], which neglects data from subsequent episodes [451]. Several extensions of Cox model are appropriate for analysis of recurrent event data such as Andersen-Gill model (AG)[453], Prentice, Williams and Peterson (PWP) (total and gap times) [389], Wei, Lin and Weissfeld (WLW) [454], and frailty models [455].

In this study, Prentice, Williams, and Peterson (PWP) (gap times) models were used to assess effects of predictors on low back pain episodes. This model analyses ordered multiple events by stratification, based on the prior number of events [389], which was in this case episodes of low back pain during the follow-up period. The gap time is the time since the previous event [451], which corresponds to the time to event in original Cox proportional hazard model. The model assumes a renewal process [451], and the time index is reset to zero after each episode. This model is suitable for analysis when a previous event increases the risk of relapse [451], as the case for low back pain [52]. The PWP models assume that recurrent event within subject are related and baseline hazard varies

from event to event [456]. The PWP models have event-specific baseline hazard, and can estimate both overall effect and event specific effect for each covariate [456]. The hazard at time t for the $j^{th}$ recurrence or episode is conditional on the entire previous events [457]. In this model, robust sandwich variance estimators for standard errors of coefficients can be calculated, and these do not require specification of the correlation matrix [454]. However, as the event order increases, the number of subjects in the risk set decreases, therefore, PWP model can give unreliable estimates for higher order events [456].

### 4.5.1 Association between risk factors and low back pain episodes

Tables 37 present the estimated coefficients and hazard ratios from unadjusted, partially adjusted, and fully adjusted analyses based on Prentice, Williams, and Peterson gap times models. There were associations between sex, older age, low income, physical activity, FBG, Blood pressure/HTN, total cholesterol, BMI and alcohol consumption with low back pain recurrence (multiple episodic) ($p$<0.05) (Table 37). Smoking status and alcohol consumption were inversely associated with LBP recurrence, whereas metabolic syndrome (MetS) variables were associated with LBP recurrence ($p$<0.05) (Table 37). In addition, premorbid spondylolisthesis and history of back injury showed inverse associations with low back pain recurrence in univariate analysis whereas spinal stenosis, IVDD and BMD were positively associated with low back pain recurrence ($p$<0.05) (Table 37).

In the univariate and fully adjusted models, a low total number of days of prescription (duration of medication) was associated with low back pain recurrence whereas high number of days of hospital admission (duration of hospitalisation) and high frequency of consultations were positively associated with low back pain recurrence ($p<0.05$) (Table 37). In univariate analysis, the stratification variable (number of preceding episodes) was positively associated with low back pain recurrence. Table 37 provides details of associations for all covariates.

**Table 37. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors in the univariate, partially adjusted and fully adjusted models using Prentice, Williams and Peterson Gap time Models with Sandwich Variance Estimates.**

| Covariate | Unadjusted* | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | β (SE) | HR (95% | *P* Value | β (SE) | HR (95% CI) | *P* | β (SE) | HR (95% CI) | *P* Value |
| **Sex** | | | | | | | | | |
| Female | 0.288 (0.004) | 1.33 (1.32-1.34) | <.0001 | 0.276 (0.004) | 1.32 (1.31-1.33) | <.0001 | 0.115 (0.005) | 1.12 (1.11-1.13) | <.0001 |
| **Age** | | | | | | | | | |
| <45 yrs. | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 45-54 yrs | 0.038 (0.005) | 1.04 (1.03-1.05) | <.0001 | 0.020 (0.005) | 1.02 (1.01-1.03) | <.0001 | 0.013 (0.005) | 1.01 (1.00-1.02) | 0.0103 |
| 55-64 yrs | 0.283 (0.005) | 1.33 (1.32-1.34) | <.0001 | 0.262 (0.005) | 1.30 (1.29-1.31) | <.0001 | 0.232 (0.005) | 1.26 (1.25-1.27) | <.0001 |
| ≥ 65 yrs | 0.446 (0.005) | 1.56 (1.55-1.58) | <.0001 | 0.427 (0.005) | 1.53 (1.52-1.55) | <.0001 | 0.376 (0.005) | 1.46 (1.44-1.47) | <.0001 |
| **Occupation/Income** | | | | | | | | | |
| High (>60%) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Medium (30-60%) | 0.064 (0.004) | 1.07 (1.06-1.07) | <.0001 | 0.082 (0.004) | 1.09 (1.08-1.09) | <.0001 | 0.073 (0.004) | 1.08 (1.07-1.08) | <.0001 |
| Low (<30%) | 0.110 (0.005) | 1.12 (1.106- | <.0001 | 0.073 (0.005) | 1.08 (1.07-1.09) | <.0001 | 0.064 (0.005) | 1.07 (1.06-1.08) | <.0001 |
| **Physical Activity/Week** | | | | | | | | | |
| High (≥ 3 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate (1-2 times) | -0.226 (0.006) | 0.80 (0.79-0.81) | <.0001 | -0.146 (0.006) | 0.86 (0.85-0.87) | <.0001 | -0.138 (0.006) | 0.87 (0.86-0.88) | <.0001 |
| Low (None) | 0.011 (0.005) | 1.01 (1.00-1.02) | 0.0245 | 0.023 (0.005) | 1.02 (1.01-1.03) | <.0001 | 0.014 (0.005) | 1.01 (1.00-1.03) | 0.0093 |
| **Smoking Status** | | | | | | | | | |
| Never | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Former | -0.527 (0.009) | 0.59 (0.58-0.60) | <.0001 | -0.404 (0.009) | 0.67 (0.66-0.68) | <.0001 | -0.365 (0.009) | 0.69 (0.68-0.71) | <.0001 |
| Current Smoker | -0.269 (0.005) | 0.76 (0.76-0.77) | <.0001 | -0.113 (0.006) | 0.89 (0.88-0.90) | <.0001 | -0.087 (0.006) | 0.92 (0.91-0.93) | <.0001 |
| **Alcohol** | | | | | | | | | |
| Rarely (< 2 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate drinker (2–3 times) | -0.319 (0.004) | 0.73 (0.72-0.73) | <.0001 | -0.164 (0.004) | 0.85 (0.84-0.86) | <.0001 | -0.132 (0.005) | 0.88 (0.87-0.88) | <.0001 |
| Heavy drinker ( ≥ 4 times) | -0.301 (0.006) | 0.74 (0.73-0.75) | <.0001 | -0.143 (0.007) | 0.87 (0.86-0.88) | <.0001 | -0.113 (0.007) | 0.89 (0.88-0.91) | <.0001 |
| **Body Mass Index** | | | | | | | | | |
| < 18.5 kg/$m^2$ | -0.052 (0.009) | 0.95 (0.93-0.97) | <.0001 | -0.088 (0.010) | 0.92 (0.90-0.93) | <.0001 | -0.106 (0.010) | 0.90 (0.88-0.92) | <.0001 |

| Covariate | Unadjusted* | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | β (SE) | HR (95% | *P* Value | β (SE) | HR (95% CI) | *P* | β (SE) | HR (95% CI) | *P* Value |
| 18.5 kg/m$^2$-24.9 kg/m$^2$ | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 25 kg/m$^2$-29.9 kg/m$^2$ | 0.048 (0.003) | 1.05 (1.04-1.06) | <.0001 | 0.050 (0.003) | 1.05 (1.05-1.06) | <.0001 | 0.057 (0.004) | 1.06 (1.05-1.07) | <.0001 |
| ≥ 30 kg/m$^2$ | 0.037 (0.008) | 1.04 (1.02-1.05) | <.0001 | 0.027 (0.008) | 1.03 (1.01-1.04) | 0.0013 | 0.027 (0.008) | 1.03 (1.01-1.05) | 0.0009 |
| **Fasting Blood Glucose** | | | | | | | | | |
| < 100 mg/dL | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 100 mg/dL-125 mg/dL | 0.019 (0.004) | 1.02 (1.01-1.03) | <.0001 | 0.001 (0.004) | 1.00 (0.99-1.01) | 0.7228 | 0.009 (0.004) | 1.01 (1.00-1.02) | 0.0164 |
| >126 mg/dL Or Rx | 0.062 (0.006) | 1.06 (1.05-1.08) | <.0001 | 0.009 (0.006) | 1.01 (0.99-1.02) | 0.1516 | 0.012 (0.006) | 1.01 (1.00-1.02) | 0.0525 |
| **Total Cholesterol** | | | | | | | | | |
| < 200 mg/dL | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 200 mg/dL-239 mg/dL | 0.048 (0.003) | 1.05 (1.04-1.06) | <.0001 | 0.021 (0.004) | 1.02 (1.01-1.03) | <.0001 | 0.026 (0.004) | 1.03 (1.02-1.03) | <.0001 |
| > 240 mg/dL | 0.115 (0.005) | 1.12 (1.11-1.13) | <.0001 | 0.061 (0.005) | 1.06 (1.05-1.07) | <.0001 | 0.065 (0.005) | 1.07 (1.06-1.08) | <.0001 |
| **Blood Pressure/HTN** | | | | | | | | | |
| SBP < 120 and DBP < 80 | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| SBP 120-139 or DBP 80-89 | 0.140 (0.004) | 1.15 (1.14-1.16) | <.0001 | 0.128 (0.004) | 1.14 (1.13-1.15) | <.0001 | 0.132 (0.004) | 1.14 (1.13-1.15) | <.0001 |
| SBP 140-159 or DBP 90-99 | 0.312 (0.005) | 1.37 (1.35-1.38) | <.0001 | 0.252 (0.005) | 1.29 (1.27-1.30) | <.0001 | 0.251 (0.006) | 1.29 (1.27-1.30) | <.0001 |
| SBP ≥ 160 or DBP ≥ 100 or Rx | 0.372 (0.010) | 1.45 (1.42-1.48) | <.0001 | 0.289 (0.010) | 1.34 (1.31-1.36) | <.0001 | 0.282 (0.010) | 1.33 (1.30-1.35) | <.0001 |
| Diagnosed IHD | 0.289 (0.189) | 1.34 (0.92-1.93) | 0.1257 | 0.123 (0.193) | 1.13 (0.78-1.65) | 0.5244 | 0.127 (0.195) | 1.14 (0.78-1.67) | 0.5151 |
| Diagnosed IVDD | 0.066 (0.005) | 1.07 (1.06-1.08) | <.0001 | 0.109 (0.005) | 1.12 (1.10-1.13) | <.0001 | 0.113 (0.005) | 1.12 (1.11-1.13) | <.0001 |
| History of Back Injury | -0.009 (0.019) | 0.99 (0.96-1.03) | 0.6373 | 0.055 (0.020) | 1.06 (1.02-1.10) | 0.0051 | 0.064 (0.020) | 1.07 (1.03-1.11) | 0.0014 |
| History of BMD Disorder | 0.198 (0.007) | 1.22 (1.20-1.24) | <.0001 | 0.668 (0.011) | 1.95 (1.91-1.99) | <.0001 | 0.093 (0.008) | 1.10 (1.08-1.11) | <.0001 |
| Spinal Stenosis | 0.063 (0.008) | 1.07 (1.05-1.08) | <.0001 | 0.013 (0.008) | 1.01 (0.99-1.03) | 0.1231 | 0.013 (0.008) | 1.01 (0.99-1.03) | 0.1144 |
| Spondylolisthesis | -0.033 (0.024) | 0.97 (0.92-1.01) | 0.1678 | -0.069 (0.024) | 0.93 (0.89-0.98) | 0.0048 | -0.067 (0.025) | 0.94 (0.89-0.98) | 0.0067 |
| **Number of Consultations** | | | | | | | | | |
| 1 day | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 2-3 days | 0.841 (0.004) | 2.32 (2.30-2.34) | <.0001 | 0.810 (0.005) | 2.25 (2.23-2.27) | <.0001 | 0.802 (0.005) | 2.23 (2.21-2.25) | <.0001 |
| ≥4 days | 0.790 (0.007) | 2.20 (2.17-2.23) | <.0001 | 0.739 (0.007) | 2.09 (2.07-2.12) | <.0001 | 0.723 (0.007) | 2.06 (2.03-2.09) | <.0001 |
| **Length of Prescription** | | | | | | | | | |
| ≥8 days | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 1-7 days | 0.246 (0.005) | 1.28 (1.27-1.29) | <.0001 | 0.329 (0.005) | 1.39 (1.38-1.41) | <.0001 | 0.324 (0.005) | 1.38 (1.37-1.40) | <.0001 |

| Covariate | Unadjusted∗ | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | β (SE) | HR (95% | *P* Value | β (SE) | HR (95% CI) | *P* | β (SE) | HR (95% CI) | *P* Value |
| None | 0.358 (0.006) | 1.43 (1.42-1.45) | <.0001 | 0.400 (0.006) | 1.49 (1.47-1.51) | <.0001 | 0.392 (0.006) | 1.48 (1.46-1.50) | <.0001 |
| **Length of Hospitalisation** | | | | | | | | | |
| 1 day | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 2-4 days | 0.818 (0.004) | 2.27 (2.25-2.28) | <.0001 | 0.788 (0.004) | 2.20 (2.18-2.22) | <.0001 | 0.780 (0.004) | 2.18 (2.16-2.20) | <.0001 |
| ≥5 days | 0.420 (0.007) | 1.52 (1.50-1.54) | <.0001 | 0.369 (0.007) | 1.45 (1.43-1.45) | <.0001 | 0.353 (0.007) | 1.42 (1.40-1.44) | <.0001 |
| Preceding Episodes | 0.189 (0.0009) | 1.21 (1.21-1.21) | <.0001 | **Stratification variable** | | | **Stratification variable** | | |

∗Unadjusted/Univariate analysis. †Partially adjusted models account for age, sex and each variable added. ‡Fully adjusted models account for Age, Sex, Income grade, Physical activity, Smoking status, alcohol consumption and each of the other risk factors [* Mets (Fasting Blood Glucose/ diabetes, Total Cholesterol, Blood Pressure/HTN, prior history of IHD, Ischemic Heart Disease] and (IVDD, Intervertebral Disc Degeneration; spondylolisthesis, spinal Stenosis; BMD, Bone Mineral Density Disorders; history of back injury)]. .

### 4.5.2 Modelling recurrence using Prentice, Williams, and Peterson models

After screening predictors based on the univariate and hierarchical cluster analysis, 16 variables including sex, age, smoking status, alcohol consumption, income grade (insurance premium), physical activity, BMI, fasting blood glucose, blood pressure, total cholesterol, disc degeneration (DD), history of back injury, bone mineral density disorders, spinal stenosis, spondylolisthesis and total days of prescription were included in the model derivation. After applying the backward variable selection procedure at $\alpha$=0.15, taking into consideration the numbers of cases for reliable variable selection ($\geq$10 cases per variable), 13 variables were retained in the parsimonious model (Table 38). The variables retained in the parsimonious model included age, sex, income grade, physical activity, smoking, alcohol consumption, BMI, fasting blood glucose, blood pressure, total cholesterol, IVDD, history of bone mineral density disorders and duration of prescription (days) (Table 38).

**Table 38. Hazard Ratios (95% confidence interval) and β-coefficients for risk predictors in the parsimonious model using Prentice, Williams, and Peterson Gap time Models**

| Covariate | $\beta$ (SE) | HR (95% CI) | *P* Value |
|---|---|---|---|
| **Sex** | | | |
| Female | 0.136 (0.005) | 1.15 (1.14-1.16) | <.0001 |
| **Age** | | | |
| <45 yrs. | Reference | Reference | |
| 45-54 yrs | -0.029 (0.006) | 0.97 (0.96-0.98) | <.0001 |
| 55-64 yrs | 0.207 (0.006) | 1.23 (1.22-1.24) | <.0001 |

| Covariate | $\beta$ (SE) | HR (95% CI) | *P* Value |
|---|---|---|---|
| ≥65 yrs | 0.341 (0.006) | 1.41 (1.39-1.42) | <.0001 |
| **Income/Insurance premium** | | | |
| High (<60%) | Reference | Reference | |
| Medium (30-60%) | 0.070 (0.004) | 1.07 (1.06-1.08) | <.0001 |
| Low (<30%) | 0.024 (0.005) | 1.02 (1.01-1.03) | <.0001 |
| **Physical Activity** | | | |
| High (≥3 times/week) | Reference | Reference | |
| Moderate (1-2 times/week) | -0.138 (0.007) | 0.87 (0.86-0.86) | <.0001 |
| Low (None) | 0.020 (0.006) | 1.02 (1.01-1.03) | 0.0007 |
| **Smoking Status** | | | |
| Never | Reference | Reference | |
| Former Smoker | -0.323 (0.008) | 0.72 (0.71-0.74) | <.0001 |
| Current Smoker | -0.077 (0.006) | 0.93 (0.92-0.94) | <.0001 |
| **Alcohol** | | | |
| Rarely (< 2 times) | Reference | Reference | |
| Moderate drinker (2–3 times) | -0.135 (0.005) | 0.87 (0.87-0.88) | <.0001 |
| Heavy drinker ( ≥ 4 times) | -0.105 (0.007) | 0.90 (0.89-0.91) | <.0001 |
| **Body Mass Index** | | | |
| <18.5 $kg/m^2$ | -0.073 (0.009) | 0.93 (0.91-0.95) | <.0001 |
| 18.5 $kg/m^2$-24.9 $kg/m^2$ | Reference | Reference | |
| 25 $kg/m^2$-29.9 $Kgm^2$ | 0.039 (0.004) | 1.04 (1.03-1.05) | <.0001 |
| ≥30 $kg/m^2$ | 0.006 (0.009) | 1.01 (0.99-1.02) | 0.4986 |
| **Total Cholesterol** | | | |
| <200 mg/dL | Reference | Reference | |
| 200 mg/dL-239 mg/dL | 0.015 (0.004) | 1.02 (1.01-1.02) | 0.0001 |
| >240 mg/dL | 0.048 (0.005) | 1.05 (1.04-1.06) | <.0001 |
| **Fasting Blood Glucose** | | | |
| < 100 mg/dL | Reference | Reference | |
| 100 mg/dL-125 mg/dL | 0.0003 (0.004) | 1.00 (0.99-1.01) | 0.9402 |
| ≥126 mg/dL Or Rx | 0.016 (0.006) | 1.02 (1.00-1.03) | 0.0123 |
| **Blood Pressure/HTN** | | | |
| SBP < 120 and DBP < 80 | Reference | Reference | |
| SBP 120-139 or DBP 80-89 | 0.129 (0.004) | 1.14 (1.13-1.15) | <.0001 |
| SBP 140-159 or DBP 90-99 | 0.249 (0.006) | 1.28 (1.27-1.30) | <.0001 |
| SBP ≥ 160 or DBP ≥100 or Rx | 0.282 (0.011) | 1.33 (1.30-1.36) | <.0001 |
| Diagnosed IVDD | 0.097 (0.006) | 1.10 (1.09-1.11) | <.0001 |
| Bone Mineral Disorders | 0.090 (0.008) | 1.09 (1.08-1.11) | <.0001 |

| Covariate | $\beta$ (SE) | HR (95% CI) | *P* Value |
|---|---|---|---|
| **Total Days of Prescription** | | | |
| ≥8 days | Reference | Reference | |
| 1-7 days | 0.335 (0.005) | 1.40 (1.39-1.41) | <.0001 |
| None | 0.395 (0.005) | 1.49 (1.47-1.50) | <.0001 |

### 4.5.3 Validation of Prentice, Williams, and Peterson prediction equation

The Harrell's C-statistic was 0.688 (95% CI, 0.683-0.692) and 0.676 (95% CI, 0.669 to 0.681), with brier score of 0.375 and 0.363 for the derivation and validation cohorts, respectively. Using the optimal threshold determined by Youden's index to define high risk individuals, the model's sensitivity was 49.0% (95% CI, 48.8% to 49.2%) and 49.3% (95% CI, 49.0% to 49.5%) whereas specificity was 80.5% (95% CI, 80.3% to 80.6%) and 80.6% (95% CI, 80.4% to 80.9%) in the derivation and validation cohorts. The calibration was (Nam and D'Agostino's $\chi^2$= 4.67, $p$=0.3107 and $\chi^2$= 4.85, $p$=0.1997) for the derivation and validation cohorts, respectively (Table 39). The prediction model showed modest discrimination based on Harrell's C-Statistics but sensitivity was low compared to specificity models. Table 39 and Figures 17-19 present model calibration and discrimination performance. There was agreement between observed risks and mean predicted risks of low back pain recurrence across each decile of the predicted risk. In addition, comparing the Hazard Ratios between the lowest risk stratum and the highest risk stratum shows that the model highest risk group is 18,994 times more likely to experience multiple low back pain recurrent episodes

than the lowest risk group. The model generally showed modest performance in separation of individual in the lower risk groups and high-risk groups (Figure 15).

**Table 39. Model validation and performance evaluation of the Prentice, Williams, and Peterson Gap time Model equation based on discrimination and calibration in derivation and validation cohorts**

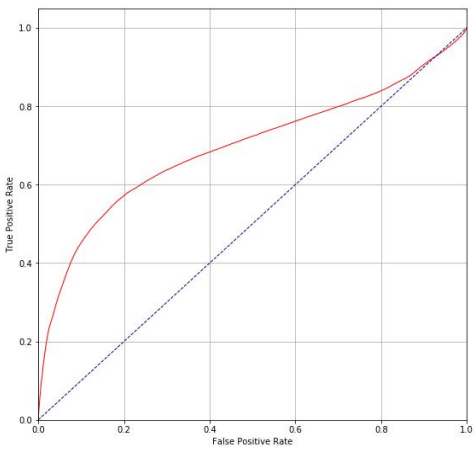
| Performance Evaluation statistic | Derivation Cohort | Validation cohort |
|---|---|---|
| Brier Score† | 0.375 | 0.363 |
| Nam and D'Agostino test ‡ | $\chi^2$=4.67 , $p$=0.3107 | $\chi^2$=4.85, $p$=0.1997 |
| Harrell's C statistic (95% CI) # | 0.688 (0.683-0.692) | 0.676 (0.669 to 0.681) |
| Sensitivity (95% CI) | 49.0% (48.8% to 49.2%) | 49.3% (49.0% to 49.5%) |
| Specificity (95% CI) | 80.5% (80.3% to 80.6%) | 80.6% (80.4% to 80.9%) |
| Positive Likelihood Ratio (95% CI) | 2.51 (2.49 to 2.53) | 2.54 (2.51 to 2.57) |
| Negative Likelihood Ratio (95% CI) | 0.63 (0.63 to 0.64) | 0.63 (0.63 to 0.63) |
| Positive Predictive Value (95% CI) | 75.4% (75.2% to 75.6%) | 75.6% (75.4% to 75.8%) |
| Negative Predictive Value (95% CI) | 56.4% (56.3% to 56.5%) | 56.6% (56.5% to 56.8%) |
| Accuracy (95% CI) | 63.2% (63.1% to 63.3%) | 63.4% (63.2% to 63.6%) |
| **Risk Strata Comparisons** | **(Hazard Ratio, *P* value)** | **(Hazard Ratio, *P* value)** |
| **Good** | **Reference** | **Reference** |
| Good Vs Fairly Good | 4.15 (4.07-4.24), $p$<.0001 | 3.87 (3.76-3.99), $p$<.0001 |
| Good Vs Fairly Poor | 22.2 (21.7-22.8), $p$<.0001 | 18.8 (18.1-19.6) , $p$<.0001 |
| Good Vs Poor | 411.6 (398.7-424.8), $p$<.0001 | 278.6 (266.4-291.4), $p$<.0001 |
| Good Vs Very Poor | 18994.5(18107.4-19925.1), $p$<.0001 | 13596.9 (12682.3-14577.6),$p$ <.0001 |

**Abbreviation: CI=confidence interval.**

†Measures both discrimination and calibration; lower values indicate higher accuracy, ‡A modification of Hosmer Lemeshow test suited for survival data; measure of calibration that is specific to censored survival data (lower $\chi^2$ and higher p values) indicate better calibration, #A measure of discrimination for which higher values indicate better discrimination. The Youden's J statistics was 0.296 for both cohorts corresponding to a risk probability of 0.717.

**Figure 17. Discrimination and calibration plots in the derivation cohort for Prentice, Williams, and Peterson Gap Time equation. (A) Discrimination. (B) Calibration**

**A** **B**



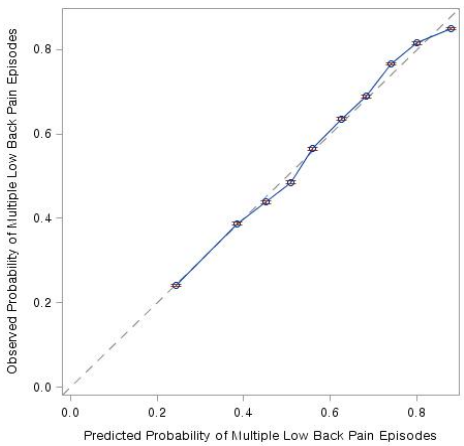
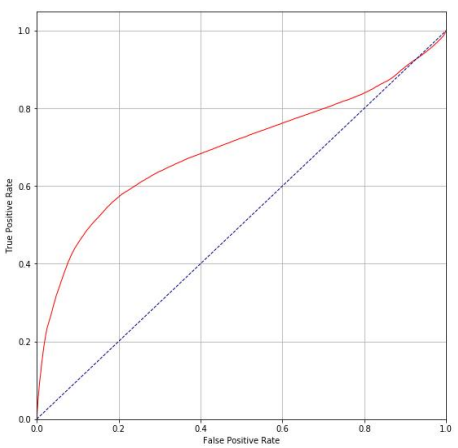




**Figure 18. Discrimination and calibration plots in the validation cohort for Prentice, Williams, and Peterson Gap Time equation. (A) Discrimination. (B) Calibration**

**A** **B**



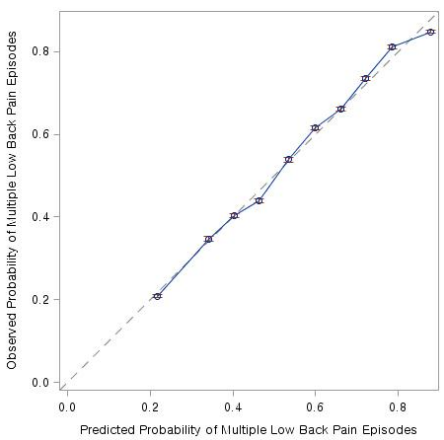
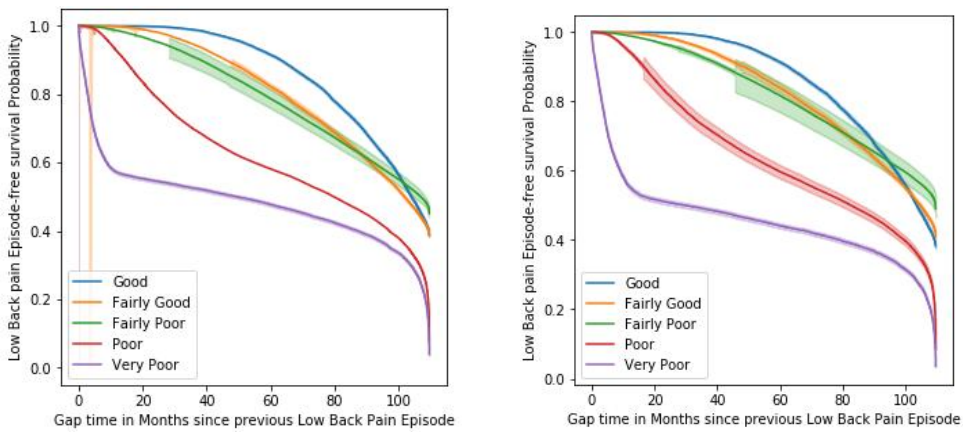



**Figure 19. Kaplan-Meier curves for multiple low back pain episodes-free survival in 5 risk groups in the derivation and validationcohorts based on the PWP-GT Prognostic Index. (A) Derivation. (B) Validation**

**A** **B**



### 4.5.4 Model discrimination at different thresholds of predicted risk

Table 40 shows the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy for Prentice, Williams and Peterson Gap time models of experiencing multiple episodic low back pain for various risk probability thresholds based on subjects in the derivation and validation cohorts. The risk probability threshold for the top 3% at highest risk of experiencing multiple episodic low back pain in the next 8 years was 0.994, for the top 5% was 0.971, for the top 10% was 0.924, for the top 25% was 0.791, and for the top 50% was 0.641. With a risk probability threshold of 0.924 over 8 years to identify the 10% of participants with the highest risk of experiencing multiple episodic low back pain, the sensitivity for identifying multiple episodic low back pain was 12.7% (95% CI, 12.5%-12.9%), specificity 93.3% (95% CI, 93.2%-93.4%), positive predictive value 69.7% (95% CI, 69.2%-70.2%), negative predictive value 46.8% (95% CI, 46.7%-46.8%), and accuracy value 49.1% (95% CI, 48.9%-49.2%) (Table 40). The corresponding thresholds for risk of experiencing multiple episodic low back pain over 8 years and the model's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 40). Table 39 shows the sensitivity and specificity based on the optimal cut-off determined by Youden's J statistic for the Prentice, Williams, and Peterson Gap-time prediction equation of multiple episodic low back pain.

