QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCES

FRAGILITY FRACTURE INCIDENCE AND RISK IN PATIENTS WHO UNDERGONE BONE MINERAL DENSITY TESTING IN QATAR: A RETROSPECTIVE COHORT STUDY.

BY

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ABSTRACT

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Title: Fragility Fracture Incidence and Risk in Patients Who Undergone Bone Mineral Density Testing in Qatar: A Retrospective Cohort Study.

Supervisor of Thesis: Dr. Manar, E, Elhassan.

Background: Osteoporosis and its associated fragility fractures pose a significant public health issue in the elderly population. Additionally, diabetes has been linked to an increased risk of fragility fractures. In Qatar, little is known about the burden of fragility fractures and their association with osteoporosis or diabetes.

Aims: Determining the burden of incident fragility fractures, following a bone mineral density (BMD) test, and the effects of having lower BMD levels and being diabetic on the risk of fragility fractures in the population aged fifty and older. Additionally, assessing the impact of database selection for the BMD reference range used to establish osteoporosis diagnosis on fracture risk estimates in the Qatari women subpopulation.

Methods: In this retrospective hospital-based cohort study, patients who underwent BMD testing between May 2016 and June 2019 were followed through their health records from the date of the first test until the first fracture or their last encounter (before April 2020), whichever came first. The incidence rate of fractures per 1000 person-months of follow-up was estimated. Univariate and multivariate Cox proportional hazards regression analyses were performed to determine the effect of BMD and the effect of diabetes on fracture-free survival. Fracture rates among patients with osteoporosis and sensitivity for detecting incident fractures were estimated and

compared using the National Health and Nutrition Examination Survey (NHANES) and the Qatari databases.

Results: The cohort consisted of 705 patients who had a median follow-up time of 31.03 months (IQR=12.05). The incidence rate was 1.73 (95% CI= (1.23-2.42)). The crude hazard ratio (HR) for fragility fracture per standard deviation reduction in BMD was 1.82 (95% CI= (1.34-2.48)) and 1.93 (95% CI= (1.37-2.71)) when adjusted for age and gender. Compared to not being diabetic, HR for being diabetic was 1.36 (95% CI= (0.69-2.68)). Using the NHANES database yielded higher incidence rates among female patients with osteoporosis and more sensitivity in detecting incident fracture.

Conclusion: Among older adults, BMD is a significant predictor for fragility fractures, and the association between diabetes and fractures remains equivocal. The NHANES database is superior to the Qatari database in detecting incident fracture cases among older Qatari women.

DEDICATION

I dedicate this work to my mother, Farida Sobhi, for the sacrifices she made and for her everlasting faith.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1: Introduction

Osteoporosis is the most prevalent disease affecting bones in humans (1), which poses a major global public health issue. It is characterized by low bone mass, an increase in bone fragility, and susceptibility to fracture (2). Worldwide, the incidence of osteoporotic fractures differs with geographical variations (3). Nonetheless, the deterioration in bone mass that occurs after menopause in women, and that is age-related in both men and women (1) indicates that osteoporosis becomes more prevalent with increasing age. It also indicates that the incidence of the associated fragility fractures will increase, especially with the continuously increasing life expectancy of the population.

Osteoporosis diagnosis is established based on a T-score of bone mineral density (BMD) of -2.5 or lower (4). The T-score compares an individual's BMD measurement to that of the young normal (4). It was found that the use of BMD alone has a predictive ability for fractures that is similar to that of blood pressure to stroke and serum cholesterol to coronary artery diseases (CADs) (5). However, this threshold identifies only 20% of women as having osteoporosis by dual-energy X-ray absorptiometry (DXA) scan measurements at the hip site (6), indicating lower sensitivity. In addition, many people will sustain fractures despite the fact they have normal BMD values. An example is provided by the findings from a large longitudinal cohort study of postmenopausal women in the USA, where 82% of women who had fractures had a T-score over -2.5 (7). Accordingly, in order to improve fracture risk assessment, other risk factors that are known to increase the risk of fractures must be considered along with BMD (8).

A plethora of medical conditions and the use of many medications have been linked to increased fracture risk (9), and many computational algorithms have been

developed to incorporate risk factors in the calculations of fracture probabilities (10) (11, 12). The silent nature of osteoporosis contributes, in part, to the globally observed gap in healthcare among older people. However, identifying those with a high risk of fragility fractures through proper risk assessment approach help close this gap and prevent fragility fractures and their associated adverse health outcomes.

Diabetes Mellitus, especially type 2, represents a continuously rising public health problem. The number of people living with diabetes increased four times from 1980 till 2014 (13). Osteoporosis, which becomes more common with age, will pose an additional problem in the expanding population of diabetic patients and negatively influence their quality of life. Recent evidence suggested the association between diabetes and increased fracture risk (14). However, other results that do not support this evidence were found as well (15). The implication of these conflicting results is that other factors are potentially influencing this relationship.

It has been suggested that the risk of fragility fractures changes according to ethnic and racial backgrounds, evident by the different lifetime risks observed in both men and women in different countries such as the US and China, and the highest fracture rates observed in Northern European countries (16). Additionally, it was found that the same T-score derived from different sites and technologies will give inconsistent information about the prevalence of osteoporosis and the risk of fracture (17). An example is the variation observed in the estimated gradient of risk for the effect of BMD on fracture risk. This observation could be explained, in part, by the differences in the BMD standard deviation (SD) of populations used at different sites and with different equipment to derive T-scores (17). Accordingly, despite the fact that the use of a uniform standard reference population for the derivation of T-scores provides a common platform, estimation of fracture risk based on this reference range might yield

different results from when an ethnic-specific reference range were to be used. Currently, the recommended reference range is from the third National Health and Nutrition Examination Survey (NHANES III, 1988-1994) database for femoral neck measurements in women aged 20-29 years (17, 18), which marks the peak bone mass of a Caucasian woman and denotes the normal BMD reference standard. However, the reference ranges obtained in various Eastern Mediterranean Region (EMR) countries, (19-22), were generally different from that of Caucasian and among each other. Whereas in Qatar, BMD at the femoral site reaches the maximum values at 40–49 years, among Qatari women and the total femur BMD values were generally higher in Qatari females than their Caucasians counterparts in the age group of 40–59, but lower in the age group of 60–69 (23).

In the state of Qatar, the combined prevalence rate of osteoporosis and low bone mass between 2011 and 2012 was 4% at the femur and 16% at the spine (24). Moreover, 17% of the adult population is living with diabetes, which is double the global prevalence (25). However, little is known about the burden of fragility fractures and their association with osteoporosis or diabetes. Accordingly, we sought to determine the incidence rate of fragility fractures and estimate the effect of having lower BMD levels -compared to the young normal BMD- on the risk of fragility fractures in patients aged fifty and older, who underwent BMD testing at Hamad Medical Corporation (HMC), between May 1st, 2016 and June 30th, 2019. Additionally, the association between diabetes and incident fragility fractures was explored in the study sample. Moreover, we investigated the impact of using the NHANES database on the one hand, and the Qatari database, on the other hand, in the derivation of total hip BMD T-scores on the obtained fracture risk estimates in the subpopulation of Qatari female patients.

Chapter 2: Literature Review

2.1 Osteoporosis: Definition and Types

In their review of the evolution of the term osteoporosis in 1992, D. Schapira and C. Schapira discuss how the definition of osteoporosis continues to reflect what we know about the disorder itself, how the balance between criteria of the physiological process and those of the clinical manifestation remains a challenge and how researchers are in desperate need for a unified definition (26). In the following year, an international consensus provided the following definition for osteoporosis in its statement: "Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (27). This definition encompasses both the impact on bone structure and the clinical aspect of the disease.

The world health organization (WHO) then published a new and more operational definition that included specific criteria for diagnosis, and osteoporosis was simply defined as a BMD T-score of -2.5 or lower and low bone mass (LBM) as BMD that is ranging between -1 and -2.5 (4). Table 1 summarizes the different cut-off T-scores values to categorize individuals according to their BMD results as established by the WHO. The classification presented is not applicable to children, premenopausal women, and men under 50 years of age (28). This definition accomplished at least two important things; acknowledging BMD as an important etiological factor in the pathogenesis of osteoporosis and aiding osteoporosis prevalence research (2). In the same WHO technical report of 1994 (4), an emphasis was made on the importance of separating fracture risk assessment from osteoporosis diagnosis, which indeed simplifies matters for researchers and clinicians alike. This -2.5 T-score value has become a defining point of osteoporosis diagnosis since then (29).

Table 1. Criteria for Osteoporosis Diagnosis

Category	DXA BMD result
Normal	BMD within 1.0 SD below the young adult female reference mean (T-score ≥ –1.0)
Low bone mass	BMD between 1.0 and 2.5 SDs below the young adult female reference mean (T-score < –1.0 and > –2.5)
Osteoporosis	BMD ≥ 2.5 SDs below the young adult female reference mean (T-score ≤ –2.5)
Severe/established osteoporosis	BMD ≥ 2.5 SDs below the young adult female reference mean and the presence of one or more fragility fractures

Appr. DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; SD standard deviation.

There are two types of osteoporosis; primary, in which aging under the influence of sex hormones is the underlying process and secondary, which occurs in response to the existence of a certain health condition or the use of certain medications (30). Primary osteoporosis can be further divided into type 1, which affects a subset of women who are postmenopausal and usually are between fifty to sixty-five years old and which typically has no symptoms. The resultant fractures are predominantly of the wrist and the spine. Type 2, however, is called senile osteoporosis and the characteristic fractures sustained in this type are those of the hip, pelvis, tibia, and humerus (30). Primary osteoporosis affects mostly elderly people; accordingly, it is also referred to, in some of the literature, as age-related osteoporosis, and in the case of women, the term postmenopausal osteoporosis is also used (31). When it occurs in younger people and children, it is referred to as idiopathic.

Generally speaking, the normal bone biological process involves a balance between bone formation-predominant in younger ages with a maximum peak between ages 20 and 25-and bone resorption. The disruption of this process leads to weakened

bone and, later on, to osteoporosis when the balance tips towards excessive resorption at older ages (32).

Osteoporosis in men is also defined based on the same T-score cutoff points mentioned earlier for LBM and osteoporosis; however, estimation of the prevalence of the latter two among men is highly dependent on using a male or a female cut-off for the reference range. This is evident by the different prevalence rate results for men obtained from the third National Health and Nutrition Examination Survey (NHANES III, 1988-1994), which were 3-6% (1-2-million) of men recognized as having osteoporosis and 28-47% (8-13 million) as having LBM; when male cutoffs were used. However, 1-4% (280,000-1 million) had osteoporosis, and 15-33% (4-9 million) had LBM when female cut-offs were used (33). Accordingly, it seems fitting to use sex-specific reference values for the definition of osteoporosis and estimating the risk of fracture (34). However, the recommendation by the UK National Osteoporosis Guideline Group (NOGG), for both men and women, is to use the reference range of the NHANES survey of Caucasian women who are between 20 and 29 years old (35).

Bone loss in men is a slow and gradual process starting from midlife and increasing with age, which is different than what occurs in women, who experience menopause with midlife sex hormones loss and the resultant increased bone loss and fracture risk (34). Although women have a higher risk of fractures as compared to men, owing to the accelerated loss associated with menopause and the lower peak bone mass (32), the guidelines concerning the diagnosis of osteoporosis and fracture risk assessment for postmenopausal women and men aged 50 and older are generally similar.

2.2 Burden of Osteoporosis

Osteoporosis is a health issue affecting people worldwide, but its overall prevalence is hard to pinpoint because of the heterogeneity of assessment methods and

the extent to which this problem receives awareness, but it was estimated that in Europe, the USA, Japan, and India, 125 million are living with the disease (32). In a report dedicated to defining the burden of osteoporosis in the EU countries for the year 2010 and after, estimates from the EU show that the numbers are about 22 million women and 5.5 million men (36).

It is well known that osteoporosis is a silent disease, and its real burden lies in its consequences if it was allowed to continue without detection and proper management. The most important of these consequences is the increased risk of fragility fractures, the subsequent sequelae on the health of an individual and the economic and societal burden in the case of their occurrence.

Fragility fractures are those fractures caused by the type of trauma with a given force that usually do not lead to fracturing in a young adult, such as those with a low force that is equal to falling from a standing level or lower (37). The distinction between fragility fractures and osteoporotic fractures is not clear in the literature, and it seems that the two terms are sometimes used interchangeably. However, Kanis *et al.* define osteoporotic fractures as those that occur at sites that have low BMD and those that increase in occurrence with age (38). The classical sites for osteoporotic fractures are the hip, the vertebrae, and the wrist (39), although other sites may be affected as well.

Worldwide and for the year 2000, the incidence of osteoporotic fractures was estimated to be 9.0 million, comprised of 1.6 million hip fractures, 1.7 million forearm fractures, and 1.4 million, which were considered to be clinical vertebral fractures. All of them were responsible for 0.83% of the global burden of non-communicable diseases and 1.75% of that in Europe (40).

In the same previously mentioned EU report, the economic burden of new and old fragility fractures was estimated to be € 37 billion. 66% of the cost was due to new

fractures, 29% was due to the care of fractures for extended durations, and 5% was due to prevention using drugs, wherein a 25% increment in costs is expected by 2025 (36).

In the USA, over 2 million new fractures at $17 billion cost were predicted for the year 2005, with total costs including prevalent fractures being $19 billion. 29% of fractures and 25% of costs were attributed to men. New fractures, according to the site, were distributed as follows: vertebral (27%), wrist (19%), hip (14%), pelvic (7%), and others (33%). In comparison, total costs were: vertebral (6%), hip (72%), wrist (3%), pelvic (5%), and other (14%). There is a 50% projected increase in fractures per year and in costs by 2025 (41).

In Canada, in the years 2010/2011, the number of fractures that is due to osteoporosis was 131,443, which led to 64,884 acute care admissions and 983,074 acute hospital days (42). Costs related to acute care reached $1.5 billion, and those due to long term care were 33.4 times the previous estimate in 2008 (43) ($31 million versus $1.03 billion), owing to better data capture. That, in addition to rehabilitation and further admissions, add up to an overall cost of osteoporosis that was more than $4.6 billion, which equates to an 83% increase over the 2008 estimate.

In a study conducted in Switzerland to investigate hospitalization incidence rate due to fractures and the direct medical costs due to hospitalizations for the year 2000, the results were compared to other non-communicable diseases such as chronic obstructive pulmonary disease (COPD), heart failure, and diabetes. Osteoporosis ranked first in women and second in men-after COPD-in terms of direct medical costs due to hospitalization (44), which incurs a huge burden on the Swiss health system.

The total disability-adjusted life years (DALYs) lost due to osteoporotic fractures in 2002 was 5.8 million, around half of this is attributed to Europe and the Americas, where DALYs lost in Europe due to osteoporotic fractures are more than

those of the most frequent cancers aside from lung cancer (40). Functional disabilities involving walking, grooming, and transfer are among the reported consequences that are associated with hip fractures (45). As for vertebral fractures, which are mostly asymptomatic, reduced pulmonary function, chronic back pain, kyphosis, loss of self-esteem, loss of independence, and death are among the reported associated consequences (46). Added to that are back pain and disability, which are associated with new fractures more than they are with prevalent ones (47).

In Germany, Bleibler *et al.* constructed an economic Markov state transition simulation model for the estimation of costs and lost quality-adjusted life years (QALYs) due to new osteoporotic fractures in the German population that is older than 50 years of age between the years 2010 and 2025. It was found that fractures count will increase from 115,248 in 2010 to 273,794 in 2050. The discounted (3 %) cumulated costs will be 88.5 billion Euros, and the discounted QALYs will reach 2.5 million (48).

The increased mortality rate is a known complication of hip fractures, as evident by the time-to-event meta-analysis of prospective cohort studies (22 women cohorts and 17 men cohorts) for individuals who are 50 years or older, which reported that the relative hazard of all-cause mortality in the three-months duration after a fracture equals 5.75 (95% CI: (4.94-6.67)) in women and 7.95 (95% CI: (6.13 to 10.30)) in men, which represents five to eight times more risk as compared to the age and sex-matched controls (49).