**Table 40. Sensitivity, specificity, likelihood ratio, predictive values, and accuracy for low back pain at different thresholds of predicted risk of low back pain recurrence for Prentice, Williams and Peterson Gap time prediction equation**

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values and accuracy for low back pain at different thresholds of predicted risk of low back pain recurrence over 8 years in derivation cohort (Based on Prentice, William and Peterson models)**

| Threshold (centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | 1.000 | 257,745 | 334,676 | 16,287 | 0 | 0.00 (0.00-0.00) | 94.1 (94.0-94.1) | 0.00 | 1.06 (1.06-1.06) | 0 | 43.5 (43.5-43.5) | 42.3 (42.2-42.5) |
| 97% | ≥0.994 | 257,705 | 332,835 | 16,323 | 1,845 | 0.55 (0.53-0.58) | 94.1 (94.0-94.1) | 0.09 (0.09-0.10) | 1.06 (1.06-1.06) | 10.2 (9.73-10.6) | 43.6 (43.6-43.7) | 42.6 (42.5-42.8) |
| 95% | ≥0.971 | 257,220 | 321,051 | 16,914 | 13,523 | 4.04 (3.98-4.11) | 93.8 (93.7-93.9) | 0.66 (0.64-0.67) | 1.02 (1.02-1.02) | 44.4 (43.9-45.0) | 44.5 (44.5-44.5) | 44.5 (44.4-44.6) |
| 90% | ≥0.924 | 255,585 | 292,238 | 18,554 | 42,331 | 12.7 (12.5-12.8) | 93.2 (93.1-93.3) | 1.87 (1.84-1.90) | 0.94 (0.94-0.94) | 69.5 (69.2-69.9) | 46.7 (46.6-46.7) | 48.9 (48.8-49.1) |
| 75% | ≥0.791 | 243,716 | 212,894 | 30,225 | 121,873 | 36.4 (36.2-36.6) | 89.0 (88.9-89.1) | 3.30 (3.26-3.34) | 0.71 (0.71-0.72) | 80.1 (79.9-80.3) | 53.4 (53.3-53.5) | 60.1 (59.9-60.2) |
| 50% | ≥0.641 | 173,745 | 130,531 | 100,199 | 204,233 | 61.0 (60.8-61.2) | 63.4 (63.2-63.6) | 1.67 (1.66-1.68) | 0.61 (0.61-0.62) | 67.1 (67.0-67.2) | 57.1 (57.0-57.2) | 62.1 (62,0-62.2) |
| 25% | ≥0.504 | 76,556 | 75,591 | 197,719 | 258,842 | 77.4 (77.3-77.5) | 27.9 (27.7-28.1) | 1.07 (1.07-1.08) | 0.81 (0.80-0.82) | 56.7 (56.6-56.8) | 50.3 (50.1-50.5) | 55.1 (55.0-55.2) |
| 10% | ≥0.324 | 27,644 | 33,260 | 246,553 | 301,251 | 90.1 (90.0-90.2) | 10.1 (9.97-10.2) | 1.00 (1.00-1.00) | 0.99 (0.97-1.00) | 55.0 (55.0-55.0) | 45.4 (45.0-45.8) | 54.0 (53.9-54.2) |
| 5% | ≥0.220 | 13,775 | 16,615 | 260,542 | 317,776 | 95.0 (95.0-95.1) | 5.02 (4.94-5.10) | 1.00 (1.00-1.00) | 0.99 (0.97-1.01) | 55.0 (54.9-55.0) | 45.3 (44.8-45.9) | 54.5 (54.3-54.6) |

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values and accuracy for low back pain at different thresholds of predicted risk of low back pain recurrence over 8 years in validation cohort (Based on Prentice, William and Peterson models)**

| Threshold (centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | 1.000 | 128,892 | 166,511 | 8,229 | 0 | 0.00 (0.00-0.00) | 94.0 (93.9-94.1) | 0.00 | 1.06 (1.06-1.07) | 0 | 43.6 (43.6-43.7) | 42.5 (42.3-42.6) |
| 97% | ≥0.994 | 128,869 | 165,568 | 8,256 | 939 | 0.56 (0.53-0.60) | 94.0 (93.9-94.1) | 0.09 (0.09-0.10) | 1.06 (1.06-1.06) | 10.2 (9.61-10.8) | 43.8 (43.7-43.8) | 42.8 (42.6-42.9) |
| 95% | ≥0.971 | 128,638 | 159,817 | 8,381 | 6,796 | 4.08 (3.98-4.17) | 93.9 (93.8-94.0) | 0.67 (0.65-0.69) | 1.02 (1.02-1.02) | 44.8 (44.0-45.6) | 44.6 (44.6-44.6) | 44.6 (44.4-44.8) |
| 90% | ≥0.924 | 127,812 | 145,467 | 9,202 | 21,151 | 12.7 (12.5-12.9) | 93.3 (93.2-93.4) | 1.89 (1.85-1.93) | 0.94 (0.93-0.94) | 69.7 (69.2-70.2) | 46.8 (46.7-46.8) | 49.1 (48.9-49.2) |
| 75% Q3 | ≥0.791 | 121,977 | 105,673 | 15,235 | 60,747 | 36.5 (36.3-36.7) | 88.9 (88.7-89.1) | 3.29 (3.23-3.34) | 0.71 (0.71-0.72) | 80.0 (79.7-80.2) | 53.6 (53.5-53.7) | 60.2 (60.0-60.4) |
| 50% Q2 | ≥0.641 | 87,031 | 64,863 | 50,178 | 101,560 | 61.0 (60.8-61.3) | 63.4 (63.2-63.7) | 1.67 (1.66-1.68) | 0.61 (0.61-0.62) | 66.9 (66.8-67.1) | 57.3 (57.1-57.5) | 62.1 (61.9-62.3) |
| 25% Q1 | ≥0.504 | 38,199 | 37,740 | 98,679 | 129,014 | 77.4 (77.2-77.6) | 27.9 (27.7-28.2) | 1.07 (1.07-1.08) | 0.81 (0.80-0.82) | 56.7 (56.6-56.8) | 50.3 (50.0-50.6) | 55.1 (54.9-55.3) |
| 10% | ≥0.324 | 13,877 | 16,451 | 123,079 | 150,225 | 90.1 (90.0-90.3) | 10.1 (9.97-10.3) | 1.00 (1.00-1.01) | 0.97 (0.95-1.00) | 55.0 (54.9-55.0) | 45.8 (45.2-46.3) | 54.1 (53.9-54.2) |
| 5% | ≥0.220 | 6,893 | 8,337 | 129,943 | 158,459 | 95.0 (94.9-95.1) | 5.04 (4.92-5.15) | 1.00 (1.00-1.00) | 0.99 (0.96-1.02) | 54.9 (54.9-55.0) | 45.3 (44.5-46.0) | 54.5 (54.3-54.6) |

Note: The counts in this table represent the episodes. Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages]. The threshold of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.5.5 Prediction equation of low back pain recurrence using PWP-GT Models

Using the estimated coefficients, personalized probability of experiencing a recurrent low back pain episode within the gap time (ŧ) can be estimated using the following equation:

$$P(\text{Recurrent low back pain episode}) = \lambda_{ik}(ŧ) = \lambda_{0k}(ŧ - ŧ_{k-1})e^{x}\mathrm{x}_{ik}\beta$$

where $\lambda_{ik}(ŧ)$ denotes the hazard function for the $k^{th}$event of the $i^{th}$subject at time ŧ, $\lambda_{0k}$ represents the event-specific baseline hazard for $k^{th}$event, and $\mathrm{x}_{ik}\beta$ denotes the covariate vector (p fixed effects) for the $i^{th}$subject with respect to the $k^{th}$event, where $\mathrm{x}_{ik}$ is the covariate matrix.

The Youden's J statistic suggested a risk probability of ≥0.717 as the optimal cutoff point to define high-risk individuals based on the Prentice, Williams, and Peterson Gap-time prediction equation. This threshold showed a sensitivity of 49.3% (95% CI, 49.0%-49.5%), specificity of 80.6% (95% CI, 80.4%-80.9%), positive likelihood ratio (LR+) of 2.54 (95% CI, 2.51-2.57), negative likelihood ratio (LR-) of 0.63 (95% CI, 0.63-0.63), positive predictive value (PPV) of 75.6% (95% CI, 75.4%-75.8%), negative predictive value (NPV) of 56.6% (95% CI, 56.5%-56.8%) and accuracy of 63.4% (95% CI, 63.2%-63.6%) in prediction of the risk of experiencing multiple episodic low back pain recurrence over 8 years in the validation cohort (Table 39).

## 4.6 Prediction of Nephrolithiasis Risk

### 4.6 Prediction of nephrolithiasis Risk

#### 4.6.1 Cohort baseline characteristics for newly diagnosed nephrolithiasis

Table 41 shows baseline characteristics of the derivation and validation cohorts use to develop prediction models for first onset of Nephrolithiasis. The extracted data comprised of 502,342 participants. In this study, 5,371 participants with history of nephrolithiasis at baseline were excluded from the analysis. The entire cohort used in analysis comprised of 496,971 participants. During a median follow-up of 8.5 years (Range=2.0-8.9) and among 496,971 participants, there were 18,205 (3.7%) cases of nephrolithiasis (first time medical utilisation due to Nephrolithiasis). The total number of person-years of follow-up was 4,186,809 years. The mean (SD) of covariates and the distribution of the baseline characteristics stratified by nephrolithiasis in both derivation and validation cohorts are presented in (Tables 41), and there were no discrepancies between the derivation and validation cohorts. In both cohorts, there was significant difference in baseline characteristics between those who developed and those who did not develop nephrolithiasis ($p$<0.05) (Tables 41).

**Table 41. Baseline characteristic of participants in derivation and validation cohorts for newly diagnosed nephrolithiasis [Mean (SD) or n (%)]**

| | Derivation Cohort (n=331,792) | | | Validation Cohort (n=165,179) | | |
|---|---|---|---|---|---|---|
| **Covariate** | **Without Nephrolithiasis** | **With Nephrolithiasis** | ***P* value** | **Without Nephrolithiasis** | **With Nephrolithiasis** | ***P* value** |
| | **319,646 (96.3)** | **12,146 (3.7)** | | **159,120 (96.3)** | **6,059 (3.7)** | |
| Years of follow up | 8.5 (1.0) | 5.3 (2.0) | <.0001 | 8.5 (1.0) | 5.3 (2.0) | <.0001 |
| Height (cm) | 163.2 (9.0) | 164.1 (8.8) | <.0001 | 163.2 (8.9) | 163.9 (8.8) | <.0001 |
| Weight (kgs) | 62.4 (11.0) | 65.0 (11.2) | <.0001 | 62.4 (11.0) | 64.9 (11.1) | <.0001 |
| BMI ($kg/m^{2)}$ | 23.4 (3.2) | 24.1 (3.2) | <.0001 | 23.4 (3.2) | 24.1 (3.2) | <.0001 |
| SBP (mm Hg) | 123.0 (17.3) | 124.6 (17.0) | <.0001 | 123.0 (17.2) | 124.5 (16.9) | <.0001 |
| DBP (mm Hg) | 77.3 (11.4) | 78.5 (11.2) | <.0001 | 77.3 (11.4) | 78.6 (11.2) | <.0001 |
| FBG (mg/dL) | 93.6 (27.6) | 94.8(27.8) | <.0001 | 93.5 (27.7) | 94.9 (27.8) | 0.0002 |
| Total Cholesterol (mg/dL) | 191.9 (38.6) | 196.5 (37.7) | <.0001 | 191.8 (38.6) | 196.2 (38.2) | <.0001 |
| **Sex** | | | <.0001 | | | <.0001 |
| Male | 160,037 (50.1) | 7,518 (61.9) | | 79,716 (50.1) | 3,708 (61.2) | |
| Female | 159,609 (49.9) | 4,628 (38.1) | | 79,404 (49.9) | 2,351 (38.8) | |
| **Age** | | | <.0001 | | | <.0001 |
| <25 yrs. | 47,978 (15.0) | 1,039 (8.5) | | 23,902 (15.0) | 483 (7.9) | |
| 25-34 yrs | 65,771 (20.6) | 2,279 (18.8) | | 32,565 (20.5) | 1,142 (18.9) | |
| 35-44yrs | 79,032 (24.7) | 3,301 (27.2) | | 39,586 (24.9) | 1,630 (26.9) | |
| 45-54 yrs | 60,261 (18.9) | 2,843 (23.4) | | 29,983 (18.8) | 1,468 (24.2) | |
| ≥55 yrs | 66,604 (20.8) | 2,684 (22.1) | | 33,084 (20.8) | 1,336 (22.1) | |
| **Income/Insurance** | | | <.0001 | | | <.0001 |
| Low (<30%) | 47,264 (14.8) | 1,564 (12.9) | | 23,635 (14.9) | 753 (12.4) | |
| Medium (30-60%) | 115,278 (36.1) | 4,167 (34.3) | | 57,186 (35.9) | 2,113 (34.9) | |
| High (>60%) | 157,104 (49.1) | 6,415 (52.8) | | 78,299 (49.2) | 3,193 (52.7) | |
| **Physical Activity/Week** | | | <.0001 | | | <.0001 |
| Low (None) | 187,271 (58.6) | 6,746 (55.5) | | 93,082 (58.5) | 3,377 (55.7) | |

| | Derivation Cohort (n=331,792) | | | Validation Cohort (n=165,179) | | |
|---|---|---|---|---|---|---|
| **Covariate** | **Without Nephrolithiasis** | **With Nephrolithiasis** | ***P* value** | **Without Nephrolithiasis** | **With Nephrolithiasis** | ***P* value** |
| | **319,646 (96.3)** | **12,146 (3.7)** | | **159,120 (96.3)** | **6,059 (3.7)** | |
| Moderate (1-2 times/week) | 109,445 (34.2) | 4,430 (36.5) | | 54,683 (34.4) | 2,172 (35.9) | |
| High (>3 times) | 22,930 (7.2) | 970 (8.0) | | 11,355 (7.1) | 510 (8.4) | |
| **Smoking Status** | | | <.0001 | | | <.0001 |
| Never | 214,157 (67.0) | 7,489 (61.7) | | 106,637 (67.0) | 3,791 (62.6) | |
| Former Smoker | 13,588 (4.3) | 622 (5.1) | | 6,940 (4.4) | 289 (4.7) | |
| Current Smoker | 91,901 (28.7) | 4,035 (33.2) | | 45,543 (28.6) | 1,979 (32.7) | |
| **Alcohol Consumption** | | | | | | 0.0022 |
| Rarely (< 2 times) | 163,931 (51.3) | 5,914 (48.7) | | 81,527 (51.2) | 2,967 (49.0) | |
| Moderate drinker (2–3 times) | 126,085 (39.4) | 5,061 (48.7) | | 62,508 (39.3) | 2,481 (40.9) | |
| Heavy drinker ( ≥ 4 times) | 29,630 (9.3) | 1,171 (9.6) | | 15,085 (9.5) | 611 (10.1) | |
| **Body Mass Index** | | | <.0001 | | | <.0001 |
| < 18.5 | 18,054 (5.7) | 392 (3.3) | | 9,061 (5.7) | 205 (3.4) | |
| 18.5 $kg/m^2$-24.9 $kg/m^2$ | 207,879 (65.0) | 7,254 (59.7) | | 103,592 (65.1) | 3,593 (59.3) | |
| 25 $kg/m^2$-29.9 $kg/m^2$ | 85,237 (26.7) | 4,037 (33.2) | | 42,265 (26.6) | 2,047 (33.8) | |
| ≥30 $kg/m^2$ | 8,476 (2.6) | 463 (3.8) | | 4,202 (2.6) | 214 (3.5) | |
| **Fasting Blood Glucose** | | | 0.0329 | | | 0.0026 |
| < 100mg/dL | 207,737 (65.0) | 7,815 (64.3) | | 103,747 (65.2) | 3,820 (63.0) | |
| 100mg/dl-125 mg/dL | 77,373 (24.2) | 2,928 (24.1) | | 38,224 (24.0) | 1,544 (25.5) | |
| ≥ 126 mg/dl Or Rx | 34,536 (10.8) | 1,403 (11.6) | | 17,149 (10.8) | 695 (11.5) | |
| **Blood Pressure/HTN** | | | <.0001 | | | <.0001 |
| SBP < 120 and DBP < 80 | 116,548 (36.5) | 3,846 (31.6) | | 58,208 (36.6) | 1,886 (31.1) | |
| SBP 120-139 or DBP 80-89 | 165,031 (51.6) | 6,668 (54.9) | | 82,183 (51.6) | 3,332 (55.0) | |
| SBP 140-159 or DBP 90-99 | 33,312 (10.4) | 1,418 (11.7) | | 16,367 (10.3) | 741 (12.2) | |
| SBP ≥160 or DBP ≥100 or Rx | 4,755 (1.5) | 214 (1.8) | | 2,362 (1.5) | 100 (1.7) | |

| | Derivation Cohort (n=331,792) | | | Validation Cohort (n=165,179) | | |
|---|---|---|---|---|---|---|
| **Covariate** | **Without Nephrolithiasis** | **With Nephrolithiasis** | ***P* value** | **Without Nephrolithiasis** | **With Nephrolithiasis** | ***P* value** |
| | **319,646 (96.3)** | **12,146 (3.7)** | | **159,120 (96.3)** | **6,059 (3.7)** | |
| **Total cholesterol** | | | <.0001 | | | <.0001 |
| <200 mg/dL | 190,942 (59.7) | 6,629 (54.6) | | 95,374 (59.9) | 3,342 (55.2) | |
| 200 mg/dL-239 mg/dL | 93,179 (29.2) | 3,982 (32.8) | | 46,272 (29.1) | 1,943 (32.0) | |
| >240 mg/dL | 35,525 (11.1) | 1,535 (12.6) | | 17,474 (11.0) | 774 (12.8) | |
| **Diagnosed IBD** | | | 0.0006 | | | 0.5941 |
| No | 318,410 (99.6) | 12,075 (99.4) | | 158,531 (99.6) | 6,034 (99.6) | |
| Yes | 1,236 (0.4) | 71 (0.6) | | 589 (0.4) | 25 (0.4) | |
| **Diagnosed CKD** | | | 0.9407 | | | 0.2010 |
| No | 319,311 (99.9) | (99.9) | | 158,967 (99.9) | 6,050 (99.8) | |
| Yes | 335 (0.1) | 13 (0.1) | | 153 (0.1) | 9 (0.2) | |
| **Hyperparathyroidism** | | | 0.3780 | | | 0.0133 |
| No | 316,660 (99.1) | 12,023 (99.0) | | 157,602 (99.0) | 5,982 (98.7) | |
| Yes | 2,986 (0.9) | 123 (1.0) | | 1,518 (1.0) | 77 (1.3) | |
| **Diagnosed IHD** | | | <.0001 | | | 0.0698 |
| No | 316,176 (98.9) | 11,962 (98.5) | | 157,410 (98.9) | 5,979 (98.7) | |
| Yes | 3,470 (1.1) | 184 (1.5) | | 1,710 (1.1) | 80 (1.3) | |
| **Diagnosed Gout** | | | 0.0004 | | | 0.0241 |
| No | 319,031 (99.8) | 12105 (99.7) | | 158,786 (99.8) | 6,038 (99.6) | |
| Yes | 615 (0.2) | 41 (0.3) | | 334 (0.2) | 21 (0.4) | |

The student's *t*-test for continuous variables and $\chi^2$-test for categorical variables were used to examine the differences in baseline characteristics between participants in the derivation and validation cohorts stratified based on newly diagnosed nephrolithiasis outcome

### 4.6.2 Cumulative incidence and incidence probabilities of nephrolithiasis

During the follow up period, the cumulative risk of nephrolithiasis increased from 1.1 (95% CI, 1.1 to 1.2) in 2004 to 4.0 (95% CI, 4.0 to 4.1) at the end of the follow up period (31st December, 2010). The details of the incidence trends and cumulative risks are presented (Table 42).

**Table 42. Follow-up times, cumulative incidence and incidence probabilities of Nephrolithiasis**

| Calendar Year | Censored | Events | Total participants | *CR (95% CI) |
|---|---|---|---|---|
| 2004 | 2,447 | 2,914 | 5,361 | 1.1 (1.1-1.2 ) |
| 2005 | 3,734 | 2,679 | 6,413 | 1.7 (1.7-1.7) |
| 2006 | 8,219 | 2,625 | 10,844 | 2.2 (2.2-2.3) |
| 2007 | 12,913 | 2,306 | 15,219 | 2.7 (2.7-2.8) |
| 2008 | 24,570 | 2,365 | 26,935 | 3.2 (3.2-3.3) |
| 2009 | 159,469 | 2,326 | 161,795 | 3.9 (3.8-3.9) |
| 2010 | 263,765 | 259 | 264,024 | 4.0 (4.0-4.1) |
| **Totals** | **478,766** | **18,205** | **496,971** | |

*CR=Cumulative Risk

### 4.6.3 Association between risk predictors and newly diagnosed nephrolithiasis

Tables 43 present the estimated coefficients and hazard ratios of covariates in the unadjusted, partially adjusted, and fully adjusted analyses. With exception of physical activity that showed an inverse relationship, all risk factors were positively associated with nephrolithiasis in the univariate analysis ($p$<0.05) (Table 43). The risk factors that showed positive significant association with nephrolithiasis in the multivariate analysis included, sex, age, income grade, blood pressure/HTN, and premorbid IHD, IBD, hyperparathyroidism and premorbid gout

($p$<0.05) (Table 34). Among modifiable risk factors, physical activity, smoking, and alcohol consumption showed significantly inverse associations with nephrolithiasis in the fully adjusted models ($p$<0.05) (Table 43). In this study, MetS variables showed positive associations with nephrolithiasis except for fasting blood glucose which was inversely associated in the multivariate analysis whereas among premorbid conditions, chronic kidney disease was not significantly associated with nephrolithiasis both in the univariate and multivariate analysis ($p$<0.05) (Table 43).

**Table 43. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors in the univariate, partially adjusted and fully adjusted models for newly diagnosed nephrolithiasis**

| Covariate | Unadjusted* | | | Partially Adjusted† | | | Fully Adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | *β* (SE) | HR (95% CI) | *P* Value | *β* (SE) | HR (95% CI) | *P* Value | *β* (SE) | HR (95% CI) | *P* Value |
| **Sex** | | | | | | | | | |
| Male | 0.504 (0.015) | 1.66 (1.61-1.71) | <.0001 | 0.509 (0.015) | 1.66 (1.61-1.71) | <.0001 | 0.560 (0.020) | 1.75 (1.68-1.82) | <.0001 |
| **Age** | | | | | | | | | |
| < 25 yrs. | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 25-34yrs | 0.496 (0.031) | 1.64 (1.55-1.75) | <.0001 | 0.435 (0.031) | 1.54 (1.45-1.64) | <.0001 | 0.424 (0.031) | 1.53 (1.44-1.62) | <.0001 |
| 35-44 yrs | 0.654 (0.029) | 1.92 (1.82-2.04) | <.0001 | 0.636 (0.029) | 1.89 (1.78-2.00) | <.0001 | 0.612 (0.030) | 1.85 (1.74-1.95) | <.0001 |
| 45-54 | 0.771 (0.030) | 2.16 (2.04-2.29) | <.0001 | 0.762 (0.030) | 2.14 (2.02-2.27) | <.0001 | 0.736 (0.030) | 2.09 (1.97-2.21) | <.0001 |
| ≥55 yrs | 0.620 (0.030) | 1.86 (1.75-1.97) | <.0001 | 0.625 (0.030) | 1.87 (1.76-1.98) | <.0001 | 0.594 (0.031) | 1.81 (1.71-1.92) | <.0001 |
| **Income/Insurance** | | | | | | | | | |
| Low (<30%) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Medium (31-60%) | 0.105 (0.024) | 1.11 (1.06-1.17) | <.0001 | 0.055 (0.024) | 1.06 (1.01-1.11) | 0.0258 | 0.055 (0.024) | 1.06 (1.01-1.11) | 0.0244 |
| High (>60%) | 0.212 (0.023) | 1.24 (1.18-1.29) | <.0001 | 0.110 (0.023) | 1.12 (1.07-1.17) | <.0001 | 0.105 (0.023) | 1.11 (1.06-1.16) | <.0001 |
| **Physical Activity/Week** | | | | | | | | | |
| High (>3 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate (1-2 times) | -0.068 (0.029) | 0.93 (0.88-0.99) | <.0001 | -0.057 (0.029) | 0.95 (0.89-1.00) | 0.0490 | -0.056 (0.029) | 0.95 (0.89-1.00) | 0.0535 |
| Low (None) | -0.177 (0.028) | 0.84 (0.79-0.89) | <.0001 | -0.073 (0.028) | 0.93 (0.88-0.98) | 0.0095 | -0.067 (0.028) | 0.94 (0.89-0.99) | 0.0167 |
| **Smoking Status** | | | | | | | | | |
| Never | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Former Smoker | 0.251 (0.034) | 1.29 (1.20-1.38) | <.0001 | -0.064 (0.036) | 0.94 (0.87-1.01) | 0.0736 | -0.057 (0.036) | 0.95 (0.88-1.01) | 0.1154 |
| Current Smoker | 0.248 (0.016) | 1.28 (1.24-1.32) | <.0001 | -0.056 (0.019) | 0.95 (0.91-0.98) | 0.0041 | -0.039 (0.019) | 0.96 (0.93-0.99) | 0.0445 |
| **Alcohol** | | | | | | | | | |
| Rarely (< 2 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate drinker (2–3 | 0.114 (0.016) | 1.12 (1.09-1.16) | <.0001 | -0.065 (0.017) | 0.94 (0.91-0.97) | 0.0002 | -0.062 (0.017) | 0.94 (0.91-0.97) | 0.0003 |
| Heavy drinker ( ≥ 4 times) | 0.122 (0.026) | 1.13 (1.07-1.19) | <.0001 | -0.138 (0.028) | 0.87 (0.83-0.92) | <.0001 | -0.131 (0.028) | 0.88 (0.83-0.93) | <.0001 |
| **Body Mass Index** | | | | | | | | | |

| Covariate | Unadjusted* | | | Partially Adjusted† | | | Fully Adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | *β* (SE) | HR (95% CI) | *P* Value | *β* (SE) | HR (95% CI) | *P* Value | *β* (SE) | HR (95% CI) | *P* Value |
| < 18.5 $Kgm^2$ | -0.441 (0.042) | 0.64 (0.59-0.69) | <.0001 | -0.193 (0.043) | 0.83 (0.76-0.90) | <.0001 | -0.192 (0.043) | 0.83 (0.76-0.90) | <.0001 |
| 18.5 $Kgm^2$-24.9 $Kgm^2$ | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 25 $Kgm^2$-29.9 $Kgm^2$ | 0.297 (0.016) | 1.35 (1.30-1.39) | <.0001 | 0.203 (0.016) | 1.23 (1.19-1.27) | <.0001 | 0.203 (0.016) | 1.23 (1.19-1.27) | <.0001 |
| >30 $Kgm^2$ | 0.405 (0.040) | 1.50 (1.39-1.62) | <.0001 | 0.381 (0.040) | 1.46 (1.35-1.58) | <.0001 | 0.384 (0.040) | 1.47 (1.36-1.59) | <.0001 |
| **Fasting Blood Glucose** | | | | | | | | | |
| < 100mg/dl | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 100mg/dl-125 mg/dl | 0.031 (0.018) | 1.03 (0.99-1.07) | 0.0743 | -0.017 (0.018) | 0.98 (0.95-1.02) | 0.3356 | -0.014 (0.018) | 0.99 (0.95-1.02) | 0.4323 |
| >126 mg/dl or Tx | 0.073 (0.024) | 1.08 (1.03-1.13) | 0.0022 | -0.009 (0.024) | 0.99 (0.95-1.04) | 0.7109 | -0.004 (0.023) | 0.99 (0.95-1.04) | 0.8837 |
| **Total Cholesterol** | | | | | | | | | |
| < 200µmol/l | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 200µmol-239µmol/l | 0.188 (0.016) | 1.21 (1.17-1.25) | <.0001 | 0.110 (0.017) | 1.12 (1.08-1.15) | <.0001 | 0.109 (0.017) | 1.12 (1.08-1.15) | <.0001 |
| ≥ 240µmol/l or Rx | 0.209 (0.023) | 1.23 (1.18-1.29) | <.0001 | 0.112 (0.024) | 1.12(1.07-1.17) | <.0001 | 0.111 (0.024) | 1.12 (1.07-1.17) | <.0001 |
| **HTN** | | | | | | | | | |
| SBP < 120 and DBP < 80 | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| SBP 120-139 or DBP 80-89 | 0.208 (0.017) | 1.23 (1.19-1.27) | <.0001 | 0.059 (0.017) | 1.06 (1.03-1.10) | 0.0005 | 0.065 (0.017) | 1.07 (1.03-1.10) | 0.0001 |
| SBP 140-159 or DBP 90-99 | 0.278 (0.025) | 1.32 (1.26-1.39) | <.0001 | 0.054 (0.026) | 1.06 (1.00-1.11) | 0.0397 | 0.065 (0.026) | 1.07 (1.01-1.12) | 0.0132 |
| SBP ≥160 or DBP ≥100 or Rx | 0.299 (0.058) | 1.35 (1.20-1.51) | <.0001 | 0.032 (0.059) | 1.03 (0.92-1.16) | 0.5865 | 0.048 (0.059) | 1.05 (0.94-1.18) | 0.4104 |
| **Premorbidities** | | | | | | | | | |
| Diagnosed IHD | 0.275 (0.062) | 1.32 (1.17-1.49) | <.0001 | 0.184 (0.062) | 1.20(1.06-1.36) | 0.0032 | 0.178 (0.062) | 1.20 (1.06-1.35) | 0.0043 |
| Diagnosed IBD | 0.299 (0.102) | 1.35 (1.10-1.65) | 0.0035 | 0.279 (0.102) | 1.32 (1.08-1.62) | 0.0064 | 0.276 (0.102) | 1.32 (1.08-1.61) | 0.0071 |
| Diagnosed CKD | 0.202 (0.213) | 1.22 (0.81-1.86) | 0.3430 | 0.084 (0.213) | 1.09 (0.72-1.65) | 0.6927 | 0.068 (0.213) | 1.07 (0.71-1.63) | 0.7500 |
| Hyperparathyroidism | 0.125 (0.071) | 1.13 (0.99-1.30) | 0.0784 | 0.221 (0.071) | 1.25 (1.08-1.43) | 0.0019 | 0.214 (0.071) | 1.24 (1.08-1.42) | 0.0027 |
| Diagnosed gout | 0.511 (0.127) | 1.67 (1.30-2.14) | <.0001 | 0.254 (0.254) | 1.29 (1.00-1.65) | 0.0465 | 0.251 (0.127) | 1.29 (1.00-1.65) | 0.0491 |

∗Unadjusted/Univariate analysis. †Partially adjusted models account for age, sex and each variable added. ‡Fully adjusted models account for Age, Sex, Income grade, Physical activity, Smoking status, Alcohol consumption and each of the other risk factors [*MetS (Fasting Blood Glucose, Total Cholesterol, Blood Pressure/HTN, prior history of IHD, Ischemic Heart Disease; Gout; CKD, Chronic Kidney Disease, Hyperparathyroidism; IBD, Inflammatory Bowel Disease)].

### 4.6.4 Derivation of prediction equations for newly diagnosed nephrolithiasis

Based on univariate, multivariate analysis, and hierarchical cluster analysis of correlations, 16 variables were assessed in the model derivation and retained if they were significant at α=0.15. The parsimonious model comprised of age, sex, and income grade, alcohol consumption, body mass index, total cholesterol, and fasting blood glucose. Table 44 present estimated coefficients and hazard ratios for risk predictors in the parsimonious model and the risk points assigned to risk factors.

**Table 44. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors in the parsimonious model of nephrolithiasis and the risk points scoring system**

| Covariates | *β* (SE) | HR (95% CI) | *P* Value | Points* |
|---|---|---|---|---|
| **Sex** | | | | |
| Female | Reference | Reference | | 0 |
| Male | 0.539 (0.021) | 1.72 (1.65-1.79) | <.0001 | 54 |
| **Age** | | | | |
| <24 yrs. | Reference | Reference | | 0 |
| 25-34 yrs | 0.349 (0.039) | 1.42 (1.32-1.53) | <.0001 | 35 |
| 35-44 yrs | 0.527 (0.036) | 1.69 (1.58- | <.0001 | 53 |
| 45-54 yrs | 0.617 (0.037) | 1.85 (1.72- 2.0) | <.0001 | 62 |
| >55 yrs | 0.498 (0.038) | 1.65 (1.53-1.77) | <.0001 | 50 |
| **Income Grade/Insurance** | | | | |
| Low (<30%) | Reference | Reference | | 0 |
| Medium (30-60%) | 0.036 (0.030) | 1.04 (0.98-1.10) | 0.2269 | 4 |
| High (>60%) | 0.093 (0.028) | 1.10 (1.04-1.16) | 0.0011 | 9 |
| **Alcohol** | | | | |
| Rarely (<2 times) | Reference | Reference | | 0 |
| Moderate drinker (2-3 times) | -0.069 (0.021) | 0.93 (0.90-0.97) | 0.0010 | -7 |
| Heavy drinker (>3 times) | -0.154 (0.034) | 0.86 (0.80-0.92) | <.0001 | -15 |
| **Body Mass Index** | | | | |
| < 18.5 kg/m$^2$ | -0.204 (0.053) | 0.82 (0.74-0.90) | 0.0001 | -20 |

| Covariates | $\beta$ (SE) | HR (95% CI) | *P* Value | Points* |
|---|---|---|---|---|
| 18.5 kg/m$^2$-24.9 kg/m$^2$ | Reference | Reference | | 0 |
| 25 kg/m$^2$-29.9 kgm$^2$ | 0.189 (0.020) | 1.21 (1.16-1.26) | <.0001 | 19 |
| ≥30 kg/m$^2$ | 0.397 (0.048) | 1.49 (1.35-1.64) | <.0001 | 40 |
| **Total Cholesterol** | | | | |
| <200 kg/m$^2$ | Reference | Reference | | 0 |
| 200 kg/m$^2$-239 kg/m$^2$ | 0.096 (0.020) | 1.10 (1.06-1.15) | <.0001 | 10 |
| >240 kg/m$^2$ | 0.067 (0.029) | 1.07 (1.01-1.13) | 0.0209 | 7 |
| **Fasting Blood Glucose** | | | | |
| < 100 mg/dL | Reference | Reference | | 0 |
| > 100mg/dl-125 mg/dL | -0.059 (0.022) | 0.94 (0.90-0.98) | 0.0066 | -6 |
| ≥126 mg/dl or Rx | -0.040 (0.029) | 0.96 (0.91-1.02) | 0.1771 | -4 |
| **Premorbid conditions** | | | | |
| Diagnosed IBD | 0.374 (0.119) | 1.45(1.15- 1.84) | 0.0017 | 37 |
| Hyperparathyroidism | 0.156 (0.091) | 1.17 (0.98-1.40) | 0.0858 | 16 |
| History of Gout | 0.248 (0.157) | 1.28 (0.94-1.74) | 0.1129 | 25 |

*The risk points were calculated by multiplying the estimated coefficients by 100 and rounding to the next integer.

### 4.6.5 Model validation for prediction equation of first onset nephrolithiasis

The performance of the prediction equation was evaluated based on discrimination and calibration abilities in the validation cohort with respect to the Harrell's C-statistic and (Nam and D'Agostino's test), a modification of Hosmer-Lemeshow type $\chi^2$ statistic; and based on specificity, sensitivity and brier score. The Harrell's C-statistic was 0.820 (95% CI, 0.806-0.834) and 0.819 (95% CI, 0.798-0.838) in the derivation and validation cohorts, respectively (Table 45). A value of 0.50 represents no discrimination and 1.00 represents perfect discrimination. The model showed good calibration in derivation and validation cohorts (Hosmer-Lemeshow $\chi^2$=7.931, $p$=0.8978 and $\chi^2$=8.376, $p$=0.8362). The brier score statistic which is a measure of both discrimination and calibration [436],

was 0.0366 and 0.0366 in the derivation and validation cohorts, respectively. The Brier score ranges from 0.0 to 1.0 with lower values indicating higher prediction accuracy. Using the optimal threshold determined by Youden's index to define high-risk individuals, the model's sensitivity was 76.1% (95% CI, 75.4% to 76.9%) and 76.5% (95% CI, 75.4% to 77.5%) whereas specificity was 62.1% (95% CI, 61.9% to 62.3%) and 62.0% (95% CI, 61.8% to 62.3%) in the derivation and validation cohorts, respectively (Table 45). The model performance was also evaluated by comparing the hazard ratios between the lowest risk group and the other risk strata created from prognostic index. The risk of nephrolithiasis was 80 times greater in the high-risk stratum compared to the reference stratum. Table 45 and (Figures 20-22) present the model validation results.

**Table 45. Model validation and performance evaluation of nephrolithiasis risk prediction equation based on discrimination and calibration in derivation and validation cohorts**

| Performance Evaluation statistic | Derivation Cohort | Validation cohort |
|---|---|---|
| Brier Score† | 0.0366 | 0.0366 |
| Nam and D'Agostino test‡ | $\chi^2$=7.931, p=0.8978 | $\chi^2$=8.376, p=0.8362 |
| Harrell's C statistic (95% CI) # | 0.820 (0.806-0.834) | 0.819 (0.798-0.838) |
| Sensitivity (95% CI) | 76.1% (75.4% to 76.9%) | 76.5% (75.4% to 77.5%) |
| Specificity (95% CI) | 62.1% (61.9% to 62.3%) | 62.0% (61.8% to 62.3%) |
| Positive Likelihood Ratio (95% CI) | 2.01 (1.99 to 2.03) | 2.01 (1.98 to 2.05) |
| Negative Likelihood Ratio (95% CI) | 0.38 (0.37 to 0.40) | 0.38 (0.36 to 0.40) |
| Positive Predictive Value (95% CI) | 7.1% (7.0% to 7.2%) | 7.2% (7.1% to 7.3%) |
| Negative Predictive Value (95% CI) | 98.6% (98.5% to 98.6%) | 98.6% (98.5% to 98.6%) |
| Accuracy (95% CI) | 62.6% (62.4% to 62.8%) | 62.6% (62.3% to 62.8%) |
| **Risk Strata comparison** | **HRs (95% CI), *P* value** | **HRs (95% CI), *P* value** |
| Good | Reference | Reference |
| Good Vs Fairly Good | 2.19(1.74-2.76), *p*<.0001 | 1.44 (1.09-1.90), *p*=0.0106 |
| Good Vs Fairly Poor | 4.11(3.29-5.12), *p*<.0001 | 2.93 (2.26-3.79), *p*<.0001 |
| Good Vs Poor | 13.0(10.4-16.2), *p*<.0001 | 8.50 (6.55-11.01), *p*<.0001 |
| Good Vs Very Poor | 142.2 (114.1-177.2),*p*<.0001 | 79.8 (61.6-103.3), *p*<.0001 |

**Abbreviation: CI=confidence interval.**

†Measures both discrimination and calibration; Range (0 to 1) and lower values indicate higher accuracy, ‡A modification of Hosmer Lemeshow test suited for survival data; measure of calibration that is specific to censored survival data (lower $\chi^2$ and higher p values) indicate better calibration. #A measure of discrimination for which higher values indicate better discrimination. The Youden's J statistics was 0.447 for both cohorts corresponding to risk probability of 0.969.

**Figure 20. Discrimination and calibration plots for nephrolithiasis prediction equation in the derivation cohort. (A) Discrimination. (B) Calibration.**

**A** **B**

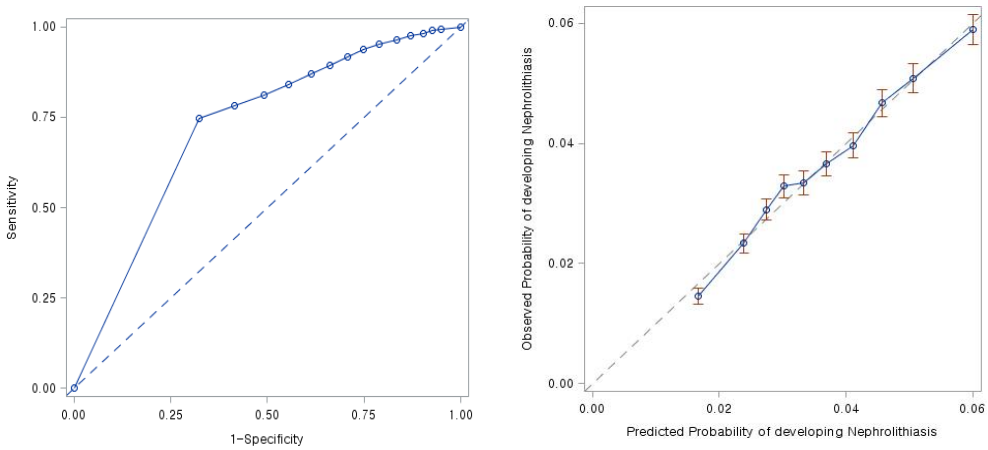



**Figure 21. Discrimination and calibration plots for nephrolithiasis prediction equation in the validation cohort. (A) Discrimination. (B) Calibration.**

**A** **B**

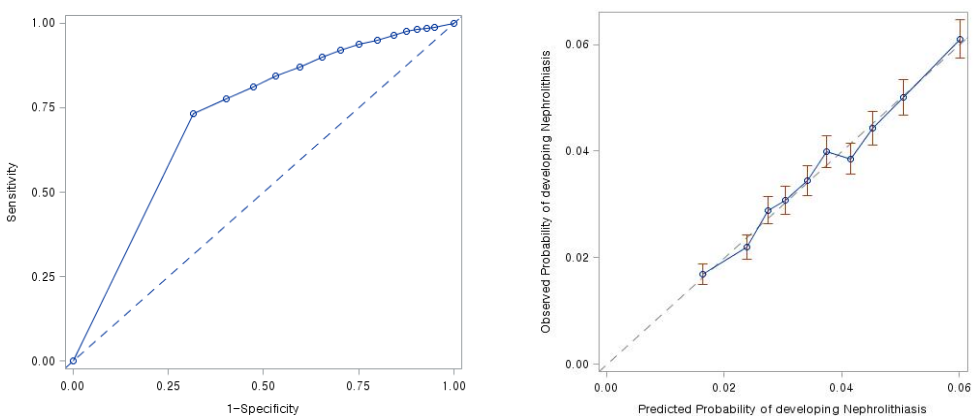
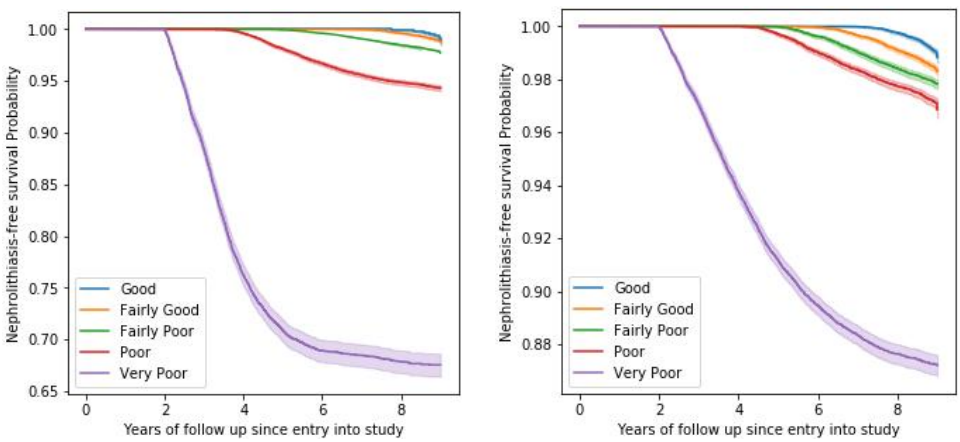


**Figure 22. Kaplan-Meier curves for nephrolithiasis-free survival in 5 risk groups in the derivation and validation cohorts based on the Prognostic Index. (A) Derivation. (B) Validation**

**A** **B**



### 4.6.6 Model discrimination at different thresholds of predicted risk

Table 46 shows the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy for nephrolithiasis equation for various risk probability thresholds based on subjects in the derivation and validation cohorts. The risk probability threshold for the top 3% at highest risk of developing nephrolithiasis in the next 8 years was 0.988, for the top 5% was 0.986, for the top 10% was 0.983, for the top 25% was 0.974, and for the top 50% was 0.966 in both cohorts. With a risk probability threshold of 0.983 over 8 years to identify the 10% of participants with the highest risk of developing nephrolithiasis, the sensitivity for identifying nephrolithiasis was 46.5% (95% CI, 45.2%-47.8%), specificity 91.4% (95% CI, 91.2%-91.5%), positive likelihood ratio 5.38 (95% CI, 5.22-5.56), negative likelihood ration 0.59 (95% CI, 0.57-0.60), positive predictive value 16.9% (95% CI, 16.5%-17.4%), negative predictive value 97.8% (95% CI, 97.8%-97.9%), and accuracy value 89.7% (95% CI, 89.6%-89.9%) in the validation cohort (Table 46). The corresponding thresholds for risk of developing nephrolithiasis over 8 years and the model's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 46). Table 45 shows the results based on the optimal cut off determined by Youden's J statistic for the nephrolithiasis risk equation.

**Table 46. Sensitivity, specificity, likelihood ratio, predictive values and accuracy at different thresholds of predicted risk of nephrolithiasis over 8 years in derivation and validation cohorts**

**Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values and accuracy for nephrolithiasis at different thresholds of predicted risk of nephrolithiasis over 8 years in derivation cohort**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥0.996 | 317,672 | 10,799 | 2,028 | 1,293 | 10.7 (10.2-11.3) | 99.4 (99.3-99.4) | 16.9 (15.8-18.0) | 0.90 (0.89-0.90) | 38.9 (37.4-40.6) | 96.7 (96.7-96.7) | 96.1 (96.1-96.2) |
| 97% | ≥0.988 | 313,750 | 8,110 | 5,935 | 3,997 | 33.0 (32.2-33.9) | 98.1 (98.1-98.2) | 17.8 (17.2-18.4) | 0.68 (0.67-0.69) | 40.2 (39.4-41.1) | 97.5 (97.5-97.5) | 95.8 (95.7-95.8) |
| 95% | ≥0.986 | 307,767 | 7,525 | 11,783 | 4,717 | 38.5 (37.7-39.4) | 96.3 (96.3-96.4) | 10.5 (10.2-10.8) | 0.64 (0.63-0.65) | 28.6 (28.0-29.2) | 97.6 (97.6-97.7) | 94.2 (94.1-94.3) |
| 90% | ≥0.983 | 292,147 | 6,498 | 27,455 | 5,692 | 46.7 (45.8-47.6) | 91.4 (91.3-91.5) | 5.44 (5.32-5.56) | 0.58 (0.57-0.59) | 17.2 (16.9-17.5) | 97.8 (97.8-97.9) | 89.8 (89.7-89.9) |
| 75% | ≥0.974 | 244,951 | 3,902 | 74,753 | 8,186 | 67.7 (66.9-68.6) | 76.6 (76.5-76.8) | 2.90 (2.86-2.94) | 0.42 (0.41-0.43) | 9.87 (9.75-9.99) | 98.4 (98.4-98.5) | 76.3 (76.2-76.4) |
| 50% | ≥0.966 | 163,757 | 2,252 | 155,902 | 9,881 | 81.4 (80.7-82.1) | 51.2 (51.1-51.4) | 1.67 (1.65-1.69) | 0.36 (0.35-0.38) | 5.96 (5.91-6.01) | 98.6 (98.6-98.7) | 52.3 (52.2-52.5) |
| 25% | ≥0.954 | 82,207 | 766 | 237,496 | 11,323 | 93.7 (93.2-94.1) | 25.7 (25.6-25.9) | 1.26 (1.25-1.27) | 0.25 (0.23-0.26) | 4.55 (4.53-4.57) | 99.1 (99.0-99.1) | 28.2 (28.0-28.3) |
| 10% | ≥0.944 | 33,070 | 241 | 286,616 | 11,865 | 98.0 (97.7-98.3) | 10.3 (10.2-10.5) | 1.09 (1.09-1.10) | 0.19 (0.17-0.22) | 3.98 (3.96-3.99) | 99.3 (99.2-99.4) | 13.5 (13.4-13.7) |
| 5% | ≥0.939 | 16,639 | 101 | 303,055 | 11,997 | 99.2 (99.0-99.3) | 5.20 (5.13-5.28) | 1.05 (1.04-1.05) | 0.16 (0.13-0.19) | 3.81 (3.80-3.81) | 99.4 (99.3-99.5) | 8.63 (8.54-8.73) |

**Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values and accuracy for nephrolithiasis at different thresholds of predicted risk of nephrolithiasis over 8 years in validation cohort**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥0.996 | 158,050 | 5,484 | 1,016 | 629 | 10.3 (9.54-11.1) | 99.4 (99.3-99.4) | 16.1 (14.6-17.7) | 0.90 (0.90-0.91) | 38.2 (36.0-40.5) | 96.7 (96.6-96.7) | 96.1 (96.0-96.2) |
| 97% | ≥0.988 | 156,051 | 4,147 | 3,030 | 1,951 | 32.0 (30.8-33.2) | 98.1 (98.0-98.2) | 16.8 (16.0-17.7) | 0.69 (0.68-0.71) | 39.2 (38.0-40.4) | 97.4 (97.4-97.5) | 95.7 (95.6-95.8) |
| 95% | ≥0.986 | 153,166 | 3,671 | 6,050 | 2,292 | 38.4 (37.2-39.7) | 96.2 (96.1-96.3) | 10.1 (9.71-10.5) | 0.64 (0.63-0.65) | 27.5 (26.7-28.3) | 97.7 (97.6-97.7) | 94.1 (94.0-94.2) |
| 90% | ≥0.983 | 145,421 | 3,219 | 13,743 | 2,796 | 46.5 (45.2-47.8) | 91.4 (91.2-91.5) | 5.38 (5.22-5.56) | 0.59 (0.57-0.60) | 16.9 (16.5-17.4) | 97.8 (97.8-97.9) | 89.7 (89.6-89.9) |
| 75% | ≥0.974 | 121,824 | 2,035 | 37,238 | 4,082 | 66.7 (65.5-67.9) | 76.6 (76.4-76.8) | 2.85 (2.79-2.91) | 0.43 (0.42-0.45) | 9.88 (9.70-10.1) | 98.4 (98.3-98.4) | 76.2 (76.0-76.4) |
| 50% | ≥0.966 | 81,304 | 1,125 | 77,803 | 4,947 | 81.5 (80.5-82.4) | 51.1 (50.9-51.4) | 1.67 (1.64-1.69) | 0.36 (0.34-0.38) | 5.98 (5.91-6.05) | 98.6 (98.6-98.7) | 52.2 (52.0-52.5) |
| 25% | ≥0.954 | 40,854 | 404 | 118,209 | 5,712 | 93.4 (92.7-94.0) | 25.7 (25.5-25.9) | 1.26 (1.25-1.27) | 0.26 (0.23-0.28) | 4.61 (4.58-4.64) | 99.0 (98.9-99.1) | 28.2 (28.0-28.4) |
| 10% | ≥0.944 | 16,293 | 108 | 142,787 | 5,991 | 98.2 (97.9-98.6) | 10.2 (10.1-10.4) | 1.09 (1.09-1.10) | 0.17 (0.14-0.21) | 4.03 (4.01-4.04) | 99.3 (99.2-99.5) | 13.5 (13.3-13.7) |
| 5% | ≥0.939 | 8,057 | 39 | 151,015 | 6,068 | 99.4 (99.1-99.6) | 5.07 (4.96-5.17) | 1.05 (1.04-1.05) | 0.13 (0.09-0.17) | 3.86 (3.85-3.87) | 99.5 (99.3-99.7) | 8.55 (8.42-8.69) |

Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages]. The threshold of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.6.7 Prediction equation of 8-year nephrolithiasis risk

With reference to the derived model, individualized probability of developing Nephrolithiasis within the years of follow up (t=8), can be estimated using the following equation:

$$P(\text{Nephrolithiasis}) = 1 - \mathrm{S_o}(t)^{\exp[(\beta_1 x_1 + \beta_2 x_2 \ldots \beta_m x_m)]},$$

Where $\mathrm{S_o}(t)$ denotes the baseline survival probability at time (t) for an individual with all covariates equivalent to zero (0), $(\beta_1 \ldots . \beta_m)$ denotes the change in log hazard rate (estimated $\beta$-coefficients) and $(x_1 \ldots x_m)$ denote values of risk predictors in the model. Using the estimated coefficients ($\beta_i$) and survival probabilities $\mathrm{S_o}$ (t), the 8-year personalized probability of developing Nephrolithiasis can be calculated**.**

The Youden's J statistic suggested a risk probability of ≥0.969 as the optimal cut-off point to define high-risk individuals based on the nephrolithiasis risk prediction equation. This threshold showed a sensitivity of 76.5% (95% CI, 75.4%-77.5%), specificity of 62.0% (95% CI, 61.8%-62.3%), positive likelihood ratio (LR+) of 2.01 (95% CI, 1.98-2.05), negative likelihood ratio (LR-) of 0.38 (95% CI, 0.36-0.40), positive predictive value (PPV) of 7.2% (95% CI, 7.1%-7.3%), negative predictive value 98.6% (95% CI, 98.5%-98.6%) and accuracy of 62.6% (95% CI, 62.3%-62.8%) in prediction of the risk of developing nephrolithiasis over 8 years in the validation cohort (Table 45).

### 4.6.8 Simplified risk score for prediction of 8-year nephrolithiasis risk

Table 44 presents the regression coefficients for the Cox Proportional hazard model fit to the derivation cohort. In the right-most column of the table are the points associated with the presence of a given level of a risk factor (with the reference level assigned zero points). The points were determined by multiplying the regression coefficient by 100 and rounding to the nearest integer. Advanced age (45-54 years old) and male sex conferred the largest number of points (62 and 54 points, respectively). Among modifiable risk factors, heavy alcohol consumption (>3 times/Month) and lower BMI (<18.5 $kgm^2$) were protective (-15 and -20 points, respectively), whereas obesity (BMI >30 $kgm^2$) and high-income grade (>60%) conferred 40 and 9 points respectively, (Table 44).