It remains a challenge to separate the effect of hip fracture from that of other commonly co-existing comorbidities and other factors that contribute to both fractures and the outcome of interest, namely, mortality, disability, and cost. When comorbidities are assessed, the effect will be dependent on which and how many comorbidities were assessed and on the assessment of their severity as well (45).

2.3 Incidence of Fragility Fractures

In their systematic review of age-standardized hip fractures rate in 63 countries from 1950 to 2011, Kanis and colleagues found that the lowest incidence rates per year were found in Nigeria, South Africa, Tunisia, and Ecuador, and the highest rates were found in Denmark, Norway, Sweden, and Austria. In general, the variability of rates between countries had a ten-fold range, and a correlation was found between the rates in women and men, which was statistically significant (50). The results of the review indicated that there was a clear variability observed in rates according to geographic location, for the combined rates of both men and women, where countries such as Norway, Sweden, and Ecuador had the highest rates, consistent with the general pattern of higher risk with higher altitude. Comparable results were found in Iran and Oman, despite having a favorable altitude. This could be explained by the more body covering for women in these countries that minimizes sun exposure, which potentially leads to vitamin D deficiency and more fragile bone. That being said, a similar risk was not seen in other countries with the same tradition, and the risk is still high in men within these two countries.

The risk of hip fractures increases in the presence of disabilities; for example, in Germany, half of the burden of hip fractures occurs in people who have disabilities and in need of care (51). The risk was ten times greater among those who require care in the age group of 60 to 80, and long-term facilities rank first among settings with the highest risk of fracture.

In one study aimed to quantify the number of hip fractures that occur the year; 2010, in 58 countries- representing over 80% of the world population of people who are 50 years or older-, the number of new fractures was 2.32 million, where women had around two times greater number as compared to men (741,005 in men and 1,578,809 in women). Half of this total number could be prevented if BMD in individuals with

osteoporosis was set at a T-score of -2.5 SD. Of these, more than eighty percent occur in individuals of both genders who are 70 years or older (52).

As for vertebral fractures, the rates were different within the same study population owing to the use of different methods in defining those fractures, where some of these methods use morphometric or quantitative techniques and others are semi-quantitative (53). Despite this obstacle and the variability in age groups included in different studies, comparison of prevalence rates was easier than that of incidence rates, which were less abundant and more diverse. For example, prevalence rates in European women for the same age group-as summarized by a systematic review of the literature between 1966 and 2015 of 39 prevalence articles (53)-is highest in Scandinavia (26% and 12.2%) and lowest in Eastern Europe (18% and 11%) using two different quantitative techniques, while the trend of Scandinavia being the highest followed by the Mediterranean part, then West Europe and finally East Europe, was consistent using both methods. Generally speaking, rates in North America for white women aged 50 and older were ranging between 20% and 24%, and the risk was 60% higher than in black women. Latin America had lower rates ranging between 11% and 19%, whereas rates in Asia were highest in Japan (24%) and lowest in Indonesia (9%) for women who are 65 years or older using the same method. As for the Middle East, very few studies on the prevalence rate of vertebral fractures were identified by the review search.

The same review resulted in 24 articles providing incidence rates for vertebral fractures, which were, according to the review authors, not easy to compare due to issues concerning the ICD code used to define vertebral fractures or the age group included. Some studies used ICD codes, and others used radiologists' reports only. Additionally, when ICD codes were selected, different versions were used. Moreover,

due to the fact that ICD codes disregard the distinction between low and high trauma fractures, high trauma fractures were over-represented when younger populations are selected. In the UK, annual incidence rates were 32 per 100,000 men and 56 per 100,000 women in a study that was conducted from the late eighties to the late nineties on a national level (54).

Generally speaking, rates of vertebral fractures were more homogenous than those of hip fractures, and some of the highest rates were observed in Asia (53). It is likely that better characterization of prevalence and incidence rates of vertebral fractures is attainable when more future studies are conducted, using similar definitions of vertebral fractures and selecting comparable age groups.

The 10-year probability of any major osteoporotic fracture-hip, clinical spine, forearm, and humerus-varies between countries, where it was lowest in Tunisia (1.9%) and Ecuador (2.5%), and highest in Denmark (23%), Sweden (21%) and Norway (19%) (50). The probability was 23% higher in women than in men, but a correlation between the probabilities in the two demographic groups was observed within countries (50). Worth mentioning is that probability, unlike incidence rates, takes into account mortality, which represents an additional reason for the heterogeneity of results between countries. Generally speaking, it was found that the absolute incidence of hip and vertebral fractures was also higher among women (55, 56).

2.4 Determinants of Fragility Fractures

2.4.1 Fracture Risk Assessment

The mainstay of Fracture risk assessment, which aims to identify high-risk individuals, is to assess either the presence-or lack thereof-of clinical risk factors (CRFs) associated with the risk of fractures or skeletal mass measurements, mainly, via BMD evaluation (30).

Clinical risk factors. One of the most important CRFs, according to the result

of a meta-analysis performed on a dozen population-based prospective studies, is low Body Mass Index (BMI), where it was found that the risk for hip fractures associated with a BMI value of 20 kg/m^2, for instance, is twice that associated with a BMI value of 25 kg/m^2 (57). Additionally, low BMI constitutes a risk for all fractures independent of age and sex, yet still dependent on BMD. On the other hand, obesity was found to be associated with higher BMD in adults (58). Moreover, the increase in adipose tissue associated with the increase in BMI among postmenopausal women results in increased estrogen production and subsequent decreased bone loss, given that estrogen inhibits bone resorption (59).

The previous history of osteoporotic fractures is associated with an increased risk of subsequent fracture. For example, it was found in a Norwegian study from the NORwegian EPidemiologic Osteoporosis Studies (NOREPOS) collaboration that the age-standardized risk of a subsequent hip fracture between the years 1999 and 2008 was 2.5-fold (95% CI: (2.5-2.6)) in women and 4.6-fold (95% CI: (4.5-4.7)) in men (60). Each of the female gender, residing in institutions, osteoporosis, low vision, dementia, Parkinson's disease, and cardiac and respiratory diseases were statistically significantly associated with increased risk of subsequent fractures as reported in a meta-analysis of 22 studies that collectively evaluated many factors (61). Similarly, the obtained results from the US Medicare administrative data showed that the prevalence of a subsequent fracture in women who had a previous fracture was 10% during the first year, 18% during the second, and approximately the third of all women during the three-year period (62).

Abnormalities related to menstruation, such as premature menopause, whether it was natural or induced, late onset of menstruation, or primary and secondary cessation, are all associated with decreased BMD and fractures (30). Concerning

smoking, it was found that smoking is associated with a higher risk of hip fractures among women and that cessation for a period of ten years or longer reduces the risk (63). Smoking cigarettes among women is implicated by various pathways, such as reducing appetite and subsequently decreasing fat content, which increases estrogen metabolism at peripheral sites or accelerating menopause as a consequence of being thin due to smoking (30). The role of vitamin D deficiency related to osteoporotic fractures remains controversial; however, its effects on bones and muscles via direct and indirect pathways are potentially involved in bone loss acceleration that is caused by the aging process (64).

Some of the secondary causes of bone loss are type 2 diabetes and Cushing's disease and those that are less frequent, such as malabsorption, osteogenesis imperfecta, and chronic renal failure (30). Certain conditions have an association with fracture risk, which could be independent of BMD. For example, the use of corticosteroids is known to increase the risk of both osteoporosis and fractures, but a BMD-independent role has been described, while rheumatoid arthritis increases the risk of fractures without the influence of BMD or corticosteroids use (65). In addition to the risk related to the use of corticosteroids, the risk associated with certain drugs such as those prescribed for hypothyroidism and alcohol consumption is dose-dependent (30).

There are a plethora of conditions both medical and otherwise that can predispose to osteoporosis and/or fragility fractures, and some are summarized in Table 2, which is adapted with modification from the clinician's guide of Cosman and colleagues on the prevention and treatment of osteoporosis (9) that summarized the 2004 Report of the Surgeon General on osteoporosis and bone health (31). It is also of importance to assess an individual's risk of falls that predispose them to fractures, which include assessing whether they use medications that alter their alertness such as

Barbiturates and whether they have certain neurological conditions such as epilepsy (9). Additionally, the assessment of certain environmental factors, vision problems, and other conditions that predispose an individual to falls (66) is required. The fact that many disorders and conditions affect various aspects of individual health and lifestyle reflects the complexity of the pathogenesis of both osteoporosis and fragility fractures.