Participants in the overall sample were divided into five equally sized risk strata using the quintiles of the empirical risk score. Table 47 presents the cumulative incidence risk probabilities for nephrolithiasis in each of the risk strata in the derivation and validation cohorts. In the overall sample, there were statistically significant differences in the cumulative incidence probabilities across the five risk strata based on the Cochran–Armitage test for trend ($p$<.0001). There was a clearly defined gradation in the nephrolithiasis risk across the five risk strata. The lowest risk stratum comprised subjects with a very low nephrolithiasis incidence during eight years of follow-up. In contrast, the highest risk stratum consisted of subjects with a very high incidence of nephrolithiasis during eight years of follow-up. The eight-year cumulative incidence risk of nephrolithiasis in

the lowest and highest risk strata in the derivation cohort were 2.1 (95% CI, 2.0 to 2.2) and 6.0 (95% CI, 5.8 to 6.2), respectively (Table 47). Thus, the 8-year incidence of nephrolithiasis was 3.5 greater in the highest risk stratum than in the lowest risk stratum, and the Hazard Ratio was approximately 3 times greater (Table 47). Figure 1.23 presents the survival trends over 8 years for participants based on the risk score strata,

**Figure 23. Kaplan-Meier curves for nephrolithiasis-free survival in 5 risk groups in the derivation and validation cohorts based on the simplified points based risk score. (A) Derivation. (B) Validation**

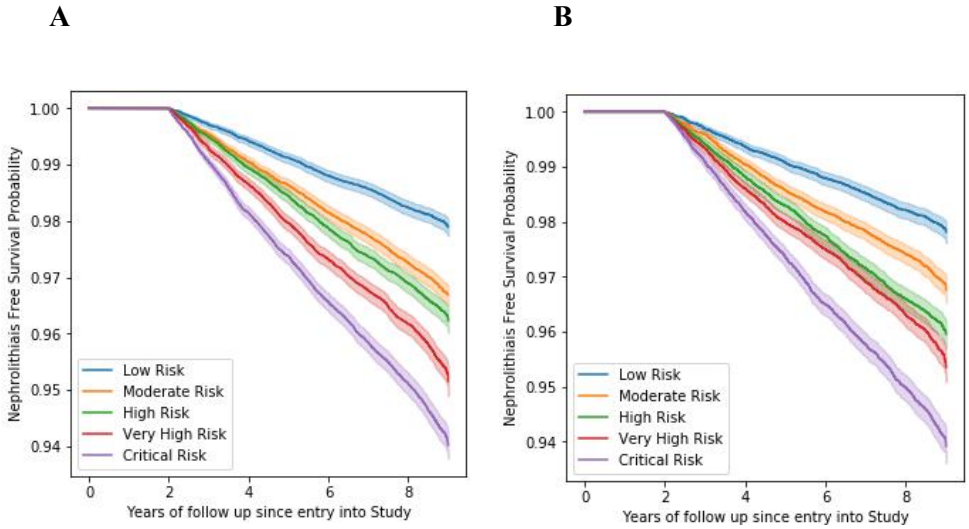


**Table 47. Nephrolithiasis risk in the derivation and validation cohorts based on the risk score strata**

| Nephrolithiasis risk in the derivation cohort based on the risk category (Quintiles of Risk Score). | | | | | | |
|---|---|---|---|---|---|---|
| **Risk Strata** | **Risk Score Range** | **Non-Event** | **Event (%)** | **Total** | ***CR (95% CI)** | **HR (95% CI), *P* value** |
| Low Risk | <50 | 63,648 (98.1) | 1,235 (1.9) | 64,883 | 2.1 (2.0 to 2.2) | Reference |
| Moderate Risk | 50 to 67 | 65,095 (97.0) | 2,044 (3.0) | 67,139 | 3.3 (3.1 to 3.4) | 1.60 (1.49-1.72), *p*<.0001 |
| High Risk | 68 to 90 | 61,227 (96.5) | 2,202 (3.5) | 63,429 | 3.8 (3.6 to 3.9) | 1.83 (1.71-1.97), *p*<.0001 |
| Very High Risk | 91 to 112 | 63,380 (95.7) | 2,829 (4.3) | 63,429 | 4.8 (4.6 to 5.1) | 2.33 (2.18 to 2.49), *p*<.0001 |
| Critical Risk | >112 | 66,296 (94.5) | 3,836 (5.5) | 70,132 | 6.0 (5.8 to 6.2) | 2.95 (2.77 to 3.15), *p*<.0001 |
| **Nephrolithiasis risk in the validation cohort, according to risk category (Quintiles of Risk Score).** | | | | | | |
| **Risk Stata** | **Risk Score Range** | **Non-Event** | **Event (%)** | **Total** | ***CR (95% CI)** | **HR (95% CI), *P* value** |
| Low Risk | <50 | 31,644 (98.0) | 638 (2.0) | 32,282 | 2.2 ( 2.0 to 2.4) | Reference |
| Moderate Risk | 50 to 67 | 32,691 (97.1) | 986 (2.9) | 33,677 | 3.2 (3.0 to 3.5) | 1.48 (1.34-1.63), *p*<.0001 |
| High Risk | 68 to 90 | 30,290 (96.3) | 1,169 (3.7) | 31,459 | 4.0 (3.8 to 4.3) | 1.89 (1.72-2.08), *p*<.0001 |
| Very High Risk | 91 to 112 | 30,290 (95.9) | 1,340 (4.1) | 32,867 | 4.6 (4.4 to 4.9) | 2.13 (1.93 to 2.34), *p*<.0001 |
| Critical Risk | >112 | 32,968 (94.5) | 1,926 (5.5) | 34,894 | 6.1 (5.8 to 6.4) | 2.86 (2.62 to 3.13), *p*<.0001 |
| **Average 8-year baseline survival probability=0.9477** | | | | | | |

***CR =Cumulative Risk

‡Cochran–Armitage test for trend (for overall cohort), *p*<.000.

### 4.6.9 Validation of simplified risk score at different risk score thresholds

The observed theoretical minimum and maximum sum of the risk points were -41 and 175, respectively. The median score was 80, while the 25$^{th}$ and 75$^{th}$ percentiles were 55 and 109, respectively. Table 48 shows the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy for nephrolithiasis risk score for various risk score thresholds based on subjects in the derivation and validation cohorts. The risk score threshold for the top 3% at highest risk of developing nephrolithiasis in the next 8 years was 138, for the top 5% was 135, for the top 10% was 126, for the top 25% was 109, and for the top 50% was 80 in both cohorts. With a risk score threshold of 126 over 8 years to identify the 10% of participants with the highest risk of nephrolithiasis, the sensitivity for identifying nephrolithiasis was 16.5% (95% CI, 15.5%-17.4%), specificity 90.2% (95% CI, 90.1%-90.4%), positive predictive value 6.05% (95% CI, 5.72%-6.39%), negative predictive value 96.6% (95% CI, 96.5%-96.6%), and accuracy value 87.5% (95% CI, 87.4%-87.7%) in the validation cohort (Table 48). The corresponding thresholds for risk of developing nephrolithiasis over 8 years and the risk score's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 48).

The Youden's J statistic suggested a risk score of ≥88 as the optimal cut-off point to define high-risk individuals based on the simplified nephrolithiasis risk score. This threshold showed a sensitivity of 56.1% (95% CI, 54.8%-57.4%), specificity of 57.5% (95% CI, 57.3%-57.7%), positive likelihood ratio (LR+) of

1.32 (95% CI, 1.29-1.35), negative likelihood ratio (LR-) of 0.76 (95% CI, 0.74-0.79), positive predictive value (PPV) of 4.78% (95% CI, 4.68%-4.89%), negative predictive value 97.2 (95% CI, 97.1%-97.3%) and accuracy of 57.4 (95% CI, 57.2-57.7) in prediction of the risk of developing nephrolithiasis over 8 years in the validation cohort (Table 48).

**Table 48. Sensitivity, specificity, likelihood ratio, predictive values, and accuracy based on different thresholds of the 8-year nephrolithiasis risk score**

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values and accuracy for nephrolithiasis at different thresholds of nephrolithiasis risk score over 8 years in derivation cohort**

| Threshold (Centiles) | Risk Score Points | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥147 | 316,210 | 11,818 | 3,505 | 259 | 2.14 (1.89-2.42) | 98.9 (98.9-98.9) | 1.96 (1.73-2.22) | 0.99 (0.99-0.99) | 6.88 (6.12-7.73) | 96.4 (96.4-96.4) | 95.4 (95.3-95.5) |
| 97% | ≥138 | 308,536 | 11,437 | 11,071 | 748 | 6.14 (5.72-6.58) | 96.5 (96.5-96.6) | 1.77 (1.65-1.90) | 0.97 (0.97-0.98) | 6.33 (5.92-6.77) | 96.4 (96.4-96.4) | 93.2 (93.1-93.3) |
| 95% | ≥135 | 303,862 | 11,152 | 15,706 | 1,072 | 8.77 (8.27-9.29) | 95.1 (95.0-95.2) | 1.78 (1.68-1.89) | 0.96 (0.95-0.96) | 6.39 (6.04-6.75) | 96.5 (96.4-96.5) | 91.9 (91.8-92.0) |
| 90% | ≥126 | 288,485 | 10,141 | 31,187 | 1,979 | 16.3 (15.7-17.0) | 90.2 (90.1-90.4) | 1.67 (1.61-1.74) | 0.93 (0.92-0.93) | 5.97 (5.74-6.21) | 96.6 (96.6-96.6) | 87.5 (87.4-87.7) |
| 75% | ≥109 | 238,370 | 7,644 | 81,171 | 4,607 | 37.6 (36.8-38.5) | 74.6 (74.5-74.8) | 1.48 (1.45-1.52) | 0.84 (0.82-0.85) | 5.37 (5.25-5.49) | 96.9 (96.9-96.9) | 73.2 (73.1-73.4) |
| **‡57.1%** | ≥88 | 184,187 | 5,272 | 135,459 | 6,874 | 56.6 (55.7-57.5) | 57.6 (57.5-57.8) | 1.34 (1.31-1.36) | 0.75 (0.74-0.77) | 4.83 (4.76-4.90) | 97.2 (97.2-97.3) | 57.6 (57.4-57.8) |
| 50% | ≥80 | 161,541 | 4,440 | 158,075 | 7,736 | 63.5 (62.7-64.4) | 50.5 (50.4-50.7) | 1.28 (1.27-1.30) | 0.72 (0.70-0.74) | 4.67 (4.60-4.73) | 97.3 (97.3-97.4) | 51.0 (50.9-51.2) |
| 25% | ≥55 | 79,674 | 1,682 | 240,014 | 10,422 | 86.1 (85.5-86.7) | 24.9 (24.8-25.1) | 1.15 (1.14-1.16) | 0.56 (0.53-0.58) | 4.16 (4.13-4.19) | 97.9 (97.8-98.0) | 27.2 (27.0-27.3) |
| 10% | ≥32 | 32,191 | 488 | 287,514 | 11,599 | 96.0 (95.6-96.3) | 10.1 (9.96-10.2) | 1.07 (1.06-1.07) | 0.40 (0.37-0.44) | 3.88 (3.86-3.89) | 98.5 (98.4-98.6) | 13.2 (13.1-13.3) |
| 5% | ≥4 | 15,843 | 234 | 303,842 | 11,873 | 98.1 (97.8-98.3) | 4.96 (4.88-5.03) | 1.03 (1.03-1.03) | 0.39 (0.34-0.44) | 3.76 (3.75-3.77) | 98.5 (98.4-98.7) | 8.35 (8.26-8.45) |

**Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values and accuracy for nephrolithiasis at different thresholds of nephrolithiasis risk score over 8 years in validation cohort**

| Threshold (Centile) | Risk Score Points | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥147 | 157,295 | 6,013 | 1,756 | 115 | 1.88 (1.55-2.25) | 98.9 (98.8-99.0) | 1.70 (1.41-2.05) | 0.99 (0.99-1.00) | 6.15 (5.15-7.32) | 96.3 (96.3-96.3) | 95.3 (95.2-95.4) |
| 97% | ≥138 | 153,559 | 5,651 | 5,600 | 369 | 6.13 (5.54-6.77) | 96.5 (96.4-96.6) | 1.74 (1.57-1.93) | 0.97 (0.97-0.98) | 6.18 (5.62-6.80) | 96.5 (96.4-96.5) | 93.2 (93.1-93.3) |
| 95% | ≥135 | 151,233 | 5,448 | 7,965 | 533 | 8.91 (8.20-9.66) | 95.0 (94.9-95.1) | 1.78 (1.64-1.94) | 0.96 (0.95-0.97) | 6.27 (5.80-6.78) | 96.5 (96.5-96.6) | 91.9 (91.8-92.0) |
| 90% | ≥126 | 143,543 | 5,084 | 15,551 | 1,001 | 16.5 (15.5-17.4) | 90.2 (90.1-90.4) | 1.68 (1.59-1.78) | 0.93 (0.92-0.94) | 6.05 (5.72-6.39) | 96.6(96.5-96.6) | 87.5 (87.4-87.7) |
| 75% | ≥109 | 118,660 | 3,729 | 40,565 | 2,225 | 37.4 (36.1-38.6) | 74.5 (74.3-74.7) | 1.47 (1.42-1.52) | 0.84 (0.82-0.86) | 5.20 (5.04-5.37) | 97.0 (96.9-97.0) | 73.2 (73.0-73.4) |
| **‡57.1%** | ≥88 | 91,480 | 2,660 | 67,640 | 3,399 | 56.1 (54.8-57.4) | 57.5 (57.3-57.7) | 1.32 (1.29-1.35) | 0.76 (0.74-0.79) | 4.78 (4.68-4.89) | 97.2 (97.1-97.3) | 57.4 (57.2-57.7) |
| 50% Median | ≥80 | 80,196 | 2,215 | 78,954 | 3,814 | 63.3 (62.0-64.5) | 50.4 (50.1-50.6) | 1.28 (1.25-1.30) | 0.73 (0.71-0.75) | 4.61 (4.52-4.70) | 97.3 (97.2-97.4) | 50.9 (50.6-51.1) |
| 25% | ≥55 | 39,610 | 863 | 119,468 | 5,238 | 85.9 (85.0-86.7) | 24.9 (24.7-25.1) | 1.14 (1.13-1.16) | 0.57 (0.53-0.60) | 4.20 (4.16-4.24) | 97.9 (97.7-98.0) | 27.2 (26.9-27.4) |
| 10% | ≥32 | 15,847 | 253 | 143,214 | 5,865 | 95.9 (95.3-96.4) | 9.96 (9.82-10.1) | 1.06 (1.06-1.07) | 0.42 (0.37-0.47) | 3.93 (3.91-3.95) | 98.4 (98.2-98.6) | 13.1 (13.0-13.3) |
| 5% | ≥4 | 7,621 | 102 | 151,460 | 5,996 | 98.3 (98.0-98.6) | 4.79 (4.69-4.90) | 1.03 (1.03-1.04) | 0.35 (0.29-0.42) | 3.81 (3.80-3.82) | 98.7 (98.4-98.9) | 8.24 (8.11-8.38) |

‡The value determined by Youden's J statistic as the optimal cut off threshold for identifying his risk group. Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages]. The threshold of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.6.10 Practical application of 8-year nephrolithiasis risk score

The following hypothetical example illustrates how nephrolithiasis risk can be estimated using the simplified points based system.

**Case**: A 52-year-old male with insurance premium of 30-60%, who is a heavy drinker (>3 times/month), obese (BMI >30 kg/$m^2$), normal total cholesterol (<200 mg/dL), with fasting blood glucose (>126 mg/dL or with medical utilisation due to diabetes), without history of inflammatory bowel disease and gout but with history of hyperparathyroidism.

**Table 49. Table of calculated nephrolithiasis risk score for a hypothetical example of a risk profile**

| Risk factor (Predictor) | Value (Risk factor Category) | Points |
|---|---|---|
| Sex | Male | 54 |
| Age | 45-54 yrs | 62 |
| Insurance Premium | Medium (30-60%) | 4 |
| Alcohol Consumption | Heavy drinker(>3 times/month) | -15 |
| Body Mass Index | >30 kg/$m^2$ | 40 |
| Total Cholesterol | <200 mg/dL | 0 |
| Fasting Blood Glucose | >126 mg/dL or Rx | -4 |
| Diagnosed IBD | No | 0 |
| Hyperparathyroidism | Yes | 16 |
| History of Gout | No | 0 |
| **Total Points** | | **157** |
| **Estimate of Risk** | | **0.228** |

***$S_o$ (t) = 0.9477**

Based on the point system, the probability of nephrolithiasis can be estimated as follows

$$P(\text{Nephrolithiasis}) = 1 - (0.9477)^{\exp[(157/100)]}$$
$$= 0.228$$

The $S_0(t)$ is the baseline survival probability at time (t=8 years) for an individual with all covariates equivalent to zero, which was estimated by Cox regression analysis. The beta coefficients were converted to integer risk points by multiplying with 100. Thus, in the actual calculation, the sum of the risk score (157 risk points) was divided by 100 to give an overall 8-year risk estimate.

# 4.7 Prediction of 5-year Nephrolithiasis Recurrence Risk

### 4.7 Prediction of 5-year nephrolithiasis recurrence risk

#### 4.7.1 Cohort baseline characteristics for 5-year nephrolithiasis recurrence

In this study, a consecutive cohort of 23,576 nephrolithiasis patients was constructed to study nephrolithiasis recurrence, and included participants who presented with nephrolithiasis in the baseline period (January 1st 2002 to December 31st 2003) and those who developed nephrolithiasis after the baseline period (January 1st 2004 to December 31st 2010). During a median follow-up period of 2.75 years (Range: 0.0-5.0), there were 7,086 (30.1%) recurrent cases of nephrolithiasis among 23,576 participants. The mean (SD) of covariates and the distribution of the baseline characteristics stratified by nephrolithiasis recurrence status in the derivation and validation cohorts are presented and there were no discrepancies between the derivation and validation cohort (Tables 50). In both cohorts, there was significant difference in baseline characteristics between those who experienced nephrolithiasis recurrence and those who did not ($p$<0.05) (Tables 50). Those who experienced nephrolithiasis recurrence had high mean values of SBP, DBP, total cholesterol, FBG, and BMI (Table 50).

**Table 50. Baseline characteristic of participants in derivation and validation cohorts for 5-year nephrolithiasis recurrence [Mean (SD) or n (%)]**

| | Derivation Cohort (n=15,656) | | | Validation Cohort (n=7,920) | | |
|---|---|---|---|---|---|---|
| **Covariate** | **Without Nephrolithiasis Recurrence 10,953 (70.0)** | **With Nephrolithiasis Recurrence 4,703 (30.0)** | **P value** | **Without Nephrolithiasis Recurrence 5,537 (69.9)** | **With Nephrolithiasis Recurrence 2,383 (30.1)** | **P value** |
| Years of follow up | 3.4 (1.8 ) | 1.2 (1.5) | <.0001 | 3.3 (1.8) | 1.3 (1.5 ) | <.0001 |
| Height (cm) | 163.8 (8.8) | 164.2 (8.7) | 0.0144 | 163.8 (8.8) | 164.5 (8.7) | 0.0004 |
| Weight (kgs) | 64.5 (11.2) | 65.9 (10.9) | <.0001 | 64.5 (11.1) | 66.2 (10.8) | <.0001 |
| BMI ($kg/m^{2)}$ | 23.9 (3.2) | 24.4 (3.1) | <.0001 | 23.9 (3.2) | 24.4 (3.1) | <.0001 |
| SBP (mm Hg) | 124.3 (16.9) | 126.0 (17.1) | <.0001 | 124.0 (16.8) | 126.6 (17.0) | <.0001 |
| DBP (mm Hg) | 78.3 (11.2) | 79.6 (11.2) | <.0001 | 78.2 (11.0) | 79.6 (11.3) | <.0001 |
| Fasting Glucose (mg/dL) | 94.8 (27.8) | 95.3 (27.5) | 0.3666 | 94.1 (27.0) | 95.7 (28.2) | 0.0201 |
| Total Cholesterol (mg/dL) | 196.4 (37.9) | 198.3 (38.3) | 0.0047 | 195.7 (37.6) | 198.5 (37.8) | 0.0029 |
| Number of consultations | 1.5 (1.6) | 1.8 (1.9) | <.0001 | 1.5 (1.4) | 1.4 (4.7) | 0.0011 |
| Length of prescription | 3.3 (7.1) | 5.1 (10.7) | <.0001 | 3.1 (6.7) | 5.0 (10.5) | <.0001 |
| Length of hospitalization | 2.2 (3.4) | 2.6 (3.7) | <.0001 | 2.2 (3.0) | 2.7 (5.7) | <.0001 |
| **Sex** | | | <.0001 | | | <.0001 |
| Male | 6,474 (59.1) | 3,080 (65.49) | | 3,221 (58.2) | 1,644 (69.0) | |
| Female | 4,479 (40.9) | 1,623 (34.51) | | 2,316 (41.8) | 739 (31.0) | |
| **Age** | | | <.0001 | | | 0.1947 |
| <25 yrs. | 917 (8.4) | 290 (6.17) | | 430 (7.8) | 156 (6.6) | |
| 25-34 yrs | 2,026 (18.5) | 799 (16.99) | | 1,027 (18.5) | 415 (17.4) | |
| 35-44yrs | 2,968 (27.1) | 1,248 (26.54) | | 1,509 (27.3) | 659 (27.6) | |
| 45-54 yrs | 2,602 (23.7) | 1,163 (24.73) | | 1,318 (23.8) | 585 (24.6) | |
| ≥55 yrs | 2,440 (22.3) | 1,203 (25.58) | | 1,253 (22.6) | 568 (23.8) | |
| **Income/Insurance Premium** | | | 0.0246 | | | 0.5945 |
| Low (<30%) | 1,436 (13.1) | 586 (12.46) | | 679 (12.3) | 295 (12.4) | |

| | Derivation Cohort (n=15,656) | | | Validation Cohort (n=7,920) | | |
|---|---|---|---|---|---|---|
| **Covariate** | **Without Nephrolithiasis Recurrence 10,953 (70.0)** | **With Nephrolithiasis Recurrence 4,703 (30.0)** | **P value** | **Without Nephrolithiasis Recurrence 5,537 (69.9)** | **With Nephrolithiasis Recurrence 2,383 (30.1)** | **P value** |
| Medium (30-60%) | 3,763 (34.4) | 1,535 (32.64) | | 1,931 (34.9) | 803 (33.7) | |
| High (>60%) | 5,754 (52.5) | 2,582 (54.90) | | 2,927 (52.8) | 1,285 (53.9) | |
| **Physical Activity** | | | 0.0291 | | | 0.2402 |
| Low (None) | 6,177 (56.4) | 2,562 (54.48) | | 3,080 (55.6) | 444 (53.9) | |
| Moderate (1-2 times/week) | 3,929 (35.9) | 1,730 (36.79) | | 2,013 (36.4) | 885 (37.2) | |
| High (>3 times/week) | 847 (7.7) | 411 (8.74) | | 444 (8.0) | 213 (8.9) | |
| **Smoking Status** | | | 0.0074 | | | 0.0207 |
| Never | 6,962 (63.6) | 2,867 (60.96) | | 3,502 (63.3) | 1,429 (60.0) | |
| Former Smoker | 536 (4.9) | 256 (5.44) | | 261 (4.7) | 118 (4.9) | |
| Current Smoker | 3,455 (31.5) | 1,580 (33.60) | | 1,774 (32.0) | 836 (35.1) | |
| **Alcohol Consumption/Month** | | | 0.0507 | | | 0.0074 |
| Rarely (< 2 times) | 5,486 (50.1) | 2,262 (48.10) | | 2,775 (50.1) | 1,103 (46.3) | |
| Moderate drinker (2–3 times) | 4,459 (40.7) | 1,971 (41.91) | | 2,229 (40.3) | 1,030 (43.2) | |
| Heavy drinker ( ≥ 4 times) | 1,008 (9.2) | 470 (9.99) | | 533 (9.6) | 250 (10.5) | |
| **Body Mass Index** | | | <.0001 | | | <.0001 |
| <18.5 $kg/m^2$ | 382 (3.5) | 111 (2.4) | | 204 (3.7) | 55 (2.3) | |
| 18.5 $kg/m^2$-24.9 $kg/m^2$ | 6,658 (60.8) | 2,650 (56.3) | | 3,340 (60.3) | 1,366 (57.3) | |
| 25 $kg/m^2$-29.9 $kg/m^2$ | 3,528 (32.2) | 2,650 (37.2) | | 1,819 (32.9) | 859 (36.1) | |
| ≥30 $kg/m^2$ | 385 (3.5) | 192 (4.1) | | 174 (3.1) | 103 (4.3) | |
| **Fasting Blood Glucose** | | | 0.5187 | | | 0.0440 |
| < 100mg/dL | 6,998 (63.9) | 2,962 (63.0) | | 3,596 (65.0) | 1,480 (62.1) | |
| 100 mg/dL-125 mg/dL | 2,700 (24.6) | 1,180 (25.1) | | 1,347 (24.3) | 616 (25.9) | |
| ≥ 126 mg/dL Or Rx | 1,255 (11.5) | 561 (11.9) | | 594 (10.7) | 287 (12.0) | |
| **Blood Pressure/HTN** | | | <.0001 | | | <.0001 |
| SBP < 120 and DBP < 80 | 3,513 (32.0) | 1,311 (27.9) | | 1,832 (33.1) | 635 (26.7) | |
| SBP 120-139 or DBP 80-89 | 5,968 (54.5) | 2,668 (56.7) | | 3,030 (54.7) | 1,363 (57.2) | |

| | Derivation Cohort (n=15,656) | | | Validation Cohort (n=7,920) | | |
|---|---|---|---|---|---|---|
| **Covariate** | **Without Nephrolithiasis Recurrence 10,953 (70.0)** | **With Nephrolithiasis Recurrence 4,703 (30.0)** | **P value** | **Without Nephrolithiasis Recurrence 5,537 (69.9)** | **With Nephrolithiasis Recurrence 2,383 (30.1)** | **P value** |
| SBP 140-159 or DBP 90-99 | 1,278 (11.7) | 625 (13.3) | | 3,030 (10.7) | 334 (14.0) | |
| SBP ≥ 160 or DBP ≥ 100 or Rx | 194 (1.8) | 99 (2.1) | | 84 (1.5) | 51 (2.1) | |
| **Total cholesterol** | | | 0.0137 | | | 0.0586 |
| < 200 mg/dL | 6,025 (55.0) | 2,476 (52.6) | | 3,067 (55.4) | 1,279 (53.7) | |
| 200 mg/dL-239 mg/dL | 3,564 (32.5) | 1,583 (33.7) | | 1,769 (31.9) | 756 (31.7) | |
| > 240 mg/dL | 3,564 (12.5) | 644 (13.7) | | 701 (12.7) | 348 (14.6) | |
| **Diagnosed IHD** | | | 0.0650 | | | 0.2689 |
| No | 10,788 (98.5) | 4,613 (98.1) | | 5462 (98.6) | 2,343 (98.3) | |
| Yes | 165 (1.51) | 90 (1.9) | | 75 (1.4) | 40 (1.7) | |
| **Diagnosed IBD** | | | 0.7953 | | | 0.0113 |
| No | 10,887 (99.4) | 4,673 (99.4) | | 5,509 (99.5) | 2,359 (99.0) | |
| Yes | 66 (0.6) | 30 (0.6) | | 28 (0.5) | 24 (1.0) | |
| **Diagnosed CKD** | | | 0.1595 | | | 0.9014 |
| No | 10,940 (99.9) | 4,693 (99.8) | | 5,527 (99.8) | 2,379 (99.8) | |
| Yes | 13 (0.1) | 10 (0.2) | | 10 (0.2) | 4 (0.2) | |
| **Hyperparathyroidism** | | | 0.5827 | | | 0.4576 |
| No | 10,818 (98.8) | 4,640 (98.7) | | 5,468 (98.7) | 2,358 (98.9) | |
| Yes | 135 (1.2) | 63 (1.3) | | 69 (1.3) | 25 (1.1) | |
| **Diagnosed Gout** | | | 0.6278 | | | 0.0306 |
| No | 10,910 (99.6) | 4,682 (99.5) | | 5,519 (99.7) | 2,367 (99.3) | |
| Yes | 43 (0.4) | 21 (0.5) | | 18 (0.3) | 16 (0.7) | |

The student's *t*-test for continuous variables and $\chi^2$-test for categorical variables were used to examine the differences in baseline characteristics between participants in the derivation and validation cohorts stratified based on 5-year nephrolithiasis recurrence outcome

### 4.7.2 Cumulative incidence probabilities of 5-year nephrolithiasis recurrence

During the follow up period, the cumulative risk of nephrolithiasis recurrence increased from 19.8 (95% CI, 19.3 to 20.4) in the first year of follow up to 37.6 (95% CI, 36.8 to 38.3) at the end of the follow up period (5 years). The details of the 5-year incidence trends and cumulative risks for nephrolithiasis recurrence are presented (Table 51).

**Table 51. Follow-up times, cumulative incidence, and incidence probabilities of nephrolithiasis recurrence within 5 years**

| Duration of follow up | Censored | Events | Total | CR* (95% CI) |
|---|---|---|---|---|
| Year 1 | 2,663 | 4,429 | 7,092 | 19.8 (19.3 to 20.4) |
| Year 2 | 1,883 | 953 | 2,836 | 24.7 (24.1 to25.3) |
| Year 3 | 1,832 | 601 | 2,433 | 28.3 (27.6 to 28.9 |
| Year 4 | 1,930 | 426 | 2,356 | 31.2 (30.6 to 31.9) |
| Year 5 | 8,182 | 677 | 8,859 | 37.6 (36.8 to 38.3) |
| **Totals** | **16,490** | **7,086** | **23,576** | |

**CR*=Cumulative Risk**

### 4.7.3 Association between risk predictors and 5-year nephrolithiasis recurrence

Tables 52 present the estimated coefficients and hazard ratios of covariates. In the univariate analysis, all risk factors were associated with nephrolithiasis recurrence except income grade, IHD, CKD, and hyperparathyroidism whereas physical activity showed an inverse association. In the multivariate analysis, smoking and alcohol consumption changed to inverse associations which were not statistically significant ($p$<0.05) (Table 52). The risk factors that were not

statistically significant in multivariate analysis included FBG, smoking, alcohol consumption, physical activity, income grade and premorbidities of CKD, gout, hyperparathyroidism, IHD and IBD ($p<0.05$) (Table 52). All medication related variables (number of previous consultations, duration of prescription and duration of hospitalization) were associated with nephrolithiasis recurrence. Among lifestyle risk factors, smoking status, alcohol consumption and physical activity were not significantly associated with nephrolithiasis recurrence in fully adjusted analyses ($p<0.05$) (Table 52). In this study, premorbidities were not associated with 5-year nephrolithiasis recurrence ($p<0.05$) (Table 52).

**Table 52. Hazard Ratios (95% confidence interval) and *β*-coefficients for risk predictors of 5-year nephrolithiasis recurrence**

| Covariate | Unadjusted* | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | *β* (SE) | HR (95% CI) | *P* Value | *β* (SE) | HR (95% CI) | *P* Value | *β* (SE) | HR (95% CI) | *P* Value |
| **Sex** | | | | | | | | | |
| Male | 0.316 (0.025) | 1.37 (1.31-1.44) | <.0001 | 0.332 (0.025) | 1.39 (1.33-1.47) | <.0001 | 0.355 (0.032) | 1.43 (1.34-1.52) | <.0001 |
| **Age** | | | | | | | | | |
| <25 yrs. | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 25-34yrs | 0.122 (0.055) | 1.13 (1.01-1.26) | 0.0271 | 0.074 (0.056) | 1.08 (0.97-1.20) | 0.1848 | 0.077 (0.056) | 1.08 (0.97-1.20) | 0.1692 |
| 35-44 yrs | 0.148 (0.053) | 1.16 (1.05-1.29) | 0.0049 | 0.135 (0.053) | 1.15 (1.03-1.27) | 0.0101 | 0.129 (0.053) | 1.14 (1.03-1.26) | 0.0152 |
| 45-54 | 0.174 (0.053) | 1.19 (1.07-1.32) | 0.0010 | 0.179 (0.053) | 1.20 (1.08-1.33) | 0.0008 | 0.169 (0.054) | 1.18 (1.07-1.32) | 0.0016 |
| ≥55 yrs | 0.238 (0.053) | 1.27 (1.14-1.41) | <.0001 | 0.255 (0.053) | 1.29 (1.16-1.43) | <.0001 | 0.242 (0.054) | 1.27 (1.15-1.42) | <.0001 |
| **Income/Insurance** | | | | | | | | | |
| Low (<30%) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Medium (30-60%) | -0.018 (0.040) | 0.98 (0.91-1.06) | 0.6440 | -0.034 (0.040) | 0.97 (0.89-1.04) | 0.3861 | -0.034 (0.040) | 0.97 (0.90-1.05) | 0.3975 |
| High (60%) | 0.043 (0.037) | 1.04 (0.97-1.12) | 0.2488 | 0.007 (0.038) | 1.01 (0.94-1.08) | 0.8579 | 0.005 (0.038) | 1.01 (0.93-1.08) | 0.3975 |
| **Physical Activity/ Week** | | | | | | | | | |
| High (≥3 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate (1-2 times) | -0.070 (0.045) | 0.93 (0.86-1.02) | 0.1178 | -0.054 (0.045) | 0.94 (0.87-1.03) | 0.2272 | 0.053 (0.045) | 0.94 (0.87-1.04) | 0.2361 |
| Low (None) | -0.120 (0.043) | 0.89 (0.82-0.97) | 0.0053 | -0.055 (0.043) | 0.95 (0.87-1.03) | 0.2073 | -0.051 (0.044) | 0.95 (0.87-1.04) | 0.2423 |
| **Smoking Status** | | | | | | | | | |
| Never | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Former Smoker | 0.125 (0.054) | 1.13 (1.02-1.26) | 0.0206 | -0.047 (0.056) | 0.96 (0.86-1.07) | 0.4052 | -0.048 (0.056) | 0.95 (0.85-1.06) | 0.3875 |
| Current Smoker | 0.124 (0.025) | 1.13 (1.08-1.19) | <.0001 | -0.048 (0.030) | 0.95 (0.90-1.01) | 0.1130 | -0.045 (0.030) | 0.96 (0.90-1.02) | 0.1392 |
| **Alcohol** | | | | | | | | | |
| Rarely (<2 times) | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| Moderate Drinker (2-3 times) | 0.095 (0.025) | 1.10 (1.05-1.16) | 0.0001 | -0.008 (0.027) | 0.99 (0.94-1.05) | 0.7769 | -0.003 (0.028) | 0.99 (0.94-1.05) | 0.9114 |
| Heavy Drinker (≥4 times) | 0.134 (0.041) | 1.14 (1.06-1.24) | 0.0011 | -0.010 (0.043) | 0.99 (0.91-1.08) | 0.8227 | -0.001 (0.044) | 0.99 (0.92-1.09) | 0.9783 |
| **Body Mass Index** | | | | | | | | | |
| < 18.5 kg/m$^2$ | -0.287 (0.079) | 0.75 (0.64-0.88) | 0.0003 | -0.173 (0.080) | 0.84 (0.72-0.98) | 0.0307 | -0.172 (0.080) | 0.84 (0.72-0.99) | 0.0316 |

| Covariate | Unadjusted* | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | *β* (SE) | HR (95% CI) | *P* Value | *β* (SE) | HR (95% CI) | *P* Value | *β* (SE) | HR (95% CI) | *P* Value |
| 18.5 kg/m$^2$-24.9 kg/m$^2$ | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 25 kg/m$^2$-29.9 kg/m$^2$ | 0.157 (0.025) | 1.17 (1.11-1.23) | <.0001 | 0.118 (0.025) | 1.13 (1.07-1.18) | <.0001 | 0.117 (0.025) | 1.12 (1.07-1.18) | <.0001 |
| ≥30 kg/m$^2$ | 0.203 (0.060) | 1.22 (1.09-1.38) | 0.0008 | 0.195 (0.060) | 1.22 (1.08-1.37) | 0.0012 | 0.196 (0.060) | 1.22 (1.08-1.37) | 0.0012 |
| **Fasting Blood Glucose** | | | | | | | | | |
| <100 mg/dL | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 100 mg/dL-125 mg/dL | 0.042 (0.028) | 1.04 (0.99-1.10) | 0.1355 | 0.016 (0.028) | 1.02 (0.96-1.07) | 0.5650 | 0.018 (0.028) | 1.02 (0.96-1.08) | 0.5217 |
| >126 mg/dL or Rx | 0.088 (0.037) | 1.09 (1.02-1.18) | 0.0190 | 0.046 (0.038) | 1.05 (0.97-1.13) | 0.2282 | 0.048 (0.038) | 1.05 (0.97-1.13) | 0.2107 |
| **Total Cholesterol** | | | | | | | | | |
| < 200 mg/dL | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 200 mg/dL-239 mg/dL | 0.053 (0.026) | 1.06 (1.00-1.11) | 0.0431 | 0.033 (0.027) | 1.03 (0.98-1.09) | 0.2139 | 0.033 (0.027) | 1.03 (0.98-1.09) | 0.2169 |
| > 240 mg/dL | 0.108 (0.036) | 1.11 (1.04-1.19) | 0.0026 | 0.083 (0.036) | 1.09 (1.01-1.17) | 0.0207 | 0.084 (0.036) | 1.09 (1.01-1.17) | 0.0203 |
| **Blood Pressure/HTN** | | | | | | | | | |
| SBP <120 and DBP <80 | Reference | | | Reference | Reference | | Reference | Reference | |
| SBP 120-139 or DBP 80-89 | 0.170 (0.028) | 1.19 (1.12-1.25) | <.0001 | 0.104 (0.028) | 1.11 (1.05-1.17) | 0.0002 | 0.104 (0.028) | 1.11 (1.05-1.17) | 0.0002 |
| SBP 140-159 or DBP 90-99 | 0.273 (0.040) | 1.31 (1.22-1.42) | <.0001 | 0.170 (0.041) | 1.19 (1.09-1.28) | <.0001 | 0.171 (0.041) | 1.19 (1.10-1.29) | <.0001 |
| SBP ≥160 or DBP ≥100 or Rx | 0.341 (0.085) | 1.41 (1.19-1.66) | <.0001 | 0.237 (0.085) | 1.27 (1.07-1.50) | 0.0056 | 0.236 (0.086) | 1.27 (1.07-1.50) | 0.0059 |
| **Premorbidities** | | | | | | | | | |
| Diagnosed IHD | 0.154 (0.089) | 1.17 (0.98-1.39) | 0.0817 | 0.117 (0.089) | 1.12 (0.94-1.34) | 0.1887 | 0.114 (0.089) | 1.12 (0.94-1.34) | 0.2010 |
| Diagnosed IBD | 0.206 (0.137) | 1.23 (0.94-1.61) | 0.1322 | 0.208 (0.137) | 1.23 (0.94-1.61) | 0.1285 | 0.205 (0.137) | 1.23 (0.94-1.60) | 0.1342 |
| Diagnosed CKD | 0.342(0.267) | 1.41 (0.83-2.38) | 0.2009 | 0.286 (0.267) | 1.33 (0.79-2.25) | 0.2852 | 0.292 (0.267) | 1.34 (0.79-2.26) | 0.2750 |
| Hyperparathyroidism | -0.027 (0.107) | 0.97 (0.79-1.20) | 0.8003 | 0.066 (0.108) | 1.07 (0.87-1.32) | 0.5383 | 0.064 (0.108) | 1.07 (0.86-1.32) | 0.5506 |
| History of gout | 0.274 (0.165) | 1.32 (0.95-1.82) | 0.0962 | 0.140 (0.165) | 1.15 (0.83-1.59) | 0.3950 | 0.139 (0.165) | 1.15 (0.83-1.59) | 0.4009 |
| **Number of Consultations** | | | | | | | | | |
| 1 day | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 2-3 days | 0.249 (0.026) | 1.28 (1.22-1.35) | <.0001 | 0.238 (0.026) | 1.27 (1.21-1.33) | <.0001 | 0.238 (0.026) | 1.27 (1.21-1.34) | <.0001 |
| ≥4 days | 0.479 (0.060) | 1.62 (1.35-1.82) | <.0001 | 0.482 (0.060) | 1.33 (1.44-1.82) | <.0001 | 0.481 (0.060) | 1.62 (1.44-1.82) | <.0001 |
| **Duration of Prescription** | | | | | | | | | |
| None | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 1-7 days | -0.027 (0.026) | 0.97 (0.93-1.03) | 0.3076 | -0.019 (0.026) | 0.98 (0.93-1.03) | 0.4777 | -0.018 (0.026) | 0.98 (0.93-1.03) | 0.4997 |

| Covariate | Unadjusted* | | | Partially Adjusted† | | | Fully adjusted‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | *β* (SE) | HR (95% CI) | *P* Value | *β* (SE) | HR (95% CI) | *P* Value | *β* (SE) | HR (95% CI) | *P* Value |
| ≥8 days | 0.543 (0.036) | 1.72 (1.60-1.85) | <.0001 | 0.519 (0.036) | 1.68 (1.57-1.80) | 0.4777 | 0.518 (0.036) | 1.68 (1.57-1.80) | <.0001 |
| **Length of Hospitalisation** | | | | | | | | | |
| 1 day | Reference | Reference | | Reference | Reference | | Reference | Reference | |
| 2-4 days | 0.241 (0.026) | 1.27 (1.21-1.34) | <.0001 | 0.233 (0.026) | 1.26 (1.20-1.33) | <.0001 | 0.233 (0.026) | 1.26 (1.20-1.33) | <.0001 |
| ≥5 days | 0.304 (0.039) | 1.36 (1.26-1.46) | <.0001 | 0.289 (0.039) | 1.34 (1.24-1.44) | <.0001 | 0.289 (0.039) | 1.34 (1.24-1.44) | <.0001 |

∗Unadjusted/Univariate analysis. †Partially adjusted models account for age, sex and each variable added. ‡Fully adjusted models account for Age, Sex, Income grade, Physical activity, Smoking status, Alcohol consumption and each of the other risk factors [MetS (Fasting Blood Glucose, Total Cholesterol, Blood Pressure/HTN, prior history of (Ischemic Heart Disease (IHD ) and Gout; CKD, Chronic Kidney Disease, Hyperparathyroidism; IBD, Inflammatory Bowel Disease)].

### 4.7.4 Derivation of prediction equation for 5-year nephrolithiasis recurrence

Based on univariate and hierarchical cluster analysis of correlations, 11 variables were assessed in the model derivation and retained if they were significant at α=0.15. The parsimonious model comprised of sex, age, body mass index, and length of hospitalization during the first episode of diagnosed nephrolithiasis. The estimated coefficients and hazard ratios for each predictor in the nephrolithiasis recurrence parsimonious model and the risk points assigned for risk factors are presented (Table 53).

**Table 53. Hazard Ratios (95% confidence interval) and β-coefficients for risk predictors in the parsimonious model of 5-year nephrolithiasis recurrence and the risk points scoring system**

| Covariates | *β* (SE) | HR (95% CI) | *P* | Points |
|---|---|---|---|---|
| **Sex** | | | | |
| Female | Reference | Reference | | 0 |
| Male | 0.259 (0.031) | 1.30 (1.22-1.38) | <.0001 | 26 |
| **Age** | | | | |
| <24 yrs. | Reference | Reference | | 0 |
| 25-34 yrs | 0.076 (0.069) | 1.08 (0.94-1.24) | 0.2720 | 8 |
| 35-44 yrs | 0.114 (0.066) | 1.12 (0.99-1.28) | 0.0836 | 11 |
| 45-54 yrs | 0.154 (0.067) | 1.17 (1.02-1.33) | 0.0203 | 15 |
| ≥55 yrs | 0.220 (0.066) | 1.25 (1.09-1.42) | 0.0009 | 22 |
| **Body Mass Index** | | | | |
| < 18.5 kg/m$^2$ | -0.109 (0.098) | 0.90 (0.74-1.09) | 0.2646 | -11 |
| 18.5 kg/m$^2$-24.9 kg/m$^2$ | Reference | Reference | | 0 |
| 25 kg/m$^2$-29.9 kg/m$^2$ | 0.135 (0.031) | 1.15 (1.08-1.22) | <.0001 | 14 |
| >30 kg/m$^2$ | 0.155 (0.075) | 1.17 (1.01-1.35) | 0.0388 | 16 |
| **Days of prescription** | | | | |
| 1 day | Reference | Reference | | 0 |

| Covariates | $\beta$ (SE) | HR (95% CI) | *P* | Points |
|---|---|---|---|---|
| 2-4 days | -0.023 (0.032) | 0.98 (0.92-1.04) | 0.4685 | -2 |
| ≥5 days | 0.509 (0.044) | 1.66 (1.53-1.81) | <.0001 | 51 |

*The risk points were calculated by multiplying the estimated coefficients by 100 and rounding to the nearest integer.

### 4.7.5 Model validation for nephrolithiasis recurrence prediction equation

The prediction equations were validated by evaluating their discrimination and calibration abilities in the validation cohort with respect to the Harrell's C-statistic and (Nam and D'Agostino's test), a modification of H-L type $\chi^2$ statistic; specificity, sensitivity, and brier score. The Harrell's C-statistic was 0.926 (95% CI, 0.907-0.945) and 0.909 (95% CI, 0.879-0.935) in the derivation and validation cohorts, respectively (Table 54). A value of 0.50 represents no discrimination and 1.00 represents perfect discrimination. The model showed good calibration in derivation and validation cohorts (Hosmer-Lemeshow $\chi^2$=3.932, *p*=0.9476 and $\chi^2$=3.988, p=0.969). The brier score statistic which measures both discrimination and calibration [436], was 0.275 and 0.274 in the derivation and validation cohorts, respectively (Table 54). The Brier score ranges from 0.0 to 1.0 with lower values indicating higher prediction accuracy.

Using the optimal threshold determined by Youden's index to define high-risk individuals, the model's sensitivity was 66.1% (95% CI, 64.7% to 67.4%) and 66.0% (95% CI, 64.1% to 68.0%) whereas specificity was 76.5% (95% CI, 75.7% to 77.3%) and 77.5% (95% CI, 76.4% to 78.6%) in the derivation and validation cohorts (Table 54). Table 54 and (Figures 24-26) present the model validation

results. In addition, comparing the hazard ratios (HRs) between the lowest risk stratum and the highest risk stratum shows that the highest risk group is 7264 times more likely to experience nephrolithiasis recurrence than the lowest risk group (Table 54). Furthermore, the model performed well in separation of individual in the lower risk groups from the high-risk groups based on the Kaplan Meier survival curve graphical displays (Figure 26). However, the model performed poorly in separation of the lowest risk group and the neighboring risk group (Figure 26).

**Table 54. Model validation and performance evaluation of the prediction equation of 5-year nephrolithiasis recurrence risk based on discrimination and calibration in derivation and validation cohorts**

| Performance Evaluation statistic | Derivation Cohort | Validation cohort |
|---|---|---|
| Brier Score† | 0.275 | 0.274 |
| Nam and D'Agostino test‡ | $\chi^2$=3.932, *P*=0.9476 | $\chi^2$=3.988, *P*=0.969 |
| Harrell's C statistic (95% CI) # | 0.926 (0.907-0.945) | 0.909 (0.879-0.935) |
| Sensitivity (95% CI) | 66.1% (64.7% to 67.4%) | 66.0% (64.1% to 68.0%) |
| Specificity (95% CI) | 76.5% (75.7% to 77.3%) | 77.5% (76.4% to 78.6%) |
| Positive Likelihood Ratio (95% CI) | 2.81 (2.70 to 2.92) | 2.93 (2.77 to 3.11) |
| Negative Likelihood Ratio (95% CI) | 0.44 (0.43 to 0.46) | 0.44 (0.41 to 0.46) |
| Positive Predictive Value (95% CI) | 55.0% (54.1% to 56.0%) | 55.1% (53.7% to 56.5%) |
| Negative Predictive Value (95% CI) | 83.8% (83.2% to 84.3%) | 84.5% (83.7% to 85.3%) |
| Accuracy (95% CI) | 73.3% (72.6% to 74.0%) | 74.1% (73.1% to 75.1%) |
| **Risk Strata Comparisons** | **Hazard Ratio, *P* value** | **Hazard Ratio, *P* value** |
| Good | Reference | Reference |
| Good Vs Fairly Good | 0.67 (0.59-0.75), *p*<.0001 | 0.93 (0.68-1.28), *p*=0.6521 |
| Good Vs Fairly Poor | 0.84(0.75-0.94), *p*=0.0030 | 3.25 (2.44-4.32), *p*<.0001 |
| Good Vs Poor | 7.82 (6.86-8.91), *p*<.0001 | 65.4(48.6-88.0), *p*<.0001 |
| Good Vs Very Poor | 6235.3(3632.4-10703.2), *p*<.0001 | 7264.3(4597.3-11478.3), *p*<.0001 |

**Abbreviation: CI=confidence interval.**

†Measures both discrimination and calibration; Range (0 to 1) and lower values indicate higher accuracy, ‡A modification of Hosmer Lemeshow test suited for survival data; measure of calibration that is specific to censored survival data (lower $\chi^2$ and higher p values) indicate better calibration. #A measure of discrimination for which higher values indicate better discrimination. The Youden's J statistics was 0.429 for both cohorts corresponding to risk probability of 0.788.

**Figure 24. Discrimination and calibration plots for prediction equation of 5-year nephrolithiasis recurrence in the derivation cohort. (A) discrimination. (B) calibration.**

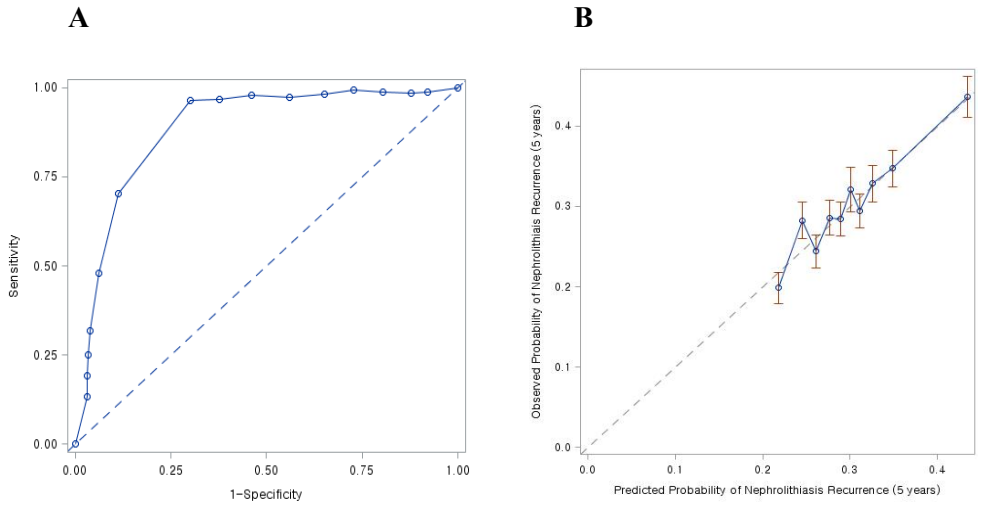



**Figure 25. Discrimination and calibration plots for prediction equation of nephrolithiasis recurrence in the validation cohort. (A) Discrimination. (B) Calibration.**

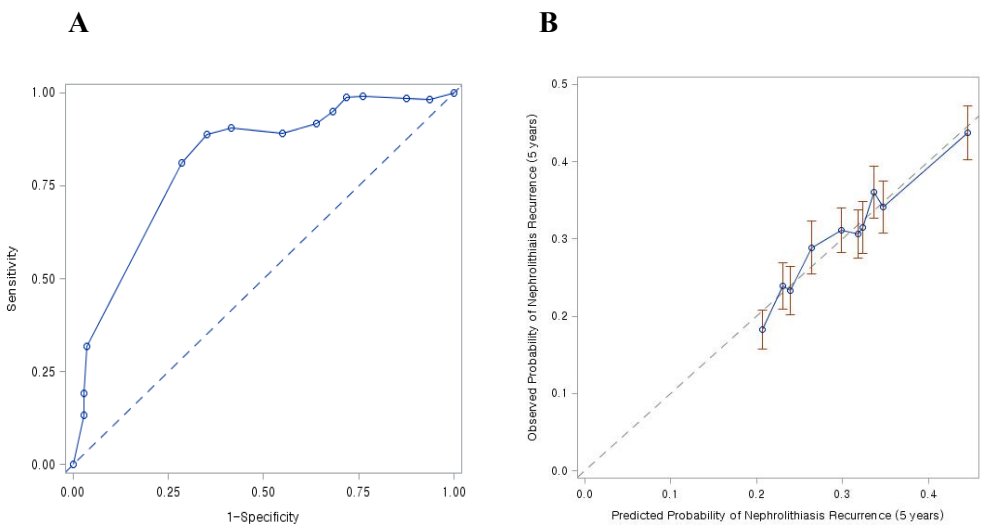
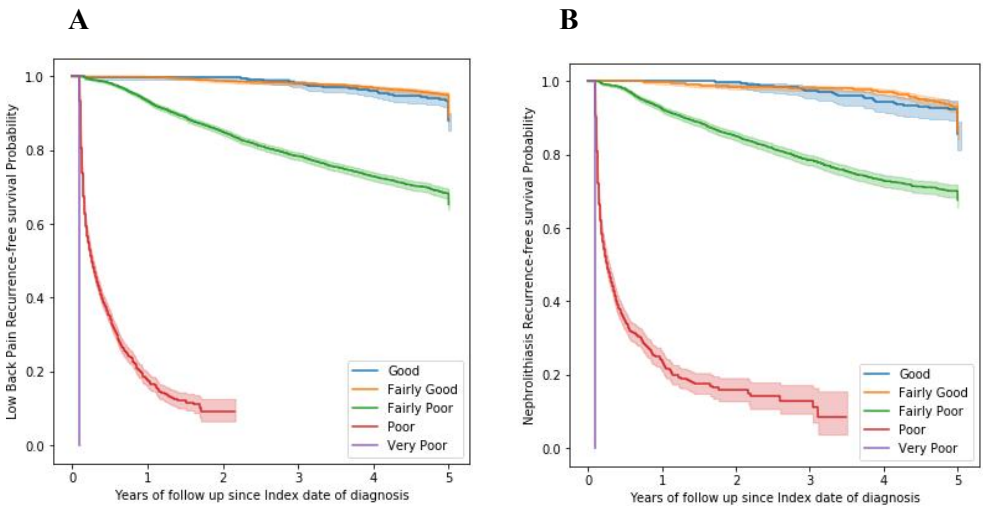


**Figure 26. Kaplan-Meier curves for nephrolithiasis recurrence-free survival in 5 risk groups in the derivation and validation cohort based on the Prognostic Index. (A) Derivation. (B) Validation**



### 4.7.6 Model discrimination at different thresholds of predicted risk

Table 55 shows the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy for nephrolithiasis recurrence equation for various risk probability thresholds based on subjects in the derivation and validation cohorts. The risk probability threshold for the top 3% at highest risk of nephrolithiasis recurrence in the next 5 years was 0.994, for the top 5% was 0.975, for the top 10% was 0.929, for the top 25% was 0.836, and for the top 50% was 0.740 in both cohorts. With a risk probability threshold of 0.929 over 5 years to identify the 10% of participants with the highest risk of nephrolithiasis recurrence, the sensitivity for identifying 5-year nephrolithiasis recurrence was 22.3 (95% CI, 20.6%-24.0%), specificity 95.3% (95% CI, 94.7%-95.8%), positive predictive value 66.1% (95% CI, 62.9%-69.2%), negative predictive value 74.7% (95% CI, 74.3%-75.1%), and accuracy value 73.9% (95% CI, 72.9%-74.8%) in the validation cohort (Table 55). The corresponding thresholds for risk of experiencing nephrolithiasis recurrence over 5 years and the model's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 55). Table 54 shows the results based on the optimal cut-off determined by Youden's J statistic for the prediction equation of nephrolithiasis recurrence.