Table 2. Factors that Predispose to Osteoporosis and Fragility Fractures [a]

Factor Category	Examples
Lifestyle factors	Alcohol abuse Excessive thinness Excess vitamin A Frequent falling Immobilization Inadequate physical activity Low calcium intake Smoking (active or passive) Vitamin D insufficiency
Genetic factors	Cystic fibrosis Ehlers-Danlos Gaucher's disease Glycogen storage diseases Hemochromatosis Homocystinuria Hypophosphatasia Marfan syndrome Osteogenesis imperfect Parental history of hip fracture
Hypogonadal states	Androgen insensitivity Anorexia nervosa Athletic amenorrhea Hyperprolactinemia Panhypopituitarism Premature menopause (<40 years)

Factor Category	Examples
Endocrine disorders	Central obesity Cushing's syndrome Diabetes mellitus (types 1 and 2) Hyperparathyroidism Thyrotoxicosis
Gastrointestinal disorders	Celiac disease Gastric bypass Gastrointestinal surgery Inflammatory bowel disease Malabsorption
Blood disorders	Hemophilia Leukemia and lymphomas Multiple myeloma Sickle cell disease
Rheumatologic/autoimmune diseases	Rheumatoid arthritis Systemic lupus erythematosus
Neurological disorders	Epilepsy Multiple sclerosis Parkinson's disease
Other disorders	End-stage renal disease Hypercalciuria Post-transplant bone disease Depression
Medications	Lithium Cyclosporine A and tacrolimus Methotrexate parental nutrition Proton pump inhibitors Selective serotonin reuptake inhibitors Tamoxifen® (premenopausal use) T Thiazolidinediones Thyroid hormones Glucocorticoids (≥5 mg/day prednisone or equivalent for ≥3 months) Cancer chemotherapeutic drugs

[a] Adapted from Cosman *et al* (9) with modification

Bone mineral density assessment. The quantitative BMD assessment is currently the mainstay approach for osteoporosis diagnosis and fracture risk assessment, and it is mainly carried out using dual-energy X-ray absorptiometry (DXA)

(30). Despite its several limitations such as exposure to ionizing radiation, being an expensive and large device and the fact that BMD assessment, in general, does not provide information regarding the quality of bone, DXA remains the most important reliable available assessment technique (30).

In addition to diagnosis and fracture risk assessment, DXA BMD measurement of the hip and spine is useful as a tool to monitor patients. The assessment is done by calculating the areal BMD in its absolute form in scanned grams of mineral per square centimeter (g/cm^2) and normalizing the latter by comparing it to the BMD of a matched reference population (Z-score) in terms of age, sex and ethnicity or alternatively to a young-adult reference population of the same sex (T-score) (9). The scores are calculated by obtaining the difference between the individual's BMD and the mean BMD of the reference population, which is then divided by the reference population's standard deviation. The recommended reference range is from the NHANES III database for femoral neck measurements in women aged 20-29 years (17, 18).

It is a commonly accepted practice to screen for low BMD using DXA in women who are 65 years or older in the presence of risk factors-or lack thereof-and in younger women who have risk factors such as rheumatoid arthritis, glucocorticoid use, malabsorption syndromes, and increased function of the thyroid and parathyroid glands (67). However, depending on BMD alone in fracture risk assessment offers high specificity but low sensitivity, which indicates that the majority of fragility fractures will happen in women who do not fit the definition of osteoporosis that is based on a T-score $\leq$-2.5 (68). Accordingly, the updated guidelines of the UK (NOGG), which is accredited by the UK National Institute of Health and Care Excellence (NICE) and approved by the International Osteoporosis Foundation (IOF), do not encourage complete reliance on BMD testing for population screening (35).

Other Considerations. A recent meta-analysis found that increased parity number reaching five live births among postmenopausal women was associated with a reduced risk of osteoporotic fractures in general and with a linear decrease in the risk of hip fractures with a 26% (95% CI: (17–35%); I^2=19.5%), p=0.287) less risk seen in women who have at least one child compared to those who have no children (69).

In a systematic review of good quality cross-sectional studies, evidence was found to support the association positively linking education and BMD in women, whereas the financial and occupational association with BMD could not be established (70).

One should take into consideration the geographical aspect when assessing fracture risk; for example, and as stated earlier, the incidence of hip fracture varied tremendously in different regions of the world. In a comprehensive review that included 33 countries where the rates of hip fractures were standardized according to age and sex, Scandinavian countries ranked first while rates were lowest in Africa (71). The rest of Europe showed closely related rates, whereas Asia showed variabilities such as relatively high rates in Iran and low rates in China. The reviewers suggested that these variations can shed light on the cause of fractures and the means to prevent them. In addition to this, the regional variation in time trends of hip fracture age-adjusted incidence was observed and further investigated by Cooper and colleagues. They found that overall, the incidence rate increased up to the latter half of the twentieth century in the different regions of the western world. It then became stable according to studies that continued to monitor trends over the last decade of the previous millennium and the 1st decade in current one (72). Some reported a decreasing trend and others reported an opposite trend seen in Asia.

Ethnicity is an important factor as well, as noted from the lower osteoporosis

prevalence and the higher bone mineral content (BMC) observed in African Americans compared to Caucasians (71). Added to the racial differences in bone content are the anatomical differences such as the shorter hip axis in Asian and black females, rendering them at a relatively lower risk of hip fractures (73). Another example is the closely related hip fracture rates in Ontario with those in England, an observation that is likely explained by the fact that Ontario residents of the older age groups are mainly descendants from England (74). Thus, it seems reasonable to consider the ethnic heterogeneity-which in part reflects genetic variability-within any given study sample when investigating osteoporosis or osteoporotic fractures alike. Generally speaking, the differences in fracture rates between different regions of the world indicates the influence of a mixture of genetic and environmental factors, which are still not adequately understood (75).

2.4.2 Fracture Risk Assessment Tools

As stated earlier, it is not recommended to rely on BMD testing alone for population screening. Although the WHO definition has been used to determine the stage by which treatment should be initiated, and it could work on a population level, it was found that fractures do occur in a lot of individuals at zero value of T-score, which made it vital to develop tools that consider clinical risk factors in risk assessment.

The most famous tool is FRAX (www.shef.ac.uk/FRAX), which is basically an algorithm to calculate the probability of fracture based on certain CRFs, which are listed in Table 3, with or without consideration of BMD results from femur bone neck (10). The decision to include these CRFs was based on the review of several meta-analyses that independently examined the effect of each factor independently on fracture risk (10). Among these factors, some were internationally validated for their BMD-independent role and assessed by age, gender, and the duration of follow-up. These

include neck of femur BMD, low BMI, a previous fragility fracture, use of glucocorticoids, parental history of fracture, smoking, excessive intake of alcohol, and rheumatoid arthritis, whereas total hip BMD was considered useful but less validated (76).

The ten-year probability is calculated for hip fractures and other major osteoporotic fractures, and the FRAX models were available for 58 different countries by 2016, with calculations being made available through the website in many languages and via BMD machines, smartphones, or physical calculators (77). The probability of death is incorporated in the overall calculated probability (78). In addition to its country-specific modifications, the improvement in prediction, in the case of hip and spine discordance by using the difference between the two BMD readings and making due adjustments, is another example of enhancing this tool (79). Among its limitations are the lack of specification of the dose of corticosteroids used and the lack of certain risk parameters such as the risk of falls and lumbar spine BMD (29).

Regarding the use of the FRAX tool without BMD, it was found that predictions of the high probability of fractures tend to be linked to low BMD on the one hand, and that the initial BMD does not influence treatment efficacy on the other hand (78). This makes the use of this tool alone useful especially when there is access limitation to BMD testing (78).

Other Fracture tools include QFracture, which was developed using a Cox regression model on data from the UK general practice (11), which render its validity limited for the UK population, and the Garvan fracture prediction tool, which was derived from the Dubbo Osteoporosis Epidemiology Study (DOES) data (80). Worldwide, FRAX is more accepted as a prediction tool when compared to either QFracture or Garvan and has been both approved by NICE and the food and drug

administration and incorporated in DXA scanners (81).