**Table 55. Sensitivity, specificity, likelihood ratios, predictive values, and accuracy at different thresholds of predicted risk for the prediction equation of nephrolithiasis recurrence**

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values and accuracy for nephrolithiasis at different thresholds of predicted risk of nephrolithiasis recurrence over 5 years in derivation cohort**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | 1.000 | 10,453 | 4749 | 454 | 0 | 0.00 (0.00-0.08) | 95.8 (95.5-96.2) | 0.00 | 1.04 (1.04-1.05) | 0 | 68.8 (68.7-68.8) | 66.8 (66.0-67.5) |
| 97% | ≥0.994 | 10,453 | 4,726 | 451 | 26 | 0.55 (0.36-0.80) | 95.9 (95.5-96.2) | 0.13 (0.09-0.20) | 1.04 (1.03-1.04) | 5.45 (3.74-7.87) | 68.9 (68.8-67.0) | 66.9 (66.2-67.7) |
| 95% | ≥0.975 | 10,437 | 4,430 | 450 | 339 | 7.11(6.40-7.87) | 95.9 (95.5-96.2) | 1.72 (1.50-1.97) | 0.97 (0.96-0.98) | 43.0 (39.7-46.4) | 70.2 (70.0-70.4) | 68.8 (68.1-69.6) |
| 90% | ≥0.929 | 10,363 | 3,717 | 530 | 1,046 | 22.0 (20.8-23.2) | 95.1 (94.7-95.5) | 4.51 (4.09-4.98) | 0.82 (0.81-0.83) | 66.4 (64.1-68.5) | 73.6 (73.3-73.9) | 72.9 (72.2-73.6) |
| 75% | ≥0.836 | 9,448 | 2,255 | 1,482 | 2,471 | 52.3 (50.5-53.7) | 86.4 (85.8-87.1) | 3.86 (3.65-4.07) | 0.55 (0.54-0.57) | 62.5 (61.2-63.8) | 80.7 (80.3-81.2) | 76.1 (75.5-76.8) |
| 50% | ≥0.740 | 6,784 | 998 | 4,172 | 3,702 | 78.8 (77.6-79.9) | 61.9 (61.0-62.8) | 2.07 (2.01-2.13) | 0.34 (0.32-0.36) | 47.0 (46.3-47.7) | 87.2 86.587.8) | 67.0 (66.2-67.7) |
| 25% | ≥0.666 | 3,506 | 406 | 7,379 | 4,365 | 91.5 (90.7-92.3) | 32.2 (31.3-33.1) | 1.35 (1.33-1.37) | 0.26 (0.24-0.29) | 37.2 (36.8-37.5) | 89.6 (88.7-90.5) | 50.3 (49.5-51.1) |
| 10% | ≥0.601 | 1,363 | 155 | 9,514 | 4,624 | 96.8 (96.2-97.2) | 12.5 (11.9-13.2) | 1.11 (1.10-1.12) | 0.26 (0.22-0.30) | 32.7 (32.5-32.9) | 89.8 (88.2-91.2) | 38.2 (37.5-39.0) |
| 5% | ≥0.578 | 690 | 95 | 10,189 | 4,682 | 98.0 (97.6-98.4) | 6.34 (5.89-6.82) | 1.05 (1.04-1.05) | 0.31 (0.25-0.39) | 31.5 (31.4-31.6) | 87.9 (85.5-90.0) | 34.3 (33.6-35.1) |

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values and accuracy for nephrolithiasis at different thresholds of predicted risk of nephrolithiasis recurrence over 5 years in validation cohort**

| Threshold (Centiles) | Risk probability threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | 1.000 | 5,370 | 2,337 | 213 | 0 | 0.00 (0.00-0.16) | 96.2(95.7-96.7) | 0.00 | 1.04 (1.03-1.05) | 0 | 69.7 (69.6-69.8) | 67.8 (66.8-68.8) |
| 97% | ≥0.994 | 5,370 | 2,320 | 216 | 14 | 0.60 (0.33-1.00) | 96.1 (95.6-96.6) | 0.16 (0.09-0.27) | 1.03 (1.03-1.04) | 6.09 (3.65-9.99) | 69.8 (69.7-70.0) | 68.0 (66.9-69.0) |
| 95% | ≥0.975 | 5,363 | 2,169 | 240 | 148 | 6.39 (5.43-7.46) | 95.7 (95.2-96.2) | 1.49 (1.22-1.82) | 0.98 (0.97-0.99) | 38.1 (33.5-42.9) | 71.2 (71.0-71.5) | 69.6 (68.6-70.6) |
| 90% | ≥0.929 | 5,332 | 1,806 | 265 | 517 | 22.3 (20.6-24.0) | 95.3(94.7-95.8) | 4.70 (4.09-5.41) | 0.82 (0.80-0.83) | 66.1 (62.9-69.2) | 74.7 (74.3-75.1) | 73.9 (72.9-74.8) |
| 75% | ≥0.836 | 4,844 | 1,137 | 716 | 1,223 | 51.8 (49.8-53.9) | 87.1 (86.2-88.0) | 4.02 (3.72-4.35) | 0.55 (0.53-0.58) | 63.1 (61.2-64.9) | 81.0 (80.3-81.6) | 76.6 (75.7-77.5) |
| 50% | ≥0.740 | 3,460 | 547 | 2,074 | 1,839 | 77.1 (75.3-78.8) | 62.5 (61.2-63.8) | 2.06 (1.98-2.14) | 0.37 (0.34-0.40) | 47.0 (46.0-48.0) | 86.4 (85.4-87.2) | 66.9 (65.9-67.9) |
| 25% | ≥0.666 | 1,774 | 209 | 3831 | 2,106 | 91.0 (89.7-92.1) | 31.7 (30.4-32.9) | 1.33 (1.30-1.36) | 0.29 (0.25-0.33) | 35.5 (35.0-36.0) | 89.5 (88.1-90.7) | 49.0 (47.9-50.1) |
| 10% | ≥0.601 | 702 | 78 | 4,911 | 2,229 | 96.6 (95.8-97.3) | 12.5 (11.7-13.4) | 1.10 (1.09-1.12) | 0.27 (0.22-0.34) | 31.2 (31.0-31.5) | 90.0 (87.7-91.9) | 37.0 (35.9-38.1) |
| 5% | ≥0.578 | 354 | 37 | 5,257 | 2,272 | 98.4 (97.8-98.9) | 6.31 (5.69-6.98) | 1.05 (1.04-1.06) | 0.25 (0.18-0.36) | 30.2 (30.0-30.4) | 90.5 (87.3-93.0) | 33.2 (32.1-34.2) |

Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages].The threshold of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.7.7 Prediction equations of 5-year nephrolithiasis recurrence risk

With reference to the derived model, individualized probability of nephrolithiasis recurrence within the years of follow up (t=5 years), can be estimated using the following equation:

$$P(\text{Nephrolithiasis recurrence}) = 1 - \mathrm{S_o}(t)^{\exp[(\beta_1 x_1 + \beta_2 x_2 \ldots \beta_m x_m)]},$$

Where $\mathrm{S_o}(t)$ denotes the baseline survival probability at time (t) for an individual with all covariates equivalent to zero (0), $(\beta_1 \ldots . \beta_m)$ denotes the change in log hazard rate (estimated $\beta$-coefficients) and $(x_1 \ldots x_m)$ denotes values of risk predictors in the model. Using the estimated coefficients ($\beta_i$) and survival probabilities $\mathrm{S_o}$ (t), the 5-year personalized probability of nephrolithiasis recurrence can be calculated**.**

The Youden's J statistic suggested a risk probability of ≥0.788 as the optimal cut-off point to define high-risk individuals based on the nephrolithiasis recurrence prediction equation. This threshold showed a sensitivity of 66.0% (95% CI, 64.1%-68.0%), specificity of 77.5% (95% CI, 76.4%-78.6%), positive likelihood ratio (LR+) of 2.93 (95% CI, 2.77-3.11), negative likelihood ratio (LR-) of 0.44 (95% CI, 0.41-0.46), positive predictive value (PPV) of 55.1% (95% CI, 53.7%-56.5%), negative predictive value of 84.5% (95% CI, 83.7%-85.3%) and accuracy of 48.4% (95% CI, 47.3%-49.5%) and accuracy 74.1% (73.1%-75.1%) in the prediction of the nephrolithiasis recurrence over 5 years in the validation cohort (Table 54).

### 4.7.8 Simplified risk score for prediction of nephrolithiasis recurrence risk

Table 53 presents the regression coefficients for the Cox Proportional hazard model fit to the derivation cohort. In the right-most column of the table are the points associated with the presence of a given level of a risk factor (with the reference level assigned zero points). The risk points were derived by multiplying the regression coefficient by 100 and rounding to the nearest integer. Long duration of medication and male sex conferred the largest number of points (51 points and 26 points, respectively). Among modifiable risk factors, lower BMI (<18.5 kg/m$^2$) was protective with (-11 points) whereas advanced age (>55 years) conferred a risk of 22 points (Table 53).

Participants in the overall sample were divided into five equally sized risk strata using quintiles of the empirical risk score. Table 56 presents the cumulative incidence risk probabilities for nephrolithiasis recurrence in each of the risk strata in the derivation and validation cohorts. There were statistically significant differences in the cumulative incidence risk probabilities across the five risk strata based on the Cochran–Armitage test for trend ($p$<.0001). There was a clearly defined gradation in nephrolithiasis recurrence risk across the five risk strata. The lowest risk stratum comprised of subjects with a very low nephrolithiasis recurrence during the years of follow-up. In contrast, the highest risk stratum consisted of subjects with a very high nephrolithiasis recurrence risk during years of follow-up. The cumulative incidence risk of nephrolithiasis recurrence in the lowest and highest risk strata in the derivation cohort were 29.5 (95% CI, 27.7 to

31.4) and 44.6 (95% CI, 42.6 to 46.6), respectively. Thus, the 5-year nephrolithiasis recurrence risk was 1.7 times greater in the highest risk stratum than in the lowest risk stratum, and the HZ ratio was 1.7 times greater (Table 56). Figure 27 presents the survival trends over 5 years for participants based on the risk score strata.

**Figure 27. Kaplan-Meier curves for 5-year nephrolithiasis recurrence-free survival in five risk groups in the derivation and validation cohorts based on the simplified points based risk score. (A) Derivation. (B) Validation**

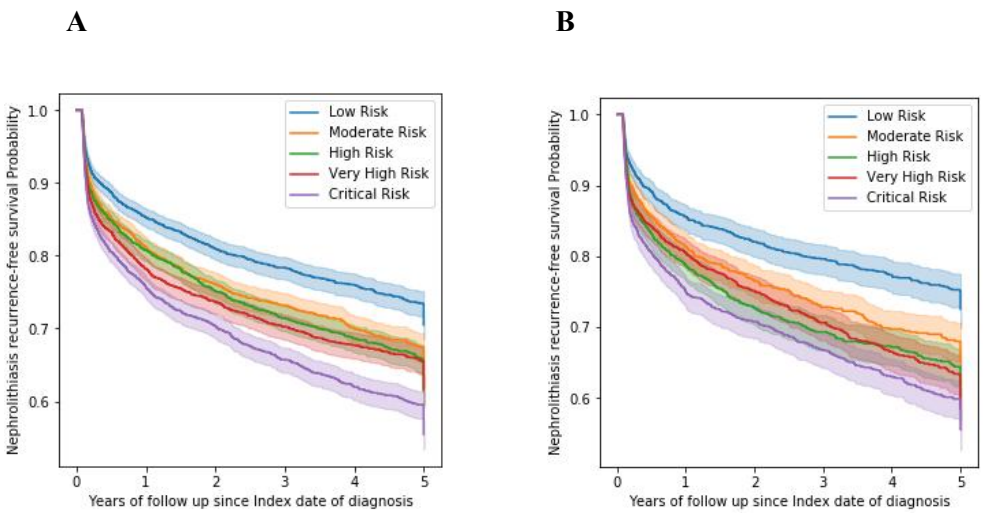


**Table 56. Nephrolithiasis recurrence risk in the derivation and validation cohorts based on the risk score strata**

| Risk of nephrolithiasis recurrence within 5 years in the derivation cohort based on risk category (Quintile of Risk Score). | | | | | | |
|---|---|---|---|---|---|---|
| **Risk Strata** | **Risk Score Range** | **Non-Event** | **Event (%)** | **Total** | **CR* (95% CI)** | **HR (95% CI), *P* value** |
| Low Risk | <15 | 2453 (76.4) | 756 (23.6) | 3209 | 29.5 (27.7 to 31.4) | Reference |
| Moderate Risk | 15 to 33 | 2071 (71.5) | 825 (28.5) | 2896 | 35.9 (33.8 to 38.1) | 1.281 (1.160-1.414), *p*<.0001 |
| High Risk | 34 to 38 | 2132 (69.8) | 921 (30.2) | 3053 | 38.6 ( 36.5 to 40.8) | 1.371 (1.245-1.509), *p*<.0001 |
| Very High Risk | 39 to 48 | 2147 (68.8) | 973 (31.2) | 3120 | 38.3 (36.3 to 40.4) | 1.421 (1.293 to 1.563), *p*<.0001 |
| Critical Risk | >48 | 2150 (63.6) | 1228 (36.4) | 3378 | 44.6 (42.6 to 46.6) | 1.703 (1.555 to 1.864), *p*<.0001 |
| **Risk of nephrolithiasis recurrence within 5 years in the validation cohort based on risk category (Quintile of Risk Score).** | | | | | | |
| **Risk Strata** | **Risk Score Range** | **Non-Event** | **Event (%)** | **Total** | **CR* (95% CI)** | **HR (95% CI), *P* value** |
| Low Risk | <15 | 1254 (78.1) | 352 (21.9) | 1606 | 27.4 (24.9 to 30.1) | Reference |
| Moderate Risk | 15 to 33 | 1081 (72.4) | 411 (27.6) | 1492 | 34.9 (32.0 to 37.9) | 1.354 (1.174 to 1.561), *p*<.0001 |
| High Risk | 34 to 38 | 1073 (67.8) | 510 (32.2) | 1583 | 40.2 (37.3 to 43.2) | 1.585 (1.384 to 1.816), *p*<.0001 |
| Very High Risk | 39 to 48 | 1067 (67.8) | 507 (32.2) | 1574 | 41.5 (38.5 to 44.6) | 1.579 (1.378 to 1.809), *p*<.0001 |
| Critical Risk | >48 | 1062 (63.8) | 603 (36.2) | 1665 | 44.4 (41.6 to 47.3) | 1.816 (1.592 to 2.071), *p*<.0001 |
| **Average 5-year survival=0.6607** | | | | | | |

*CR=Cumulative Risk.

‡The Cochran–Armitage test for trend (for overall cohort), p<.0001

### 4.7.9 Validation of the simplified risk score at different risk score thresholds

The theoretical minimum and maximum sum of the points were -13 and 115, respectively. The median score was 36, while the 25$^{th}$ and 75$^{th}$ percentiles were 22 and 48, respectively. Table 57 shows the sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy for nephrolithiasis recurrence risk score for various risk score thresholds based on subjects in the derivation and validation cohorts. The risk score threshold for the top 3% at highest risk of nephrolithiasis recurrence in the next 5 years was 77, for the top 5% was 62, for the top 10% was 55, for the top 25% was 48, and for the top 50% was 36 in both cohorts. With a risk score threshold of 55 over 5 years to identify the 10% of participants with the highest risk of nephrolithiasis recurrence, the sensitivity for identifying 5-year nephrolithiasis recurrence was 14.5% (95% CI, 13.1%-16.0%), specificity 89.2% (95% CI, 88.3%-90.0%), positive predictive value 35.5% (95% CI, 32.7% -38.4%), negative predictive value 71.7 (95% CI, 71.3%-72.1%), and accuracy value 67.4% (95% CI, 66.3%-68.4%) in the validation cohort (Table 57). The corresponding thresholds for risk of experiencing nephrolithiasis recurrence over 5 years and the risk score's discrimination based on the thresholds are presented for both the derivation and validation cohorts (Table 57).

The Youden's J statistic suggested a risk score of ≥32 as the optimal cutoff point to define high-risk individuals based on the simplified nephrolithiasis recurrence risk score. This threshold showed a sensitivity of 68.1% (95% CI,

66.2%-70.0%), specificity of 40.0% (95% CI, 38.7%-41.3%), positive likelihood ratio (LR+) of 1.13 (95% CI, 1.10-1.18), negative likelihood ratio (LR-) of 0.80 (0.75-0.85), positive predictive value (PPV) of 32.8% (95% CI, 32.0%-33.5%), negative predictive value of 74.5% (95% CI, 73.2%-75.8%) and accuracy of 48.4% (95% CI, 47.3%-49.5%) in the prediction of the risk of nephrolithiasis recurrence over 5 years in the validation cohort (Table 57).

**Table 57. Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values and accuracy for nephrolithiasis at different thresholds of the risk score of nephrolithiasis recurrence over 5 years in the derivation and validation cohorts**

**Sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values and accuracy for nephrolithiasis at different thresholds of risk score of nephrolithiasis recurrence over 5 years in derivation cohort**

| Threshold (Centiles) | Risk score threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥92 | 10,784 | 4,668 | 121 | 83 | 1.75 (1.39-2.16) | 98.9 (98.7-99.1) | 1.57 (1.19-2.08) | 0.99 (0.99-1.00) | 40.7 (34.2-47.5) | 69.8 (69.7-69.9) | 69.4 (68.7-70.1) |
| 97% | ≥77 | 10,713 | 4,604 | 185 | 154 | 3.24 (2.75-3.78) | 98.3 (98.0-98.5) | 1.91 (1.54-2.35) | 0.98 (0.98-0.99) | 45.4 (40.3-50.7) | 69.9 (69.8-70.1) | 69.4 (68.7-70.1) |
| 95% | ≥62 | 10,286 | 4,405 | 596 | 369 | 7.73 (6.99-8.52) | 94.5 (94.1-94.9) | 1.41 (1.25-1.60) | 0.98 (0.97-0.99) | 38.2 (35.3-41.2) | 70.0 (69.8-70.2) | 68.1 (67.3-68.8) |
| 90% | ≥55 | 9,714 | 4,087 | 1,166 | 689 | 14.4 (13.4-15.5) | 89.3 (88.7-89.9) | 1.35 (1.23-1.47) | 0.96 (0.95-0.97) | 37.1 (35.1-39.2) | 70.4 (70.1-70.7) | 66.5 (65.7-67.2) |
| 75% | ≥48 | 7,859 | 3,075 | 3,091 | 1,631 | 34.7 (33.3-36.0) | 71.8 (70.9-72.6) | 1.23 (1.17-1.29) | 0.91 (0.89-0.93) | 34.5 (33.4-35.7) | 71.9 (71.4-72.4) | 60.6 (59.9-61.4) |
| 50% | ≥36 | 5,537 | 2,030 | 5,405 | 2,684 | 56.9 (55.5-58.4) | 50.6 (49.7-51.5) | 1.15 (1.12-1.19) | 0.85 (0.82-0.88) | 33.2 (32.5-33.9) | 73.2 (72.4-73.9) | 52.5 (51.7-53.3) |
| **‡37%** | ≥32 | 4341 | 1423 | 6608 | 3284 | 69.8 (68.4-71.1) | 39.7 (38.7-40.6) | 1.16 (1.13-1.18) | 0.76 (0.73-0.80) | 33.2 (32.7-33.7) | 75.3 (74.4-76.2) | 48.7 (47.9-49.5) |
| 25% | ≥22 | 2,631 | 858 | 8,260 | 3,907 | 82.0 (80.9-83.1) | 24.2 (23.4-25.0) | 1.08 (1.06-1.10) | 0.75 (0.70-0.80) | 32.1 (31.7-32.5) | 75.4 (74.1-76.7) | 41.8 (41.0-42.5) |
| 10% | ≥11 | 1,076 | 291 | 9,801 | 4,488 | 93.9 (93.2-94.6) | 9.89 (9.34-10.5) | 1.04 (1.03-1.05) | 0.62 (0.54-0.70) | 31.4 (31.2-31.6) | 78.7 (76.5-80.7) | 35.5 (34.8-36.3) |
| 5% | ≥8 | 575 | 153 | 10,300 | 4,628 | 96.8 (96.3-97.3) | 5.29 (4.87-5.72) | 1.02 (1.02-1.03) | 0.61 (0.51-0.72) | 31.0 (30.9-31.2) | 79.0 (75.9-81.7) | 33.2 (32.5-34.0) |

**Sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive values and accuracy for nephrolithiasis at different thresholds of risk score of nephrolithiasis recurrence over 5 years in validation cohort**

| Threshold (Centiles) | Risk score threshold | True negative (count) | False negative (count) | False positive (count) | True positive (count) | Sensitivity (%) | Specificity (%) | Positive Likelihood Ratio | Negative Likelihood Ratio | Positive predictive value (%) | Negative predictive value (%) | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 99% | ≥92 | 5,538 | 2,303 | 47 | 32 | 1.37 (0.94-1.93) | 99.2 (98.9-99.4) | 1.63 (1.04-2.55) | 0.99 (0.99-1.00) | 40.5 (30.3-51.6) | 70.6 (70.5-70.7) | 70.3 (69.3-71.3) |
| 97% | ≥77 | 5,502 | 2,271 | 90 | 57 | 2.45 (1.86-3.16) | 98.4 (98.0-98.7) | 1.52 (1.10-2.11) | 0.99 (0.98-1.00) | 38.8 (31.3-46.8) | 70.8 (70.6-70.9) | 70.2 (69.2-71.2) |
| 95% | ≥62 | 5,293 | 2,146 | 315 | 166 | 7.18 (6.16-8.31) | 94.4 (93.8-95.0) | 1.28 (1.07-1.53) | 0.98 (0.97-1.00) | 34.5 (30.5-38.7) | 71.2 (70.9-71.4) | 68.9 (67.9-70.0) |
| 90% | ≥55 | 5,003 | 1,976 | 607 | 334 | 14.5 (13.1-16.0) | 89.2 (88.3-90.0) | 1.34 (1.18-1.51) | 0.96 (0.94-0.98) | 35.5 (32.7-38.4) | 71.7 (71.3-72.1) | 67.4 (66.3-68.4) |
| 75% | ≥48 | 4,062 | 1,565 | 1478 | 815 | 34.2 (32.3-36.2) | 73.3 (72.1-74.5) | 1.28 (1.20-1.38) | 0.90 (0.87-0.93) | 35.5 (33.9-37.2) | 72.2 (71.5-72.9) | 61.6 (60.5-62.7) |
| 50% | ≥36 | 2,844 | 1,047 | 2704 | 1,325 | 55.9 (53.8-57.9) | 51.3 (49.9-52.6) | 1.15 (1.10-1.20) | 0.86 (0.82-0.91) | 32.9 (31.9-33.9) | 73.1 (72.1-74.1) | 52.6 (51.5-53.7) |
| **‡37%** | ≥32 | 2,214 | 758 | 3,327 | 1,621 | 68.1(66.2-70.0) | 40.0 (38.7-41.3) | 1.13 (1.10-1.18) | 0.80 (0.75-0.85) | 32.8 (32.0-33.5) | 74.5 (73.2-75.8) | 48.4 (47.3-49.5) |
| 25% | ≥22 | 1,375 | 394 | 4,224 | 1,927 | 83.0 (81.4-84.5) | 24.6 (23.4-25.7) | 1.10 (1.07-1.13) | 0.69 (0.62-0.76) | 31.3 (30.8-31.8) | 77.7 (75.9-79.4) | 41.7 (40.6-42.8) |
| 10% | ≥11 | 564 | 141 | 5,049 | 2,166 | 93.9 (92.8-94.8) | 10.1 (9.27-10.9) | 1.04 (1.03-1.06) | 0.61 (0.51-0.73) | 30.0 (29.7-30.3) | 80.0 (77.0-82.7) | 34.5 (33.4-35.5) |
| 5% | ≥8 | 294 | 74 | 5,321 | 2,231 | 96.8 (96.0-97.5) | 5.24 (4.67-5.85) | 1.02 (1.01-1.03) | 0.61 (0.48-0.79) | 29.5 (29.3-29.7) | 79.9 (75.6-83.6) | 31.9 (30.9-32.9) |

Sensitivity: probability that a test result will be positive when the disease is present; Specificity, probability that a test result will be negative when the disease is not present, Likelihood ratio (LR); ratio by which the pretest probability is altered by a positive or negative test result); NPV, negative predictive value (proportion of all participants with a negative test who are disease free); NPV, negative predictive value (proportion of all subjects with a negative test who are disease free); PPV, positive predictive value (proportion of all participants with a positive test who have disease); Accuracy, overall probability that a patient is correctly classified. [Sensitivity, specificity, positive and negative predictive value as well as accuracy are expressed as percentages]. The threshold of 99%, 97%, 95%, 90% and 75% correspond to the top 1%, 3%, 5%, 10% and 25% of high risk individuals.

### 4.7.10 Practical application of risk score for 5-year nephrolithiasis recurrence

The following example illustrates how the 5-year nephrolithiasis recurrence risk can be estimated using the simplified points system.

**Case**: A 28-year-old male with body mass index of 24.5 kg/$m^2$ and who receives hospital admission for 3 days.

**Table 58. Table of calculated score for a hypothetical example of a risk profile for nephrolithiasis recurrence within 5 years**

| Risk factor (Predictor) | Value (Risk factor Category) | Points |
|---|---|---|
| Sex | Male | 26 |
| Age | 25-34 yrs | 8 |
| Body Mass Index | > 25 Kgm2-29.9 Kgm2 | 0 |
| Duration of hospitalization | 2-4 days | -2 |
| **Total Points** | | **32** |
| **Estimate of Risk** | | **0.435** |

***$S_o$ (t) = 0.6607**

Based on the point system, the probability of 5-year nephrolithiasis recurrence can be estimated as follows;

$$P(\text{Nephrolithiasis Recurrence}) = 1 - (0.6607)^{\exp[(32/100)]}$$

$$= 0.435$$

The $S_0(t)$ is the baseline survival probability at time (t=5 years) for an individual with all covariates equivalent to zero, which was estimated by Cox regression analysis. The beta coefficients were converted to integer risk points by multiplying with 100. Thus, in the actual calculation, the sum of risk score (32 risk points) was divided by 100 to give an overall 5-year recurrence risk estimate.

### 4.8 Sensitivity analysis for models based on selected subgroups

Sensitivity analysis aims at quantifying how the uncertainty in the output of a model relates to the uncertainty in its inputs. Sensitive analysis mainly assesses how "sensitive" the model is to fluctuations in the parameters and changes in data used to for model building. Both sensitivity analysis and model validation attempt to assess the appropriateness of a particular model specification and to appreciate the strength of the conclusions drawn from the derived model [458]. Sub-group analysis is a common variation of sensitivity analysis [459]. In this study, the performance of the developed models was also assessed by conducting the analysis based on subgroups.

For low back pain, sex, IVDD status, and age were selected as variables for subgroup analysis due to their significance in low back pain pathogenesis, whereas age and sex were selected for nephrolithiasis subgroup analysis. Table 59 shows the models' discrimination based on Harrell's C-Statistics in the subgroup analysis. For comparison of results, model performance in the validation cohorts in the main analyses for all outcomes (Harrell's C-Statistic) was compared with (Harrell's C-Statistic) from subgroup analysis. For low back pain outcomes, the models showed comparable performance among participants without IVDD at baseline whereas results from IVDD positive subgroup showed higher model performance than the reference model performance (Table 59). In the chronic low back pain outcome, the model performance was higher among the male subgroup and the subgroup below 45 years whereas comparable results were observed between the reference model

performance (validation cohort of chronic low back pain outcome) and female subgroup results. On the other hand, the model performance among participants without IVDD and female subgroups were comparable to the respective reference models. For prediction of newly diagnosed nephrolithiasis (first medical utilisation due to nephrolithiasis), the model performed better in the male subgroup and among participants above 45 years of age compared to the than reference model (validation cohort of newly diagnosed nephrolithiasis outcome). Generally, all models showed comparable or superior performance in the subgroups with reference to the performance observed in the validation cohorts in the main analysis. This means that the models can be applicable in identifying individuals at risk of the outcomes, although subgroups of the population may benefit more with accurate predictions than certain groups.

**Table 59. Sensitivity analysis and models' performance evaluation based on selected subgroups**

| No. | Outcome | Subgroup | Harrell's C-statistic (95% CI) | Reference Model performance |
|---|---|---|---|---|
| 1. | Newly diagnosed low back pain (first onset) | Male only | 0.856 (0.850-0.862) | 0.804 (0.796-0.812) |
| | | Female only | 0.804 (0.797-0.810) | |
| | | With IVDD | 0.861 (0.847-0.875) | |
| | | No IVDD | 0.819 (0.814-0.824) | |
| | | <45 years old | 0.920 (0.916-0.925) | |
| | | >45 years old | 0.873 (0.867-0.879) | |
| 2. | Chronic low back pain | Male | 0.714 (0.702-0.726) | 0.643 (0.629-0.656) |
| | | Female | 0.657 (0.64-0.665) | |
| | | With IVDD | 0.751 (0.729-0.772) | |
| | | No IVDD | 0.662 (0.653-0.670) | |
| | | <45 years old | 0.843 (0.833-0.852) | |
| | | >45 years old | 0.810 (0.802-0.819) | |
| 3. | Five (5) year low back pain recurrence | Male | 0.865 (0.856-0.874) | 0.857 (0.847-0.866) |
| | | Female | 0.861 (0.855-0.868) | |
| | | With IVDD | 0.901 (0.890-0.911) | |
| | | No IVDD | 0.861 (0.854-0.867) | |
| | | <45 years old | 0.925 (0.918-0.932) | |
| | | >45 years old | 0.929 (0.924-0.934) | |
| | | Male | 0.782 (0.768-0.795) | |

| | | | | |
|---|---|---|---|---|
| 4. | Twelve (12) months low back pain recurrence | Female | 0.757 (0.746-0.767) | 0.759 (0.745-0.774) |
| | | With IVDD | 0.801 (0.784-0.817) | |
| | | No IVDD | 0.767 (0.757-0.776) | |
| | | <45 years old | 0.844 (0.831-0.857) | |
| | | >45 years old | 0.842 (0.833-0.850) | |
| 5. | Multiple episodic low back pain (Prentice, Williams and Peterson Gap Time Models) | Male | 0.708 (0.703-0.714) | 0.676 (0.669-0.681) |
| | | Female | 0.701 (0.696-0.704) | |
| | | With IVDD | 0.713 (0.702-0.723) | |
| | | No IVDD | 0.689 (0.686-0.693) | |
| | | <45 years old | 0.779 (0.773-0.785) | |
| | | >45 years old | 0.697 (0.694-0.701) | |
| 6. | Newly diagnosed nephrolithiasis (first onset) | Male | 0.889 (0.877-0.901) | 0.819 (0.798-0.838) |
| | | Female | 0.839 (0.821-0.857) | |
| | | <45 years old | 0.808 (0.792-0.824) | |
| | | >45 years old | 0.890 (0.876-0.904) | |
| 7. | Five (5) year Nephrolithiasis recurrence | Male | 0.960 (0.945-0.972) | 0.909 (0.879-0.935) |
| | | Female | 0.911 (0.883-0.936) | |
| | | <45 years old | 0.911 (0.887-0.932) | |
| | | >45 years old | 0.931 (0.910-0.949) | |

*The Models' performance in the validation cohorts in main analyses were chosen as the reference performance for model comparisons

# V. Discussion

## 5.1 Newly diagnosed low back pain

### 5.1.1 Discussion

Low back pain is a complex disorder [31], associated with social and personal expenses [83], and accounts for 10.2% of the total insurance benefit in Korea [85]. This necessitates identification of risk factors and derivation of prediction tools to prevent the associated costs as well as promoting population health. This study assessed risk factors predisposing to LBP onset and developed risk prediction equations and a simplified risk score applicable in medical practice. In this study, MetS was associated with LBP onset (first medical utilisation due to low back pain), which was in agreement with previous studies that assessed LBP and MetS [21, 49, 190, 193, 198]. MetS can increase the risk of atherosclerosis events and disc degeneration, which may predispose to LBP [192, 194].

In agreement with previous studies [14, 19, 39, 48, 50], age, sex, CAD, FBG and IVDD were positively associated with LBP onset. However, high levels of fasting blood glucose or medical utilisation due to diabetes was inversely associated with LBP onset in the fully adjusted models. Advancement in age increases risk of disc degeneration [460], menopause influences pain sensitivity [461] and type 2 diabetes mellitus (T2DM) is associated with spinal stenosis [201] which may partly explain the observed relationships. Total cholesterol and CAD were associated with onset of LBP, in agreement with atherosclerosis hypothesis [193]. A previous genetic study of twins found an association between LBP and CAD [48]. Lipid profile may influence pathogenesis of LBP through occlusion of

blood vessels leading to insufficient nutrient supply to intervertebral discs and subsequent degeneration.

In the multivariate analysis, blood pressure (HTN) was inversely associated with first onset of LBP. This relation was previously reported [29], and hypertension-related hypalgesia theory has been suggested [207]. In addition, a possible interaction between cardiovascular and pain regulatory systems has been suggested [462], which may lead to hypalgesia. On the other hand, hypertension showed a positive association in the univariate analysis. This reversed direction of association observed in multivariate analysis could be a result of antagonistic interaction with one or several other covariates in the models. Similar to HTN, high fasting blood glucose or medical utilisation due to diabetes was positively associated with first onset of LBP in univariate analysis but changed to an inverse relationship in multivariate analysis. A possible role of type 2 diabetes mellitus (T2DM) in the aetiology of LBP [22] and disc degeneration [200] has been reported. Diabetes mellitus has also been linked to a lower density of proteoglycans and undersulfated glycosaminoglycans of the IVDs, which may alter the mechanical properties of the tissues there by increasing susceptibility to disc prolapse and consequent mechanical back pain [205]. The change in direction of association may be due to interaction among other risk predictors in the multivariate models.

In this study, alcohol consumption was inversely associated with first onset of LBP in all analyses. The relationship between LBP and alcohol consumption may

be attributed to alcohol abuse and dependence [154]. The consumption of alcohol in excess is associated with social and psychological problems that may significantly influence the development of LBP [151-153]. An inverse relation between alcohol consumption and LBP has also been reported [463]. The inverse relation between smoking status and LBP was different from a previous study, which reported a positive association [211]. Smoking is associated with disk degeneration (DD) [143] and disc herniation [144], and may influence pathogenesis of LBP. It should be noted that most risk factors associated with complex diseases have weaker associations [147]. Therefore, although some risk factors showed weak associations, they may significantly play a role in the onset of LBP.

### 5.1.2 Comparison with other prediction models

In spite of many studies examining risk factors associated with LBP, few studies have attempted to develop and validate low back pain risk prediction models [59]. Previous studies have developed prediction models from occupation cohorts [385], among acute LBP patients in relation to developing chronic LBP [464], and based on pain trajectories [465]. These studies comprised of few participants, fewer cases, considered only ergonomics and occupation related variables, and did not incorporate routinely collected data, which makes the current prediction equations more applicable to general population, and able to distinguish individuals at risk in general medical practice compared to these algorithms. The optimal cut-off points determined by Youden's J statistic suggested a risk

probability threshold of ≥ 0.768 and risk score threshold of ≥56 identified 70.6% and 47.2% of newly diagnosed low back pain events for the prediction equations and simplified risk score in the validation cohorts, respectively. This study developed the prediction model based on representative predictors from routinely collected health data. Based on model discrimination and calibration, the derived equations performed better or in some cases showed performance comparable to existing models developed from other risk factors [385, 464, 465].

### 5.1.3 Strength and limitations

Some of the of the strengths and limitations of studies based on general practice databases are discussed elsewhere [466], but in addition this study has strengths of representativeness, adequate sample size, duration of follow-up, and lack of selection, recall, and respondent bias. Furthermore, data collected from insurance claims contains diagnosis and prescriptions from well-trained health professionals (reliability), and therefore these risk predictions equations can be utilised in medical practice to advise individuals and reduce their risks.

A low medical care seeking behavior has been reported among LBP patients [467], with care-seeking more common among women and individuals with previous LBP, poor general health, and those with more disabling or more painful episodes [467]. Therefore, it is possible that some individuals did not seek LBP medical services; thereby possibly missing some cases. However, the prevalence of LBP pain in this study is comparable with previous studies [21, 27-30]. In addition,

this study did not incorporate psychosocial factors, genetics and ergonomics related variables since these are not routinely collected which may have affected the prediction performance of the derived equations.

A study that assessed accuracy of diagnostic codes in the KNHIS database found that diagnosis in the claims data tends to be more accurate in cases of severe diseases rather than frequently occurring mild diseases [351]. In addition, diagnostic codes exhibit greater accuracy in inpatient setting than outpatient cases, and in hospitals rather than clinics [468]. However, the concordance of diagnosis in database to the actual status of health conditions by comparing medical record reports found at least 70% of diagnoses corresponding to diagnoses in medical charts [468].

### 5.1.4 Conclusion

This study derived and validated prediction equations and a simplified risk score to estimate the risk of low back pain onset and the model showed excellent discrimination in identifying individuals at risk of developing LBP with Harrell's C-statistic of at least 0.804 in the validation cohort. To the best of my knowledge, this is the first LBP risk prediction model developed and validated using routinely collected health data in a large population based longitudinal study. Further studies should validate and update this prediction model using cohorts from other populations. This study reaffirmed an inverse association between LBP and blood pressure as reported previously [29, 462]. MetS was associated with LBP, although

the directions of associations varied. Future studies should assess the relationship between blood pressure, history of diagnosed hypertension, fasting blood glucose, and effect of antihypertensive medication on the development of low back pain.

## 5.2 Chronic low back pain

### 5.2.1 Discussion

Low back pain is associated with disability, severe pain, and prolonged sick leave at personal and social expense [23]. In order to reduce the associated disease burden, identification of risk factors and availability of prediction tools is necessary for effective prevention. This study assessed epidemiological risk factors predisposing to chronic low back pain and developed risk prediction equations and a simplified risk score applicable in medical practice.

In this study, premorbid conditions were associated with and predicted cLBP. This was in agreement with a previous study that found low back pain associated with other comorbidities [469]. Premorbid conditions may contribute to the pathogenesis of low back pain through several pathways. The study also assessed the effects of several risk factors on cLBP. MetS was associated with cLBP but different directions of associations were observed. MetS may increase the risk of disc degeneration [194] and atherosclerosis events [192], which may influence pathogenesis of cLBP. Similar to low back pain onset, this study also found an inverse relationship between blood pressure and cLBP in the multivariate analysis. Stimulation of baroreflex arch caused by increased blood pressure inhibits pain

transmission [265], possibly mediated by brain centres that control nociception and cardiovascular reflexes in the brainstem. Therefore, cardiovascular diseases may play a role in pathogenesis of cLBP.

### 5.2.2 Comparison with other prediction models

In spite of many studies examining risk factors associated with LBP, few studies have attempted to develop and validate risk prediction models and simplified risk scores for cLBP using routinely collected data. Previous studies have developed prediction models from occupation cohorts [385], among acute LBP patients in relation to developing cLBP [464] and based on pain trajectories [465]. These studies comprised of few participants, fewer cases, considered only ergonomics and occupation related variables, and did not incorporate routinely collected data, which makes the current prediction equations more applicable to general populations and able to distinguish individuals at risk of cLBP in general medical practice compared to these algorithms. The optimal cutoff points determined by Youden's J statistic as risk probability threshold of ≥0.948 and risk score threshold of ≥90 showed specificity of 94.3% and 74.2% in the identifying true negative individuals in relation to cLBP outcome for the prediction equations and simplified risk score, respectively.

This study assessed several risk factors and selected the most representative predictors using routinely collected health data. However, this model showed moderate discrimination (Harrell's C-statistic = 0.643 in validation cohort) and

there was no difference in the performance from existing models. Based on the current state of research and known risk factors, this model can be updated by incorporation of predictors related to psychological, ergonomics and genetics.

### 5.2.3 Strength and limitations

Some of the of the strengths and limitations of studies based on general practice databases are discussed elsewhere [466], but in addition this study has strengths of representativeness, adequate sample size, duration of follow-up, and lack of selection, recall, and respondent bias. Furthermore, data collected from insurance claims contains diagnosis and prescriptions from well-trained health professionals (reliability), and therefore the derived prediction equations can be utilised to advise individuals and reduce their risks.

There is a general problem of ambiguity and arbitrary case definition in studies of low back pain outcomes [102], which complicate drawing conclusions regarding prevalence and observed associations. This study did not assess effect of long-term and shorter-term durations of premorbid conditions and did not assess effects of chronic treatments of premorbidities on cLBP. These could improve accuracy in reporting their effects on cLBP and suggesting the most plausible causal pathways.

A low medical care seeking behavior has been reported among LBP patients [467], with care-seeking more common among women and individuals with previous LBP, poor general health, and those with more disabling or more painful

episodes [467] Therefore, it is possible that some individuals did not seek LBP related medical services for more than once; thereby possibly missing some cLBP cases based on the case definition. However, the prevalence of cLBP in this study was 13.2% and comparable with previous studies [470]. This study did not incorporate psychosocial factors, genetics and ergonomics related variables since these are not routinely collected. Addition of these risk predictors may help in improving the performance of the cLBP prediction equations and risk score.

### 5.2.4 Conclusion

This study derived and validated prediction equations to estimate the 8-year risk of developing cLBP. The model performance was moderate in discrimination and identifying individuals at risk of developing cLBP. Based on the survival curves for the risk strata from the prognostic index, this model performed well in identification of highest risk groups compared to the low risk groups.

To the best of my knowledge, this is the first population specific prediction equations for cLBP developed and validated using routinely collected health data in a population based longitudinal study in South Korea. Further studies should validate and update this prediction model using cohorts from other populations. This study reaffirmed an inverse association between cLBP and blood pressure as previously reported [29, 462]. In general, MetS was associated with chronic low back pain.

### 5.3 Low back pain recurrence within five (5) years

#### 5.3.1 Discussion

In this study, the 5-year LBP recurrence rate was 62.5%, and was comparable to a previous study [471]. This study was based on a wide range of risk predictors from routinely collected data, which individuals are likely to know and which can easily be applied in medical practice. The developed prediction model may be useful in informing patients about the prognosis of first time LBP episode and institution of preventive measures. In this study, premorbid conditions were associated with 5-year LBP recurrence. A previous study in German also found several comorbidities associated with LBP [469]. On the other hand, treatment duration or total days of prescription was associated with 5-year LBP recurrence. This study finding indicates that treatment is one of the preventative means to prevent LBP recurrence. Low back pain treatment is reported to have some benefit in remission of LBP [472, 473] and is indicated as one of the primary prevention measures of LBP recurrence.

MetS components were associated with 5-year LBP recurrence, in agreement with previous studies [21, 49, 190, 193, 198]. In particular, total cholesterol and CAD were associated with LBP recurrence congruent with atherosclerosis hypothesis [193], although a study conducted in Korea found no association between cLBP and predictors of cardiovascular diseases [21]. However, the risk

predictors of 5-year LBP recurrence and LBP chronicity may be different and conclusions cannot be easily be made about the relationship.

Unlike first onset of LBP and cLBP outcomes, blood pressure was positively associated with 5-year LBP recurrence in this study. This was different from the inverse association observed in LBP onset and cLBP outcomes in this study, and which has been reported previously [29]. Increase in blood pressure is related to hypoalgesic mechanism [96]. The reversed direction of association may also result from interaction with other risk factors. Unlike in the first onset of LBP outcome (first medical utilisation due to LBP), fasting blood glucose was not significantly associated with 5-year LBP recurrence in multivariate analysis. This observation was different from a previous twin study, which found a positive association between diabetes and LBP [22]. Diabetes has been linked to changes in proteoglycans' density and undersulfated glycosaminoglycans of the IVDs, which can increase susceptibility to disc prolapse and consequent mechanical back pain [205]. A previous study has reported an increase in diabetes prevalence in Korea with 4.8 million adults (13.7%) aged above 30 years affected [474], which may significantly increase LBP disease burden.

In this study, alcohol consumption was inversely associated with 5-year LBP recurrence. The mechanisms of action and modulation of effects of alcohol on pain perception is unknown [150], but may be mediated through psychological factors because alcohol dependence and stress influence onset of neuropathic pain [155].

However, there are studies that have reported on benefits of alcohol in relation to several outcomes [311].

Smoking status showed inverse associations with 5-year LBP recurrence whereas physical activity showed a week association with 5-year LBP recurrence. The inverse relation between smoking status and 5-year LBP recurrence differed from a previous study [211], which reported a positive association [211]. However, in occupational settings, smoking was associated with LBP only in people with heavy physical work [148], therefore, the relationship may be moderated by socioeconomic factors. In addition, most risk factors associated with complex diseases have weak associations [147]. Therefore, though some risk factors showed weak associations, they may significantly play a role in the 5-year LBP recurrence. In this study, prediction equations and a simplified risk score for 5-year LBP recurrence were developed and validated, using routinely collected data from general medical practice in a large population based cohort study.

### 5.3.2 Comparison with other prediction models

Few studies have attempted to derive and validate prediction equations for low back pain outcomes in longitudinal settings [475], especially using medical data. Previous studies have developed prediction models from occupation cohorts [385], among acute LBP patients in relation to developing cLBP [464], and based on pain trajectories [465].These studies comprised of few participants, fewer cases, considered only ergonomics and occupation related variables, and did not

incorporate routinely collected data. The prediction equations derived in this study significantly outperformed previous models with excellent discrimination and calibration. The model achieved discrimination of at least 0.857 in the validation sample, based on Harrell's C- statistic. Therefore, this prediction model may be more reliable, applicable to general population, and able to distinguish individuals at risk of LBP recurrence in general medical practice compared to previous models. In addition, the prediction equations have been derived from a wide range of predictors that individuals and clinicians are likely to know. The optimal cut-off points determined by Youden's J statistic as risk probability threshold of $\geq 0.567$ and risk score threshold of $\geq 81$ identified 62.7% and 62.3% of 5-year low back pain recurrent events for the prediction equations and simplified risk score, respectively.

### 5.3.3 Strength and limitations

Some of the of the strengths and limitations of studies based on general practice databases are discussed elsewhere [466], but in addition this study has strengths of representativeness, adequate sample size, duration of follow-up, and lack of selection, recall, and respondent bias.

A low medical care seeking behavior has been reported among LBP patients [467], with care-seeking more common among women and individuals with previous LBP, poor general health, and those with more disabling or more painful episodes [467]. Thus, it is possible that some individuals did not seek LBP medical

services for more than once, thereby possibly missing some recurrences. However, the LBP recurrence rate in this study was comparable with a previous studies [471]. In addition, this study did not incorporate psychosocial factors, genetics and ergonomics related variables because these are not routinely collected.

### 5.3.4 Conclusion

In this study, a prediction model of 5-year LBP recurrence was developed and internally validated in a large-scale, nationally representative data. The model showed good performance in discrimination of individuals at risk of 5-year LBP recurrence with (Harrell's C-statistic of at least 0.857 in the validation cohort). To my knowledge, this is the first risk prediction model of 5-year LBP recurrence that has been developed and internally validated using routinely collected health data in a large population based cohort study.

Further studies to validate and update this prediction model using cohorts from other populations are warranted. There was a stable positive relationship between blood pressure and 5-year LBP recurrence after adjusting for other covariates, which was different from findings in the cLBP and newly developed LBP outcomes investigated in this study, and differed from a previous study [29]. Thus, further investigations to understand the underlying mechanisms and the nature of this association are recommended. Other MetS components were associated with 5-year LBP recurrence in multivariate analysis except fasting blood glucose.

## 5.4 Low back pain recurrence within twelve (12) months

### 5.4.1 Discussion

The recurrence rate of LBP within 12 months was 29.0 %, which was lower than (64%-77%) previously reported [471]. The main objective in primary prevention is to reduce the burden of disease and number of LBP episodes experienced by a population [476]. This study assessed several epidemiological risk factors predisposing to LBP recurrence within 12 months and developed a risk prediction model applicable in medical practice. This study found a treatment effect on recurrence within 12 months. Total number of days of prescription (duration of prescription) showed an inverse association with LBP recurrence whereas individuals who had frequent medical consultations due to LBP or those who were admitted for long periods during the initial LBP episode were more likely to experience LBP recurrence within 12 months. The positive association between duration of hospitalization and frequency of consultation may be attributed to severity of initial LBP episode leading to long periods of hospital admission, which has been reported to influence recurrence [52]. In addition, duration of episode, days to seek care and pain and disability levels have been reported to predict recurrence within 12 months [52], which may partly explain the observed association between duration of hospitalization and recurrence with 12 months.

In this study, prediction equations and simplified risk score of LBP recurrence within 12 months were developed and validated, using routinely collected data from general medical practice. The study also assessed the effects of several risk factors on twelve-month LBP recurrence. Most risk factors were associated with twelve-month LBP recurrence except IHD and fasting glucose. The lack of association with fasting glucose in multivariate analysis was different from a previous study [22]. In addition, blood pressure was positively associated with LBP recurrence within 12 months. In general, MetS components were associated with LBP recurrence within 12 months. The developed prediction model might be useful in estimating risk of twelve-month LBP recurrence and inform on the possible preventive measures.

### 5.4.2 Comparison with other prediction models

In spite of many studies examining risk factors associated with LBP, few studies have attempted to develop and validate risk prediction models and risk scores for twelve-month LBP recurrence using routinely collected medical data. Previous studies have developed prediction models from occupation cohorts [385], among acute LBP patients in relation to developing cLBP [464], and based on pain trajectories [465]. These studies comprised of few participants, fewer cases, considered only ergonomics and occupation related variables and did not incorporate routinely collected data.

The prediction equations derived to estimate the twelve-month LBP recurrence in this study showed comparable or slightly outperformed previous models with good discrimination and calibration. The model achieved discrimination of at least 0.759 in the validation sample, based on Harrell's C-statistic. Therefore, these prediction equations may be more reliable, applicable to general population, and able to distinguish individuals at risk of twelve-month LBP recurrence in general medical practice compared to previous models. In addition, these equations have been derived from many predictors that clinicians and individuals are likely to know, although incorporation of other variables can still improve the prediction potential of the derived prediction equations and risk score. The optimal cut-off points determined by Youden's J statistic suggested a risk probability threshold of ≥0.839 showed specificity of 90.8% whereas risk score threshold of ≥68 showed specificity of 64.8% in relation to 12-month low back pain recurrence for the prediction equations and simplified risk score in the validation cohort, respectively.

### 5.4.3 Strength and limitations

This study has strengths of representativeness, adequate sample size, duration of follow-up, and lack of selection, recall, and respondent bias. In addition, the study was population based with excellent prescribing data linked to diagnosis [380, 466], which makes the outcome definitions reliable.

A low medical care seeking behavior has been reported among LBP patients [467], with care-seeking more common in women, and individuals with previous LBP, poor general health, and those with more disabling or more painful episodes [467]. Therefore, it is possible that some individuals did not seek LBP medical services for more than once, thereby possibly missing some recurrences. However, the LBP recurrence rate in this study was comparable with a previous studies [471]. This study did not incorporate psychosocial factors, genetics and ergonomics related variables since these are not routinely collected.

### 5.4.4 Conclusion

In this study, hypertension was associated with LBP recurrence within 12 months, which was different from the newly diagnosed or first onset of LBP outcome and needs further investigations to understand the underlying mechanisms. Other MetS components were associated with LBP recurrence within 12 months except fasting blood glucose and IHD.

In this study, prediction equations and a simplified risk score for recurrence of LBP within 12 months were derived and validated in nationally representative data for Korean population. The model showed good performance in discrimination and identifying individuals at risk of LBP recurrence within 12 months. To my knowledge, this is the first risk prediction model of LBP recurrence within 12 months, developed and validated using routinely collected health data in a large

population based cohort study. Further studies to validate and update this prediction model using cohorts from other populations are warranted.

### 5.5 Multiple episodic low back pain

#### 5.5.1 Discussion

Low back pain is typically an episodic condition [102], with 24% to 87% of acute LBP patients experiencing recurrence within 12 months [104, 477, 478]. Recurrent episodes are usually severe and costly compared to first low back episodes [479]. In order to reduce LBP associated personal and societal costs [23], derivation of prediction models applicable in general medical practice is necessary for effective prevention.

In this study, MetS components and premorbid conditions were associated with and predicted LBP recurrence (multiple episodes). However, unlike in the first onset of LBP; hypertension (blood pressure) was positively associated with experiencing multiple episodes of LBP. A previous study in Korea reported an inverse relationship between hypertension and LBP [29], whereas a positive association with LBP recurrence was reported in a Finnish industrial cohort [198]. The relationship between hypertension and LBP remains controversial, although lower susceptibility to musculoskeletal pain conditions in people with high blood pressure has been reported [462]. In general, MetS components were associated with LBP recurrence, and MetS has been suggested to mediate the effect through

increasing risk of disc degeneration [194] and atherosclerosis events [192], thereby contributing to the pathogenesis of LBP.

In this study, premorbid conditions were associated with multiple episodic LBP, in agreement with a previous study in German [469]. The association between premorbid conditions and LBP recurrence may represent multiple causal pathways in the pathogenesis of LBP because this condition has complex aetiology [32]. This model can provide information on individual risk of multiple LBP relapse, taking account of health profiles, demographics, and lifestyle and common comorbidities. Furthermore, this model is based on information that individuals and medical practitioners are likely to know which can aid diagnosis and improve decision making for both clinicians and patients.

### 5.5.2 Comparison with other prediction models

There are currently few studies that have attempted to validate prediction models of LBP in prospective studies [475]. Previous studies have used original Cox model to study time to first event, but the PWP model incorporates the order of events [457], and the correlated nature of the data [451]. Studies have attempted to developed prediction models from occupation cohorts [385],among acute LBP patients in relation to developing cLBP [464], and based on pain trajectories [465]. These studies comprised of few participants, fewer cases, considered only ergonomics and occupation related variables, and did not incorporate routinely collected data, which makes the current prediction equations more applicable to

general population and able to distinguish individuals at risk in general medical practice compared to these algorithms. However, it should be note that the current model has moderate discrimination and may not predict multiple LBP recurrent episodes with high precision.

### 5.5.3 Strength and limitations

The major strength of Prentice, Williams, and Peterson Gap-Time (PWP-GT) model is its ability to use all data from observed episodes and taking into consideration the correlated nature of the data, which makes it appropriate to investigate LBP episodes. This study was based on a large nationwide cohort and utilized data from general practice [380], which makes it generalizable. Furthermore, this study has strengths of representativeness, adequate sample size, duration of follow-up, and lack of selection, recall, and respondent bias. In addition, data collected from insurance claims contains diagnosis and prescriptions from well-trained health professionals (reliability), and therefore these risk predictions equations can be applied in general medical practice.

However, a low medical care seeking behavior has been reported among LBP patients [467], with care-seeking more common in women, and individuals with previous LBP, poor general health, and those with more disabling or more painful episodes [467]. Thus, there is a possibility that some individuals did not seek LBP medical services frequently even though they might have experienced subsequent episodes, thereby possibly missing some episodes. This study did not incorporate

psychosocial factors, genetics and ergonomics related variables since these are not routinely collected. In addition, the PWP-GT assumes renewal or recovery between episodes [451], which cannot be ascertained using claims data.

### 5.5.4 Conclusion

This study developed and validated prediction equations to estimate future risk of experiencing multiple low back pain episodes. The model showed moderate discrimination in identifying individuals at risk of experiencing multiple episodes. To my knowledge, this is the first low back pain prediction model developed and internally validated using routinely collected health data in a population-based setting and taking account of data available on episodes. This study also found MetS associated with multiple episodic low back pain recurrence with exception of premorbid IHD and spinal stenosis in adjusted analyses. There is need to validate and update this prediction model using cohorts from other populations.

## 5.6 Newly diagnosed nephrolithiasis

### 5.6.1 Discussion

Although the prevalence of nephrolithiasis and the burden of disease has increased in Korea [15], no population-specific risk prediction equations have been developed and validated in Korean to date. Tae *et al.,* has emphasised the urgent need for nephrolithiasis preventive efforts due to the rapidly changing prevalence of nephrolithiasis in Korea [480]. Knowledge of the risk of developing nephrolithiasis will therefore motivate people in the general population to change

lifestyle and other modifiable risk exposures thereby improving population health and reducing associated personal and social expenses. In addition, this study has identified major risk predictors of nephrolithiasis in Korea, which can inform health policy makers to focus on preventing population exposure to major putative risk factors. The developed and evaluated prediction equations and risk score can be availed to general population in form of web-based calculator or used by medical practitioners to assess nephrolithiasis risk among health individuals.

Predictive equations have been derived and validated in this study that can inform and assist clinicians and individuals in decision-making, especially lifestyle changes to reduce the risk of nephrolithiasis. To the best of my knowledge, this is the first research using medical data from general practice to develop a population-specific risk prediction model for nephrolithiasis in Korea. Studies have been conducted on the clinical prediction of stone-free rates or recurrence among patients based on stone characteristics [481], and prediction models for proper symptom-based diagnosis of nephrolithiasis [482], but this study aimed to predict future risks of nephrolithiasis among apparently healthy people (first use of nephrolithiasis in medicine). Previously, a model was developed to predict stone-free rate after single-tract percutaneous nephrolithotomy in Korean population [483], but this was also not intended for use among health individuals. The developed prediction equations showed excellent calibration and discrimination, with Harrell's C-statistic values of at least 0.819 in the validation cohort.

This study found associations between premorbid conditions and nephrolithiasis, which corresponded with a previous study that investigated association between multiple chronic conditions and urolithiasis [484]. Furthermore, premorbid conditions were also positively associated with nephrolithiasis in other studies [485, 486]. In this study, FBG was associated with nephrolithiasis in univariate analysis but no association was observed in the multivariate analysis. The association of MetS and diabetes with nephrolithiasis may involve insulin resistance, which is a principle metabolic disorder in both MetS and diabetes, and creates defective ammoniagenesis, resulting in low urine pH, thereby promoting uric acid stone formation [287]. In addition, Cameron *et al*., deducted that the main risk contributor for nephrolithiasis in patients with T2DM is a low urine pH [339], and insulin resistance can impair the production and transportation of ammonia [79]. This study found an association between nephrolithiasis and hypertension, in agreement with a previous study [375], although the relationship has been suggested to be bidirectional [341, 344]. A previous study found high total cholesterol predictive of a significantly higher urinary potassium and calcium [345], which may explain the observed association in this study.