Table 3. Clinical Risk Factors Included in the FRAX Tool (10)

Risk parameter
Current Age
Sex
Height
Weight
Previous fracture
Parental hip fracture
Current smoking
Alcohol consumption of three or more units a day
Chronic use of corticosteroids
Rheumatoid arthritis
Causes of secondary osteoporosis

2.5 Diabetes and Fragility Fractures

Diabetes Mellitus is a group of metabolic conditions in which insulin secretion, function, or both are impaired, leading to hyperglycemia (82). In type 1 diabetes, pancreatic cells are destroyed due to an autoimmune process, whereas in type 2 diabetes, the cells become resistant to insulin (83). Both types were found to be associated with an increased risk of fractures (84). However, type 2 diabetes accounts for 95% of the incidence of diabetes (85). In the elderly population, both type 2 diabetes and osteoporosis cause a significant health burden when considered separately.

The global prevalence of diabetes was estimated to be 85 million people in 2010, affecting predominantly people over 60 years in developed countries and people who are between 40 to 60 years in developing countries (86). This estimate was predicted to increase by over 50% by 2030 due to the growth of populations, the increase in the elderly population and the modern lifestyle. The logical extrapolation is that the co-occurrence of diabetes and osteoporosis will have an even greater impact on

both of disease burden and prevention and/or management approaches used.

In a recent meta-analysis (15) of observational-both cohort and cross-sectional-studies in postmenopausal women, it was found that the overall risk of vertebral fractures is the same in both diabetic and non-diabetic groups with an odds ratio of 1.13 (95% CI: (0.94–1.37)), where the result from the included studies was considered to be homogenous (I^2=13.7%), and free of publication bias. On the other hand, diabetes and hip fractures were found to be associated with an overall odds ratio of 1.30 (95% CI: (1.07-1.57)) from the 13 included studies. However, heterogeneity and publication bias were reported in this analysis. The odds ratio slightly increased, and heterogeneity was absent after performing a sensitivity analysis. Nonetheless, the authors discussed disease misclassification between type 2 and other types of diabetes as a limitation to these results and stated that although it seems good to add diabetes to fracture risk tools, it remains too soon.

Interestingly, a slightly earlier meta-analysis (14) of eight cohort studies-both prospective and retrospective-that investigated the association between diabetes and vertebral fractures in the two gender groups combined or separated revealed a statistically significant positive association with a pooled relative risk of 2.03 (95% CI: (1.60–2.59), p<0.0001). The difference between this result and that from the previously discussed meta-analysis on vertebral fractures could be explained by gender discrepancy, especially since the subgroup analysis in this analysis showed that relative risk was higher in males as compared to females with values of 2.70 (95% CI: (1.34–5.43), p=0.005) and 1.93 (95% CI: (1.18–3.13), p = 0.008), respectively. However, this difference could still be explained by the methodological aspects of the included studies in both meta-analyses.

In a very recent meta-analysis (87), the association between the risk of hip

fracture and diabetes was established again from 25 included cohort studies along with a marked heterogeneity. Other findings suggest that diabetes was associated with an increased risk of total, upper arm, and ankle fractures, but no association with the distal forearm and vertebral fractures was present. The variability in diabetes diagnosis, the different adjusted models in various studies, and heterogeneity that is not entirely explained are all limitations to these results, which reflect, in part, the innate methodological variability of the design of observational studies.

Many theories are currently present to explain the underlying mechanism by which type 2 diabetes influences bone health. One example is the accumulation of advanced glycated end products and possibly their receptors in the various tissues affected by diabetes, where the accumulation is hastened by hyperglycemia (88). The resultant cross-linking in the organic bone matrix may lead to weakened bones (15). Another mechanism is the reduced bone mineral content found in type 2 diabetic patients, specifically those who have poor control, who also lose more calcium in urine resulting in negative feedback, which is sustained by hyperparathyroidism (89). Many possible explanations for the increased bone pathologies in diabetic patients were put forward. Examples include the increased levels of Plasminogen activator inhibitor-1-a component of the fibrinolytic system that is involved in bone repair-which is induced by diabetes (90), the association between incident diabetes and low supplementary vitamin D intake (91), and the heightened risk of falls in diabetic patients (92) due to neurological and vision impairment, as well as, recurrent fainting during hypoglycemic attacks.

The relationship between diabetes and fracture risk cannot be simply delineated, and there are many factors that predict fracture risk among diabetic patients; for example, obesity, which usually accompanies type 2 diabetes, is associated with

decreased fracture risk, as stated earlier. Other determinants include aging, BMI greater than 30 kg/m^2, duration of diabetes above ten years, decreased physical activity, and the use of systemic corticosteroids (84). Another observation worthy of attention is that the different medications that are used to treat diabetes have different effects on fracture risk (93). For example, Thiazolidinedione was associated with an increased risk of fractures among women regardless of age and treatment duration (94), whereas Metformin showed a positive effect on any fracture risk (95). Hence, when studying the relationship between diabetes and fracture risk, it is imperative to consider many factors, including particular characteristics of the individual and their medication profiles, among others.

2.6 Osteoporosis and Fragility Fractures in Qatar and the Eastern Mediterranean Region

Many countries in the EMR performed studies to investigate BMD, and population-specific reference ranges for BMD were calculated, such as in Tunisia (19), Lebanon (20), Saudi Arabia (21), Kuwait (22), and others. Whereas in Qatar, results showed the expected decline with age, in BMD at the spinal site and at the femoral site, after reaching the maximum values at 30 to 39 years, and at 40–49 years, respectively. The spine BMD values of Qatari women were lower than Caucasian and Kuwaiti women but higher than Lebanese women and similar to their Saudi counterparts. The total femur BMD values were higher in Qatari females than Caucasians, Kuwaitis, Lebanese, and Saudis in the age group of 40–59, but lower in the age group of 60–69 (23).

In a meta-analysis of the prevalence of osteoporosis obtained from 36 studies in eight EMR countries for the duration between 2003 and 2017, which were population-based and were deemed representative for the general population by the authors, the overall pooled estimate was 24.4% (95% CI: (20.4-28.4)), and the range of prevalence

was between 15.1% in Kuwait and 32.7% in Saudi Arabia. There was a marked increase (12.9%) in the pooled estimate from the period 2000-2006 to the period 2007-2015, which was explained by the authors by the increase in life expectancy in the EMR region and the increase in the ability of more modern devices to capture osteoporosis diagnosis. However, these results are limited by the under-representation of other EMR countries and the marked heterogeneity observed in the pooled estimate. An explanation offered by the authors for this heterogeneity is the variation in sample size, study dates, the diagnostic test used, gender distribution, and ethnicity. It is worth noting that the same heterogeneity was observed on a global level, which was great enough to not be caused by methodological variability alone (96).

In an audit of the middle east and Africa on the epidemiology, costs, and burden of osteoporosis in 2011, focusing on 17 countries in the region (97), data on the incidence of hip fractures were reported in 9 studies. The age-standardized rates were close to those of Southern Europe except for Turkey. Data on vertebral fractures was minimal and diagnostic accessibility was observed to be limited. The audit called for action from the involved sectors to increase awareness and collect better quality evidence on the burden, mainly since osteoporosis will comprise an even more significant problem with the anticipated increase in the EMR populations' age.

The prevalence rate in Qatar for both osteoporosis and LBM was 4% at the femur and 16% at the spine, derived from a cross-sectional study conducted in 9 geographically representative primary health care centers (24), from July 2011 till May 2012. The study included both Qatari and Arab women who are between 40 and 60 years. Women with higher BMI and who had menstruation within the past year had greater BMD at both the femur and the spine. There was no difference observed in mean BMD between Qatari and non-Qatari women, except for the femur in the age

group from 55 to 60, which was lower in non-Qatari women.

Among the risk factors for osteoporosis in the Middle East are; being postmenopausal for more than two years, the previous history of corticosteroid use, family history of osteoporosis and hip fracture, as identified from a Lebanese public survey of women who are postmenopausal (98). In a cross-sectional study of healthy Qatari women who are between 20 and 70 years of age, which was conducted in 2005-2006 to assess the impact of lifestyle factors on BMD, dairy consumption and performing household work were associated with higher BMD, while BMI and education were strong positive predictors of BMD (99). In the same population, obesity was associated with higher BMD at the femur and at the spinal sites (100).

In the EMR, Vitamin D deficiency is common even in sunny regions (98). For example, vitamin D was severely, moderately, and mildly deficient in 9.5%, 57.6%, and 14.2%, respectively, in a random sample of 1210 participants in Iran, who are 20–64 years old (101). In this study, the levels of vitamin D were not found to be statistically significantly associated with the duration of sun exposure, BMI, or clothing style. Among Qatari people, the weighted-average prevalence of low vitamin D status -defined as serum level <75 nmol/L-was 90.4%, as reported in a systematic review of the literature (102).

Regarding the risk of fractures due to osteoporosis, the incidence of proximal femur fractures in Riyadh, Saudi Arabia, per 100,000, from 1990 to 1991 was 71 and 100 in male and female patients, respectively (103). The relatively low rate could be a reflection of the younger population at the time. In Kuwait, however, the rate between 2009 and 2012 was close to that of the US and Western Europe (104). In a systematic review and meta-analysis on the incidence of hip fractures in the EMR, that covered published results from inception till September 2018, only six countries from the region

were identified, and the rate per 100,000 people per year was 107.4 (95% CI: (83-131.8)). Lebanon and Kuwait had the highest and the lowest crude incidence rates, respectively (105). The impact of BMD on the burden of fractures in the Middle East is understudied, and few countries have established fracture registries such as Iran, Kuwait, and Lebanon.

As for Diabetes association with osteoporosis, one Turkish study of postmenopausal women found no statistically significant association, but there were some limitations to this study, such as the small sample size (106). On the other hand, a significant difference was found between diabetic and non-diabetic women in the mean spine BMD in a group of premenopausal Arab women who are 26 to 50 years old, where BMD was higher in the diabetic group (107). Among type 2 diabetic female patients in Saudi Arabia, 29.4% had osteoporosis, and 40% had LBM, as reported by a cross-sectional study conducted during 2015. This study identified age, oral hypoglycemic drugs, and vitamin D as risk factors for lower BMD and BMI as a protective factor among the female diabetic population (108). In Qatar, 17% of the adult population is living with diabetes, which is around twice the prevalence globally (25). However, there is a lack of evidence concerning the association between diabetes and fracture risk in Qatar and in the EMR region, in general.

2.7 Selection of the Reference Population in BMD T-score Derivation and its Influence on Fragility Fracture Risk Estimates

Several observations indicate that the risk of fragility fractures is dependent on factors that are country-specific or ethnicity-specific, some of which were alluded to earlier in this chapter, such as the geographical variation in the incidence of fracture and the differential role played by ethnicity in determining fracture risk. In addition to the heterogeneity in the BMD gradient of risk for osteoporotic fractures obtained by the study of different cohorts around the globe (5).

Although the standard recommended reference range to use internationally for deriving T-scores is from the NHANES III database for femoral neck measurements in women aged 20-29 years, marking the peak bone mass in Caucasian women, the reference ranges for BMD in women in the EMR region were different from those reported for Caucasian women as mentioned earlier. In fact, they were varying among different EMR countries. Additionally, it has been suggested that the differences in the SD of populations using different sites and different equipment may explain the inconsistencies related to the same T-score in terms of osteoporosis prevalence and fracture risk (17).

In Qatar, the peak bone mass is achieved at the total hip site between 40 and 49 years, with a value of 1.041 g/cm^2 and an SD of 0.129 g/cm^2 (23), which is different from that of the NHANES young female normal BMD range (0.942±0.122 g/cm^2 (33)). Accordingly, using different BMD databases for the reference ranges would yield different T-scores for the same patient and would influence the diagnosis of osteoporosis, and plausibly, the management of this patient.

Chapter 3: Methodology

3.1 Research Questions

1. Primary Questions:

a) How many new fragility fracture cases occur, on average, per month in a population of 1000 patients aged fifty and older who had their BMD tested?

b) What is the effect of having lower BMD levels relative to the young normal BMD on the risk of fragility fractures in individuals aged fifty and older living in Qatar?

c) Is there an association between diabetes mellitus and incident fragility fractures in individuals aged fifty and older living in Qatar?

2. Secondary Question:

Does the selection of the reference population from the NHANES database, on the one hand, and from the Qatari database, on the other hand, in the derivation of BMD T-scores, in the population of Qatari women aged fifty and older, influence their obtained risk estimates for fragility fractures?

3.2 Research Objectives

1. Primary Objectives:

a) To estimate the incidence rate of fragility fracture cases per 1000 person-months of follow-up of patients aged fifty and older who had their BMD tested.

b) To estimate the effect of having lower BMD levels relative to the young normal BMD, utilizing BMD T-scores, on the risk of fragility fractures in individuals aged fifty and older living in Qatar, taking into account the influence of other internationally validated risk factors of fragility fractures.

c) To assess the association between diabetes mellitus and incident fragility fractures in individuals aged fifty and older living in Qatar, taking into account the influence of other internationally validated risk factors of fragility fractures.

2. Secondary Objective:

To compare risk estimates of incident fragility fractures, obtained upon the use of the referent young normal BMD from the NHANES database, on the one hand, and the Qatari database, on the other hand, in the derivation of BMD T-scores, in the subpopulation of Qatari female patients aged fifty and older.

3.3 Study Design

This is a retrospective (record-based), hospital-based open cohort study, with an internal comparison group(s).

3.4 Study Participants

All patients aged 50 and older, who underwent DXA scan to assess their BMD, at HMC, from May 1st, 2016 until June 30th, 2019, and have their total hip absolute BMD results reported and available to view, represented the study population.

3.5 Source of Data

Data were accessed from the Cerner's Electronic Health Record (HER) currently implemented at HMC. DXA scan images for patients who underwent the scan within the aforementioned time period were retrieved via remote access to the digital radiology archive, using the search terms "BMD" and/or "DXA." Duplicate entries for patients and for examination dates-identified using patients' health card (HC) numbers-were excluded. The results were restricted to include BMD-specific examinations only. For each patient, the earliest registered report, from May 1st, 2016, was selected. Reports that were accessible and could be viewed with good resolution were chosen for patients' BMD measurement entries. Data on age, gender, nationality, height, and weight were retrieved from DXA scan reports. Clinical data were collected for each patient by accessing their digital clinical records.

3.6 Study Procedures and Data Collection

Each patient had an entry date to the cohort (time zero/baseline) that

corresponded to the date of his/her DXA scan. The follow-up time for each patient was time from baseline until one of the following endpoints occurred: sustaining a new fragility fracture, death, or loss to follow-up, whichever came first. A patient was considered lost to follow-up at the time of their last encounter registered in their records before the documentation of the occurrence of incident fragility fractures-or lack thereof-since baseline, which took place on April 1st, 2020. Extraction of data from DXA scan reports was done by an orthopedic surgery specialist at HMC orthopedic department and two nurses who were trained by the orthopedic surgeon, following a specific presentation on what data items to be collected from the report. The orthopedic surgery specialist performed ascertainment of incident fractures, disease diagnoses, and the use of medications, and the relevant data were collected, according to a prespecified definition of each clinical variable.

3.7 Time-to-Event Data and its Specific Methodological Considerations

Given that the outcome of interest was not only whether a fragility fracture occurred subsequent to the BMD test, but also when it did occur, and that incident fractures were not necessarily expected to be observed for all patients within the study period, the use of time to event (survival) data, was deemed appropriate. A number of methodological considerations are clarified as follows:

1- Time origin: The point of time at which follow-up started for each participant, which corresponded to the date of their BMD DXA scan (baseline time). It also denotes the time at which patients became at risk of sustaining a fragility fracture.

2- Time scale: Follow-up time (in months), starting from time origin for each patient and ending when the patient was no longer followed.

3- The end date: Either the date of the documented fracture or the date of the last encounter, before the study has ended, whichever came first. The death status

date of patients who died in the state of Qatar was documented at HMC, and it also corresponded to the last encounter date.

4- Patient's status/events: Refers to the occurrence of a fragility fracture or lack thereof.