Prior history of chronic kidney disease (CKD) is a known risk factor for nephrolithiasis; however, the association was not significant in the analyses, which may be due to a low prevalence of CKD in this study. The kidneys function to excrete metabolic wastes such as calcium and oxalate at supersaturated

concentrations preventing precipitation of crystals. Therefore, stone formation may be both a form of malfunction or sign of a diseased kidney [348]. There was a positive association between hyperparathyroidism and nephrolithiasis, and renal impairment is a common finding in primary hyperparathyroidism [349]. A positive association was observed between inflammatory bowel disease (IBD) and nephrolithiasis. Inflammatory bowel disease (IBD) is accompanied by diarrhea and malabsorption, both of which are predisposing factors for the formation of renal calculi [351]. There was a positive association between gout and nephrolithiasis, which was similar to a previous study that found premorbid gout associated with a twofold risk of stone formation, independent of diet, weight and medications [358]. However, the mechanism for this relation is unknown but involvement of insulin resistance and acid-base defects have been suggested [66].

There does not seem to exist a proper and confirmed method of prevention of nephrolithiasis, but less salt intake may cause no harm in general and is known to be helpful [487]. The predictors in the model are routinely assessed and likely to be known by patients, which makes the prediction equations easily applicable in general medical practice.

### 5.6.2 Comparison with previous risk prediction models

There are currently no predictive models of nephrolithiasis derived using data from general medical practice in longitudinal setting based on large population. Some prediction models were however developed based on other variables and settings. Kazemi *et al.,* used artificial neural networks and decision trees to provide

a diagnostic decision support system for determining presence and type of renal stone among 936 patients based on clinical symptoms and comorbidities [81]. Molina *et al*., aimed to quantify and describe stone characteristics based on computed axial tomography scan to predict ureteroscopy outcomes and to evaluate the characteristics influencing stone free rates [481]. Wang *et al*., aimed to externally evaluate the stone score in a multi-institutional cohort by comparing the score with physician gestalt among patients with suspected nephrolithiasis [482], and found it lacking accuracy in prediction of ureteral stone in suspected patients. The study conducted by Wang *et al.,* focused only on ureteral stone and showed excellent performance (AUC=0.78 [95% CI, 0.74 to 0.81]) whereas the current study considered all possible stone forming anatomical sites and has comparable prediction accuracy (Harrell's C-Statistic of 0.819 ([95% CI, 0.798-0.838]). The prediction equations derived in the current study slightly outperformed the clinical score for classification of patients with suspected nephrolithiasis [482] ,and showed equal performance in comparison with a clinical prediction rule for uncomplicated ureteral stone in patients eligible for computed tomography [488]. The optimal cutoff points determined by Youden's J statistic suggested a risk probability threshold of ≥ 0.969 and risk score threshold of ≥88 showed a sensitivity of 76.5% and 56.1% in relation to nephrolithiasis events for the prediction equations and simplified risk score in the validation cohort, respectively.

The existing studies developed diagnostic models among suspected nephrolithiasis patients, used small sample size and did not did not incorporate

routinely collected medical data, which limits their statistical power and generalizability. This study has developed and validated prediction equations to estimate future risk of developing nephrolithiasis in a large population based cohort, incorporating predictors from routinely collected health data. The prediction equations showed excellent calibration and discrimination, with Harrell's C-statistic values of at least 0.819 in the validation cohort.

### 5.6.3 Strength and limitations

Some of the of the strengths and limitations of studies based on general practice databases are discussed elsewhere [466], but in addition this study has strengths of representativeness, adequate sample size, duration of follow-up, and lack of selection, recall, and respondent bias. In addition, data collected from insurance claims in Korea is based on diagnosis and prescriptions from well-trained health professionals. Therefore, the current study has strong face validity and the model can be used in medical practice to advise individuals and reduce their risks. Furthermore, this study examined several risk factors, and developed the equations from representative predictors routinely collected in medical practice.

The study did not assess the effects of chronic treatments (medication) on the onset of nephrolithiasis. Medication with certain drugs has been reported to influence stone formation [300]. Capturing these details would increase accuracy in prediction and reporting effects of these risk factors on the onset of nephrolithiasis. Furthermore, the study used same underlying population for model derivation and validation; therefore, careful considerations are necessary in generalizing these

results to other populations. Nevertheless, these prediction equations showed good performance and can be useful in prediction of individualized risk of developing nephrolithiasis.

### 5.6.4 Conclusion

This study has contributed to the current knowledge of nephrolithiasis by derivation and validation of prediction equations and a simplified risk score to estimate future risk of nephrolithiasis in a large population based study using routinely collected data. These equations can be availed to the public in form of web calculator to provide information about nephrolithiasis risk and prevention strategies. This study also offers an opportunity for external validation of this model using data from other populations as well as updating the model by incorporating other risk predictors in other settings.

## 5.7 Nephrolithiasis recurrence within five (5) years

### 5.7.1 Discussion

In this study, prediction equations to estimate the 5-year risk of nephrolithiasis recurrence were derived and validated based on a combination of predictors that individuals are is likely to know and which are routinely collected in general medical practice. The equations are based on four risk predictors including age, sex, body mass index, and total number of days of prescription (duration of prescription). The prediction model can be utilised to inform and aid healthcare professionals in advising individuals or patients to reduce their risk of

nephrolithiasis recurrence. In the univariate analysis, MetS and lifestyle risk factors were associated with nephrolithiasis recurrence, which indicates the importance of lifestyle adjustment in prevention of nephrolithiasis recurrence. The prediction model consisted of few predictors and the potential of prevention based on the model can only be directed towards prevention of obesity and effective treatment of initial nephrolithiasis episode. However, this prediction model has been developed using data recorded from general medical practice and its performance may be higher in clinical practice settings compared to general population.

The prediction equations showed good calibration and discrimination with Harrell's C-statistic of at least 0.909 in the validation cohort. There does not seem to exist proper and confirmed method to prevent the nephrolithiasis and its recurrence, but less salt intake may cause no harm in general, and is known to be helpful [487]. In addition, lifestyle adjustments and treatment of comorbidities may generally reduce the risk of nephrolithiasis recurrence.

### 5.7.2 Comparison with previous risk models

Previous studies have attempted to develop prediction models for nephrolithiasis recurrence. The ROKS (Recurrence of Kidney Stone) nomogram was developed to predict risk of a second symptomatic stone episode [489], which had a C-statistic of 0.670. Kazemi *et al.*, used artificial neural networks and decision trees to provide a diagnostic decision support system for determining presence and type of renal stone among 936 patients based on clinical symptoms and comorbidities [81], which had 97.1% accuracy and performed better than the

current prediction model. Here we have developed and validated prediction equations to estimate 5-year risk of nephrolithiasis recurrence in a large population based cohort using routinely collected health data. The optimal cut-off points determined by Youden's J statistic suggested a risk probability threshold of ≥0.788 and a risk score threshold of ≥32 identified 66.0% and 68.1% of nephrolithiasis recurrent events in the validation cohort for the prediction equations and simplified risk score, respectively.

### 5.7.3 Strength and limitations

This consecutive cohort of nephrolithiasis patients was constructed from a large sample data set; thus, the study has strengths of representativeness, adequate sample size, duration of follow-up, and lack of selection, recall, and respondent bias. In addition, ICD-10-CM codes in Korean health insurance claims data have good accuracy and correspondence with actual health status based on medical charts [468].Therefore, this study has strong face validity and the model can be used in medical practice to inform individuals about their risks of experiencing nephrolithiasis recurrence and to motivate individuals to adjust lifestyle and reduce nephrolithiasis risk. Although the prediction model comprises of few variables, it was derived from a large number of variables and can be used as a simple model for estimation of 5-year nephrolithiasis recurrence risk.

The study did not assess the effects of chronic treatments (medication) on the risk of nephrolithiasis recurrence. Medication with certain drugs has been reported to influence stone formation [367]. Capturing these details would increase accuracy

in prediction and reporting of the effects of these risk factors on 5-year nephrolithiasis recurrence. Furthermore, this study did not assess the effects of genetics and heredity on the risk of nephrolithiasis recurrence since these are not routinely collected in medical practice. This study used the same population for model derivation and validation; therefore, careful considerations are necessary in generalizing these results to other populations. Nevertheless, these prediction equations showed good performance and can be useful for prediction of individualized risk of 5-year nephrolithiasis recurrence.

### 5.7.4 Conclusion

This study derived and validated prediction equations to estimate 5-year risk of nephrolithiasis recurrence from a consecutive cohort derived from a large population based cohort using routinely collected data. These prediction equations showed excellent performance based on Harrell's' C-statistic, although the prediction model consisted of few variables. These equations can be utilised in medical practice by health professions to estimate 5-year risk of nephrolithiasis recurrence among first time treated patients. Knowledge of individualized risk can help to promote lifestyle adjustments and promote health-seeking behavior to reduce nephrolithiasis recurrence risk. This study also offers an opportunity for external validation of this model using data from other populations as well as updating the model by incorporating other risk predictors in other settings.

# VI. Summaries and conclusions

### 6.1 Low Back Pain

Prediction equations aim at accurate stratification of individuals based on their health profiles into risk categories and adequate prediction of individuals' risks of occurrence of future events based on limited information. Derivation of prediction models is essential in aiding decision-making, improving health care cost-effectiveness and improving prognosis.

Based on the pre-existing state of research, the present thesis supports the atherosclerosis hypothesis, which suggests that atherosclerosis plays a role in pathogenesis of low back pain because total cholesterol and IHD were associated with and predicted low back pain in the developed models, although IHD was not included in model derivation due to correlation with total cholesterol. Premorbid conditions were associated with low back pain, which implies that treatment and managing of these conditions may be helpful in the prevention or retarding progression of low back pain.

Metabolic syndrome components were associated with low back pain and their management may indirectly reduce low back pain disease burden. This thesis also has found treatment of low back pain predictive of better prognosis, which highlights the need for low back patients to seek medical care in order to prevent and reduce risk of experiencing recurrent episodes.

In this study, prediction models for low back pain onset, chronicity, 5-year recurrence, twelve-month recurrence and multiple episodic low back pain have been developed and validated. The developed models showed varying

discrimination and calibration potentials, which necessitates further studies to update the models by incorporating other predictors in other settings and validation of the models using data from other populations. Regarding the prediction of different low back pain outcomes, the present thesis is the first study that derived and validated models and risk scores using data from general medical practice in a large population based prospective study. In comparison with previously developed models, the models derived in the thesis showed comparable or outperformed those from previous studies in predicting 5-year and 12-months low back recurrence, and at least showed comparable performance in discrimination when compared with existing models of chronic low back pain.

In this study, model discrimination based on sensitivity, specificity and accuracy was presented at different thresholds and optimal cut-off thresholds determined by Youden's J statistic However, in calculation of Youden index, specificity and sensitivity are considered to be equally important which may not be true in clinical practice because determination of a cut-off value should depend on or be guided by the clinical and economic implications of false positives and false negatives. In general, the sensitivity and specificity of a quantitative test depends on the cut-off value used to define positive and negative tests and the sensitivity of the test increase as specificity reduces based on the cut-off value, and vice versa. The ability to screen for a disease condition (diagnostic ability) depends on the discriminatory potential of the test, and disease prevalence in the population tested which influences positive predictive and negative predictive values. In this study,

the presented sensitivity and specificity values for nephrolithiasis at a range of different thresholds (centile values) of predicted risks of nephrolithiasis can be useful in the identification individuals at high risk of developing low back pain or experiencing low back pain recurrence within 5 years.

In addition, the models from this study incorporated more readily available predictors, which make them suitable for use by clinicians. Lifestyle and modifiable risk predictors including the MetS components can be targeted for the prevention of low back pain. However, with regard to the wide range of readily available predictors and the maximum achieved levels of discriminatory performance, the prediction equations of chronic low back pain and risk of multiple episodes still need to be improved. This can be achieved by incorporating psychosocial factors, ergonomics related predictors, and single nucleotide polymorphism associated with musculoskeletal conditions in polygenic risk score.

With regard to MetS, future research is needed to investigate the nature and mechanisms under which hypertension may induce hypalgesia. This thesis presents evidence that there may exists difference is risk factors predictive of onset, recurrence and chronicity of low back pain as well as the strength of associations.

The risk factors associated with low back pain including lifestyle, MetS components and cormobities are highly prevalent and increasing globally and are reported to be increasing in Korea, which raises concern about the future burden of disease. In order to counteract further increase in low back pain prevalence and to reduce the social and societal expenses due to low back pain, it is necessary to

derive applicable and informative prediction models in Korea. Therefore, the present thesis aimed to derive and validate population-specific prediction models that can be applicable to Korea population.

The risk predictors comprised of information on socio-demographic and anthropometric characteristics, lifestyle risk factors, treatment, and premorbid conditions. The findings of this thesis imply low back pain is a predictable, preventable, and treatable condition. There were discrepancies in the discrimination performance of models but comparisons between the observed and predicted probabilities for all models generally indicated similar patterns of agreement. The best approach to derive generalizable country specific risk prediction models is by means of external validation, although this was not performed in this study.

### 6.2 Nephrolithiasis

This study derived and validated prediction equations and simplified risk scores to estimate nephrolithiasis risk and its recurrence based on a combination of predictors that individuals are is likely to know, and which are routinely collected in general medical practice. The study was based on a large representative Korean population from a validated nationwide database [380]. Risk prediction models derived from routinely collected health data are more readily applicable in clinical practice. The models showed excellent calibration, a performance measure that is essential with regard to informing or making decisions in clinical practice. Model

calibration primarily determines clinical utility together with the distribution of predictions around the optimum cut-off value and the discrimination.

In this study, model discrimination based on sensitivity, specificity and accuracy was presented at different thresholds and optimal cut-off thresholds determined by Youden's J statistic However, in calculation of Youden index, specificity and sensitivity are considered to be equally important which may not be true in clinical practice because determination of a cut-off value should depend on or be guided by the clinical and economic implications of false positives and false negatives. In general, the sensitivity and specificity of a quantitative test depends on the cut-off value used to define positive and negative tests and the sensitivity of the test increase as specificity reduces based on the cut-off value, and vice versa. The ability to screen for a disease condition (diagnostic ability) depends on the discriminatory potential of the test, and disease prevalence in the population tested which influences positive predictive and negative predictive values. In this study, the presented sensitivity and specificity values for nephrolithiasis at a range of different thresholds (centile values) of predicted risks of nephrolithiasis can be useful in the identification individuals at high risk of developing nephrolithiasis or experiencing nephrolithiasis recurrence within 5 years.

Knowledge of personalized risk of nephrolithiasis may motivate individuals to reduce their risks through appropriate interventions thereby promoting population health and reducing personal and societal costs. The models can be used when a physician counsels individuals after a routine check-up by providing

information regarding nephrolithiasis risk profile and giving the exact probability of nephrolithiasis. This will motivate lifestyle adjustments and promote adherence to treatment of premorbidities, which are predictive of nephrolithiasis. Reducing risk factors associated with MetS, proper therapy for individuals with MetS and management of premorbidities can greatly reduce nephrolithiasis risk. Lifestyle modification can reduce nephrolithiasis risk conferred through MetS components (prevention of complications from obesity, diabetes, and dyslipidemia). However, these prediction models and risk scores have been developed using data from general medical practice and models' performance may be higher in clinical practice settings compared to general population. Nevertheless, the ICD-10-CM codes in Korean health insurance claims data have good accuracy and correspondence with actual health status based on medical charts [490], therefore, the derived equations are applicable in medical practice.

There does not seem to exist a proper and confirmed method of preventing nephrolithiasis, but lifestyle and dietary adjustments may be helpful, and treatment of premorbidities may generally reduce nephrolithiasis risk. The equations will also improve self-awareness of general health status because the predictors in the models are also predictive of other health outcomes, and the information might be useful when government aims at decreasing the burden of nephrolithiasis risk factors at population level. Knowledge of the overall health status of a patient with respect to nephrolithiasis risk and expert knowledge from clinical practitioners will

create a much clearer picture than either one alone. The variables in the model can easily be obtained in clinical practice and the points system is simple to use.

The existing nephrolithiasis models were developed in predominantly white populations and thus may not be appropriate and accurate in predicting nephrolithiasis risk among Asians. Racial differences in distribution and risk of nephrolithiasis have been reported in Asia. This model will improve individual decision-making, guide physicians in practice and define groups at high risk of nephrolithiasis. This study also offers an opportunity for external validation of the models using data from other populations as well as updating the model by incorporating other risk predictors in other settings especially in this era of precision medicine.

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**Korean Abstract（국문 초록）**

**배경**

복합 만성 질환은 다양한 병적 상태를 포함하는 질환으로 지역사회나 가정간호 등을 포함한 다양한 헬스케어 및 관련 기관들이 주의를 기울여야 한다. 하나의 만성적인 상태 혹은 복합적 질환의 예방과 완화를 위해서는 개선된 측정 방법과 예방법이 필요하다. 선진국에서는 만성 질환의 유병률이 급격한 고령화와 수명의 연장으로 인하여 증가하고 있고, 이러한 역학적 변화로 인해 퇴행성 질환과 생활 습관 관련 질환들은 선진국에서 감염성 질환보다 발병률 및 치사율이 더 높게 나타나고 있다. 이러한 건강 상태들은 개인과 사회 모두에게 상당한 부담을 야기하는데 지속적인 헬스케어가 필요하고, 질환으로 인한 장애가 평생 동안 지속되기 때문이다. 따라서 연령 관련 집단의 건강 상태를 관리하기 위하여 관련 전략을 세워야 하는데 고령화 인구와 이와 연관된 건강 관리 지출의 증가에 대한 고려가 필요하다. 2013 년에 한국의 질병 부담 중 장애보정생존연수(DALY)의 가장 중요한 요인 중 하나는 요통이었고, 신장 결석은 지난 20 년 동안 한국에서 꾸준히 질병부담이 증가해온 질환이다. 본 연구는 요통과 신장결석의 두 질환을 중점으로 위험도를 추정하고 질병을 예방하는 방법을 제안하고자 한다.

**배경:** 요통은 사회에 상당한 경제적 부담을 주는 신체적 질환으로, 국내 총 보험금액의 10% 이상을 차지하고 있다. 요통은 약 60-80%의 사람들이 일생에 시작될 가능성이 있고, 잠재적으로 유소년기에 나타날 수 있으며 약 6-10%의 급성 LBP 환자들 중 만성 요통이 발생하거나 반복적인 요통 증상을 경험하는 것으로 추정된다. 요통 시작 및 재발과 관련된 위험 요인에 대한 견해 차이가 존재한다. 최근엔 지질 수치, 동맥경화증, 고혈압, 당뇨병 그리고 낮은 요통과의 관계를 평가하기

위한 종적 연구가 권장된다. McIntosh 등의 2018 년 체계적 문헌고찰에 따르면 만성 요통에 대한 검증된 예측 모델이 없는 것으로 나타났다. 본 연구는 일반적인 진료 데이터를 사용하여 요통 발병의 미래 위험, 재발 및 만성 위험을 추정하기 위한 예측 모델과 위험 평가 점수를 도출하고 검증하려고 시도하였다. 이 연구는 또한 대사 증후군 위험요인과 요통 사이의 연관성을 평가하는 것을 목표로 한다.

방법: 한국의 일반적인 의료 관행에서 수집된 데이터를 사용하는 인구 기반 전향적 코호트 연구로 연구 참여자는 2002 년부터 2010 년까지 NHIS-NSC(National Health Insurance Service-National Sample Cohort)에 등록된 502,342 명으로 설정하였다. Cox 비례 위험 모델과 프렌티스, 윌리엄, 피터슨 갭타임 모델이 분석에 사용되었다.

**결과:** 8.4 년의 (범위:1.49 ~ 8.99)의 추적 관찰 중위수 기간 동안 요통이 없었던 참가자 438,713 명과 만성 요통이 없었던 455,619 명 중 처음으로 요통과 만성 요통을 경험한 환자는 138,217 명(31.5%)과 60,204 명(13.2%)였다. 503,482 명의 참가자들로부터, 170,279 명의 요통환자들의 코호트가 구성되었고, 49,462(29.0%), 106,927 명(62.8%)이 요통의 재발을 12 개월 추적 및 5 년의 추적 기간동안 경험하였다. 대사성 질환 요인과 질병 발생 전의 상태는 예측된 요통과 연관되었고 단변량 분석과 다변량 분석 시 각각 연관성의 방향이 다른 부분이 있었다.

**(요통의 초발에 대한 예측식)** 에서는 연령, 성별, 소득 등급, 알코올 소비, 흡연 상태, 신체 운동, 체질량 지수, 총 콜레스테롤 및 질병 병력을 변수로 포함하였고, 요통 재발 예측 모델에는 연령, 성별,

소득 등급, 체질량 지수, 총콜레스테롤, 수축기 혈압, 요통 치료일수, 질병의 기왕력을 포함하였다.

5 년 내 요통의 재발에대한 예측식에서는 연령, 성별, 소득 수준, 흡연여부, 알코올 소비, BMI, 총콜레스테롤, 고혈압, 신체활동력, 요통 치료 기간, 질병 기왕력 등을 포함하였다.

검증 코호트에서 Harrell 의 C-통계량은 각각 요통 초발 시 0.804 (95% CI, 0.796-0.812), 만성 요통 0.643 (95% CI, 0.629-0.656) 및 5 년 내 재발된 요통 0.857 (95% CI, 0.847-0.866), 12 개월 내 재발된 요통 0.759 (95% CI, 0.745-0.774) 였다. 간소화된 수치의 위험도, 연령, 퇴행성 디스크, 성별이 요통의 발병의 가장 큰 위험 요인으로 생각되었고 연령, 처방 일수 및 퇴행성 디스크가 5 년 내 재발의 가장 큰 위험 요인으로 나타났다.

**결론:** 이 연구는 요통이 예측 가능하고, 예방 가능하고, 첫 진단의 효과적인 치료가 재발 위험을 줄일 수 있다는 것을 암시한다. 이 연구는 또한 대사 증후군 구성 요소가 요통의 발병과 관련되어 있다는 것을 밝혀냈고, 발병 전 단계의 상태가 향후 요통 발병과 만성도, 재발을 예측할 수 있게 하였다. 특히, 고혈압과 요통 사이에는 ~~반비례~~ **(역상관관계)**가 있다. 그러나 발병, 재발, 만성의 예측요인에는 차이가 있는데 본 연구에서는 요통 발생 위험을 추정할 수 있는 예측 모델 5 개가 일반 진료 데이터를 사용하여 전국 샘플 코호트에서 개발 및 검증하였다. 예측식이 전문가를 대신하지는 못하지만 임상적 결정의 정확도를 높이는데 사용될 수 있다. 개인의 건강 상태를 신장 결석의 위험도 부분과 함께 예측하고 전문가의 의견과 함께 진단 시 사용하는 경우 더 정확도를 높일 수 있다. 또한 이 연구는 다른 위험 예측 변수를

다른 설정에 통합하여 모델을 외부 검증하거나 업데이트할 수 있는 기회를 제공한다.

### 신장결석

**배경:** 신장결석은 요로와 신장에 결석이 있는 상태를 의미하는데 염분의 용해도와 침전도의 균형이 깨졌을 때 발생한다. 신장결석은 복잡한 병인을 가진 다인성 질환으로 서구권에서 약 10%의 유병률을 보이고 있다. Romero 등에 따르면 한국에서는 약 5.0%의 신장결석 유병률을 보이며 질병부담은 점차 증가하는 것으로 나타났지만 최근까지도 신장결석에 대한 인구 특이적 위험예측모델이 한국에서 개발되고 검증되지 않은 것으로 보인다. 신장 결석은 대사 증후군과 관련이 있지만 이에 대한 결론은 도출되지 않았다. 정교히 검증된 위험 예측 모델은 개인별 질병 위험도를 판별하는 데 도움을 줄 수 있고 예방법을 찾는 데 도움을 준다. 신장결석에 대한 많은 역학연구에도 불구하고, 일상적으로 수집되는 의료 데이터를 이용하여 신장결석 모델을 검증하고자 하는 종단연구는 시도되지 않았다. 본 연구는 개인과 의료진이 파악하고자 하는 위험 예측 요인으로부터 신장결석 예측 수식을 개발하고 검증하고자 한다. 이에 더하여, 본 연구는 대사증후군, 질병이 걸리기 전의 건강 상태와 신장결석에 대한 관계를 평가하고자 한다.

**방법**: 한국의 전향적 인구 기반 코호트 연구로 2002 년부터 2010 년까지 NHIS-NSC(National Health Insurance Service-National Sample Cohort, 국민건강보험공단 - 국가 표본 코호트)의 502,342 명을 대상으로 하였다. 분석에는 Cox 비례 위험 모델을 사용하였다.

결과: 중위수 8.5 년(범위=2.0-8.9)의 추적관찰 기간 동안, 496,971 명의

대상자 중 18,205 명이 신장 결석 기록이 있었으며 단변량 분석과 다변량 분석 시 각각 연관성의 방향이 다른 부분이 있지만 대사 증후군 관련 성분과 발병 전의 건강 상태는 예측된 신장 결석과 연관이 있었다. 절약 모형의 새로 진단된 신장결석의 위험 예측 변수로는 연령, 성별, 소득 수준, 흡연 상태, 알코올 소비량, 체질량 지수, 병력, 통풍 과거력, 부갑상선 항진증, 염증성 장질환 등이 포함되었다. 과적합 보정 Harrell 의 C-statistics 를 적용하였을 때 derivation cohort 와 validation cohort 의 예측력은 각각 0.820 (95% CI, 0.806-0.834), 0.819 (95% CI, 0.798-0.838)였다. 검증 코호트의 모델의 민감도와 특이도는 각각 0.821 (95% CI, 0.760-0.888), 0.513 (95% CI, 0.390-0.656)였다. 고위험자를 정의하기 위한 Youden 의 최적 기준에 따르면 모델의 민감도와 특이도는 66%, 77.5%로 나타났다. 신장결석 위험 점수를 기반으로 한 간소화된 점수를 토대로 하였을 때 연령, 성별, BMI 가 새로 진단된 신장 결석의 가장 큰 위험 점수를 차지하였고 총 처방 일수, 성별, 연령이 5 년 내 신장결석의 재발에 가장 큰 위험요인이 되는 것으로 나타났다.

추적 기간의 중간 기간 동안 7,086 (30.1%) 건의 신장 결석 재발이 23,576 명의 참가자들로부터 발생하였다. 신장결석의 재발에 대한 누적 위험도는 2004 년에 19.8 (95% CI, 19.3 to 20.4) 에서 37.6 (95% CI, 36.8 to 38.3) 로 추적기간의 마지막 연도에 증가하였다 (8.5 년).

신장 결석의 재발은 성별, 연령, BMI, 및 처방전의 총일 요인에 의해 예측되었고 Harrell's C-통계에 따르면 해석 코호트와 검증 코호트에서 각각 0.926 (95% CI, 0.907-0.945), 0.909 (95% CI, 0.879-0.935) 이었다.

**결론**: 이 연구는 신장결석이 예측 가능한 건강상태이고, 연구에 사용된 모델은 위험군을 스크리닝하는 데 사용될 수 있음을 시사한다. 고안된 예측 방정식은 일반 인구에 웹 기반 계산기의 형태로 적용하거나 의료진들이 건강한 사람을 상대로 신장결석의 위험을 예측하는 데 적용할 수 있다. 또한 최근에 신장결석을 진단받은 사람의 예후를 예측할 수 있다. 개인의 건강 상태를 신장 결석의 위험도 부분과 함께 예측하고 전문가의 의견과 함께 진단 시 사용하는 경우 더 정확도를 높일 수 있으며 개발된 모델의 변수는 실제 임상 현장에서 적용할 수 있고 사용이 편리하다.

이 연구를 통해 정밀의료의 시대에서 또한 외적 타당도를 높이고 다른 환경에서 다른 위험인자를 포함함으로써 모델을 개선할 수 있을 것으로 보인다.

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주요 단어: 복합질환, 요통, 신장결석, 만성병, 삽화, 재발, 예측, 예측인자, 예후, 위험점수, 도출, 검증

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