5- Censoring status: It refers to patients who did not sustain a fragility fracture before their last encounter date, and those who died before the evaluation of fracture occurrence could be made. Those patients were considered to have censored interval times. Both scenarios represent type 1 censoring, where the observation of events is restricted to those that occur before a prespecified time (109).

6- Reasons for loss to follow-up (loss of records after last encounters), apart from death, were difficult to ascertain, given the nature of the study being retrospective and the fact that no contact with patients was made for the entire study period. Since censorship occurred toward the end of the study period, the patients who are lost to follow-up were regarded as right-censored.

3.8 Measures

3.8.1 Main Outcome Variable

Time-to-incident fragility fracture (in months): calculated for each patient by subtracting the date of their first DXA scan (time origin) from the date of their end of follow-up time. A censoring indicator (binary) variable was utilized to denote whether each patient was censored-according to the aforementioned definition-or if they sustained a fragility fracture.

Ascertainment of fractures: This was performed by an orthopedic surgery specialist at HMC. Fractures were ascertained by the occurrence of the **first** fragility fracture from baseline, regardless of its anatomical site, which included, but was not limited to, fractures at the hip, the spine, or wrist bones (the classical sites of osteoporotic

fractures). Fractures due to high impact trauma, such as road traffic accidents or falls from heights and pathological fractures, were excluded. Fractures documented in reviewed patient's clinical visits notes that were confirmed by radiographs or fractures documented in radiographic reports were included. Specific dates and the anatomical sites of the fractures were also documented. Given that a lot of vertebral fractures have undetermined onset and they pass unnoticed (110), only symptomatic vertebral fractures confirmed by radiographs at the time of onset of new symptoms of pain or deformity were considered.

3.8.2 Main Exposure Variables

For the primary objective**:** *Estimation of the effect of having lower BMD levels relative to the young normal BMD, utilizing BMD T-scores, on the risk of fragility fractures in the population of individuals aged fifty and older living in Qatar, taking into account the influence of other internationally validated risk factors of fragility fractures*, and for the secondary objective: *To compare risk estimates of incident fragility fractures, obtained upon the use of the referent young normal BMD from the NHANES database on the one hand and the Qatari database, on the other hand, in the derivation of BMD T-scores, in the population of Qatari women aged fifty and older:*

The main exposure variable is total hip BMD. The total hip BMD-related variables include:

(1) Areal total hip BMD result: This constitutes the absolute term, in grams of mineral per square centimeter scanned (g/cm^2), which was extracted from each patient's DXA scan report. The lowest reading was selected in cases when the results from both hips were provided.

(2) Total hip BMD T-score: This quantifies the absolute BMD in relation to the norm, which is calculated as: (Patient's areal BMD- mean BMD of the reference population

(young adult))/Standard deviation (SD) of the reference population.

According to the WHO, the reference standard to diagnose osteoporosis is a T-score value equals to or below -2.5 at the neck of the femur. However, the diagnosis could still be made using the same cutoff by a number of sites, which include, among others, total hip, in postmenopausal women, and in men who are 50 years old and above (76, 111). In this study, the neck of femur areal BMD results were not reported for all patients; hence, total hip BMD was chosen instead. Moreover, for each patient, DXA scan reports included total hip T-score values; however, different reference populations were used at different times owing to the different manufacturers of bone densitometers (Hologic® and GE Healthcare). Accordingly, to standardize our measurements, we calculated T-scores based on a recognized international standard. The WHO recommended choice of the young normal reference database utilized in T-scores calculation for men and women of all ethnic backgrounds is that of a Caucasian female. The recommended reference standard for total hip T-score calculations is from the NHANES III data (76, 111), which corresponds to the young (aged 20-29 years) Caucasian female normal mean hip BMD of 0.942±0.122 g/cm^2 (33). The rationale for using a female reference, regardless of gender, is that men and women who have the same age and BMD have the same fracture risk (8). Accordingly, the total hip BMD T-score for each patient in the study population was calculated as follows:

NHANES-based total hip T-score = (patient's areal BMD-0.942)/0.122

(3) BMD status: A categorical variable classifying each patient into one of three exposure categories, namely; osteoporosis, LBM, or normal BMD, based on their BMD results and according to the WHO criteria described earlier in chapter 2 (Table 1). A dichotomized form of the variable was used when the comparison was intended to be between patients classified as having osteoporosis and the rest of the cohort.

For the secondary objective, an additional total hip BMD T-score variable was generated for each patient in the subpopulation of Qatari women, using mean peak bone mass (PBM) of Qatari women as the reference population, which was extracted from a study of Qatari women BMD normative data (23), in which BMD peaked at the age group of 40 to 49 years with an areal total hip BMD value= 1.041 ± 0.129. T-scores were calculated as follows:

Qatari-based total hip T-score for Qatari women= (patient's areal BMD-1.041)/0.129

For the primary objective: *To assess the association between diabetes mellitus and incident fragility fractures in the population of individuals aged fifty and older living in Qatar, taking into account the influence of other internationally validated risk factors of fragility fractures:*

The main exposure variable is diabetes status: A dichotomized variable denoting whether each patient was/was not diagnosed with diabetes mellitus before baseline.

Ascertainment of diabetes mellitus diagnosis: A patient was considered to have diabetes before baseline if their available records showed evidence to satisfy either of the two following conditions:

- A documented diagnosis of diabetes mellitus.
- Documented use of diabetes treatment (either insulin or oral hypoglycemic drugs) combined with a minimum of two elevated results of either random blood sugar (a level of 11.1 millimoles per liter (mmol/L) or higher) or glycated hemoglobin (HbA1c) (6.5 percent or above).

3.8.3 Covariates and Other Study Variables

Out of the several internationally validated risk factors for fragility fractures listed earlier in chapter 2, which are also incorporated in the FRAX fracture risk assessment tool, we considered the following covariates: age, gender, BMI, use of

corticosteroids, history of previous fractures, and the presence of rheumatoid arthritis. Data on height and weight were obtained as well. The remaining validated risk factors for fragility fractures, namely, smoking, alcohol use, and family history of fractures, were difficult to obtain due to lack of information or inconsistency of reporting. Data on other important clinical conditions and medications which are associated with an increased risk for fragility fractures were also obtained. Lack of evidence of the presence of a given factor in clinical notes, clinical images, lab results, or prescription profiles was considered sufficient to assume the absence of this factor for a given patient. The confirmed diagnosis before the scan date was considered sufficient to assume the presence of a select of diseases. The list and the description of the obtained variables of the internationally validated risk factors, other factors and medications that are associated with an increased risk of fragility fractures, in addition to administrative data are provided in Table 4.

Table 4. Study Variables and their Discerption

Variable	Description
Nationality	Patient's nationality as registered in their electronic record and DXA scan report.
Age	Age of the patient at DXA scan in years, obtained from DXA scan report.
Age group (derived)	10-year age group
Gender	Patient's gender as registered in their electronic record and DXA scan report.
Last Encounter	The last "check-in" reported to the patient; set as the follow-up upper limit
BMD date	The date of the scan shown on DXA scan report. It signifies the start of the follow-up period for each patient.
Follow-up time	Time from BMD scan date till the date of either: last encounter (including death) or the first fracture after the scan (event).
Death status	Confirmed diagnosis from the clinical notes. Last encounter date was considered date of death.
Weight	Patient’s weight at DXA scan date in kilograms (kgs), obtained from DXA scan report.

Variable	Description
Height	Patient's height at DXA scan date in centimeters (cms), obtained from DXA scan report.
BMI (derived)	Body mass index calculated as weight/height (in meters)^2, derived from patient's weight and height reported on their DXA scan report.
BMI categories (derived)	Categories based on the BMI variable. Underweight: BMI<18.5, normal weight: BMI=18.5-24.9, overweight: BMI=25-29.9, obese: BMI≥30.
Previous history of fragility fracture (binary)	Fracture due to low impact trauma reported before DXA scan date in the available records, obtained from patients' clinical notes and radiographs.
Coronary artery diseases (CADs) (binary)	Documented (diagnosis) or Coronary artery bypass graft (CABG) (procedure) or Coronary artery stenting (procedure) before baseline, obtained from clinical notes.
Chronic kidney disease (CKD)(binary)	Identified by any/all of the following being reported in patient's notes/records before baseline: chronic kidney disease (diagnosis), nephrology clinic (encounter), Fahad bin Jassim center (encounter), dialysis (procedure), renal transplant (procedure).
Cancer (binary)	Diagnosis of any cancer before baseline.
Breast cancer	Diagnosis of breast cancer before baseline.
Prostate cancer	Diagnosis of prostate cancer before baseline.
Blood cancer	Diagnosis of blood cancer before baseline. This includes leukemia, lymphoma and multiple myeloma.
Rheumatological and autoimmune conditions (binary)	Diagnosis of rheumatological or autoimmune diseases before baseline. These include Ankylosing spondylitis; polymyalgia rheumatica; systemic lupus erythematosus, polymyositis; gout; Sjogren's syndrome; Behcet's disease; sicca syndrome/lupus overlap disease; alopecia areata; psoriasis; anti-phospholipid syndrome; atopic dermatitis, myasthenia gravis.
Corticosteroids use (binary)	The use of oral or injectable forms; for more than a month, taken within a year from the test (+/- 6 months).
Anti-diabetic medication use (binary)	Oral hypoglycemics and/or insulin, taken within a year from the scan date (+/- 6 months).
Thyroxin use (binary)	Thyroxin taken within a year from the scan date (+/- 6 months).
Chemotherapy (binary)	Any documented history of chemotherapy before baseline; regardless of the duration
Radiotherapy (binary)	Any documented history of radiation therapy before baseline, regardless of the duration.

3.9 Data Analysis

Data entry was performed on an excel spreadsheet, and data were checked for duplicate entries, erroneous and missing values, suitable format for each variable and ranges for each variable. Data was cleaned as appropriate, and missing values were labeled clearly. The spreadsheet was imported into Stata 16 software, STATA®, where all the remaining steps of analysis were performed. Variables were coded and labeled in a suitable manner, and categorical variables derived from continuous variables, such as those for BMI and BMD, were created based on well-established international cut-off values. Data was examined again, in Stata, for the appropriateness of the ranges and levels of continuous and categorical variables, respectively, the presence of outliers using box-plots, the distribution of continuous variables and for the missing values. The latter were coded properly to distinguish them from non-missing values.

Following these steps of data management, descriptive analysis was performed for the overall cohort in terms of patients' characteristics. These included: follow-up time-summarized by median and interquartile range (IQR)-, demographic, anthropometric, and clinical characteristics, in addition to BMD-related measurements and medication use. Mean and SD or frequency and percentage were used to describe continuous and categorical variables, respectively. The same analysis was performed to describe the subpopulation of Qatari women. Additionally, descriptive statistics of the categories of the two exposure variables, namely, BMD status and diabetes status, were computed. Descriptive statistics related to incident fragility fracture cases, in addition to the distribution of fracture cases by body region, were also obtained.

In Stata data was declared as survival data, using the time-to-incident fragility fracture and the censoring indicator variables. The type of data declared was single record and single event with right censoring. Fragility fracture incidence rate and age-

specific and gender-specific rates were estimated for the overall cohort and presented per 1000 person-months. The incidence rate was calculated as the number of patients with incident fragility fracture during follow-up time/time each person was observed totaled for all patients (in person-month). In general, with regards to the remaining objectives, survival analysis techniques were applied whenever the estimation of fracture-free survival was required. More specifically, the Kaplan-Meier (KM) method was used to estimate and visualize the fracture-free survival probabilities and their 95% confidence intervals. The median (50^{th} percentile) and percentiles of fracture-free survival time were analyzed.

The log-rank test was performed to compare the fracture-free survival distributions among groups of the exposure or groups of the aforementioned covariates. The stratified log-rank test was used to compare survival distributions among the exposure variable's levels within the strata of the covariates as a way to assess the confounding potential of these covariates.

Cox Proportional Hazards (PH) models were fitted to investigate the association between each of the main exposures and fracture-free survival time, controlling for the potentially confounding covariates. The covariates considered for the log-rank test and the Cox PH models are the internationally validated risk factors for fragility fractures. Cox PH model assumptions, namely, proportional hazards and linearity of the continuous variables in the model, were evaluated for the multivariable-adjusted models containing the exposure variables and the aforementioned covariates. The diagnostics of the multivariable Cox models, including assessment of outliers and influential observations, in addition to the overall goodness of fit were performed. The continuous total hip BMD T-score variable was utilized in Cox models evaluating BMD as the main exposure or as a covariate, since risk estimates of fragility fractures based

on BMD, should be expressed in a standardized manner, such as a gradient of risk (6). Accordingly, risk estimates obtained from the Cox models are expressed as hazard ratios (HR) per SD reduction in total hip BMD from the young normal. A brief description of key analytical methods performed is provided in section 3.9.

For the secondary objective, analysis of the receiver operating characteristic (ROC) curve was used to compare the performance of both the NHANES and the Qatari databases in terms of detection of incident fragility fractures. A p-value of$\leq$0.05 was utilized to ascertain statistical significance in hypothesis tests throughout the analysis.

The main analyses performed to achieve each of the following objectives are described as follows:

1. *To estimate the effect of having lower BMD levels relative to the young normal BMD, utilizing BMD T-scores, on the risk of fragility fractures in individuals aged fifty and older living in Qatar, taking into account the influence of other internationally validated risk factors of fragility fractures:*

- Fragility fracture incidence rates were compared among the categories of the BMD status variable, namely; osteoporosis, LBM and normal BMD**.**
- Fragility fracture incidence rates were compared among the two groups of the dichotomized BMD status variable. Incidence rate ratio (IRR) and incidence rate difference (IRD), were estimated as well.
- KM estimated fracture-free survival probabilities and KM curves, were compared between the three groups of BMD status variable.
- The difference in fracture-free survival function between the three groups of BMD status variable was tested for statistical significance, using the unstratified and stratified log-rank tests.

- HRs per SD reduction in total hip BMD were obtained, using unadjusted and multivariable-adjusted Cox PH regression analyses. Interaction between BMD T-score and the covariates and the theory-driven interactions between BMD T-score and age, between age and previous fracture and between BMI and gender were tested.
- Adjusted survival curves based on the multivariable-adjusted model were obtained for the sake of comparing different covariate patterns.

2. *To assess the association between diabetes mellitus and incident fragility fractures in individuals aged fifty and older living in Qatar, taking into account the influence of other internationally validated risk factors of fragility fractures:*

- Fragility fracture incidence rates were compared among the two categories of the diabetes status variable, namely, diabetic and non-diabetic. IRR and IRD were estimated as well.
- KM estimated fracture-free survival probabilities and KM curves were compared between the two groups of the diabetes status variable.
- The difference in fracture-free survival function between the two groups of the diabetes status variable was tested for statistical significance, using the unstratified and stratified log-rank tests.
- HRs for being diabetic compared to not being diabetic were obtained using unadjusted and multivariable-adjusted Cox PH regression analyses.
- Adjusted survival curves based on the multivariable-adjusted model were obtained for the sake of comparing different covariate patterns.

3. *To compare risk estimates of incident fragility fractures, obtained upon the use of the referent young normal BMD from the NHANES database, on the one hand, and the Qatari database, on the other hand, in the derivation of BMD T-*

scores, in the subpopulation of Qatari female patients aged fifty and older:

- The proportions of patients with osteoporosis and LBM obtained using NHANES, or Qatari databases were compared.
- Fragility fracture incidence rates were compared among categories of the BMD status variable, namely; osteoporosis, LBM, and normal BMD, when the groups were classified using NHANES-based total hip T-score and when they were classified using Qatari-based total hip T-score**.**
- Fragility fracture incidence rates were compared among the two groups of the dichotomized BMD status variable, which was categorized based on the calculated T-scores, using either the NHANES database or the Qatari database. IRR, IRD, osteoporosis attributable fraction (AF) and osteoporosis population attributable fraction (PAF), upon the use of the NHANES or the Qatari databases, were estimated and compared.
- Analysis of receiver operating characteristic (ROC) curve, for detecting patients with incident fragility fractures using a T-score cutoff value≤-2.5, was performed to compare sensitivity and specificity values obtained upon the use of the two databases.
- KM estimated fracture-free survival probabilities and KM curves were compared between the categories of the dichotomized BMD status variable obtained according to the database. The four KM curves-one pair for each database-were compared.
- The difference in fracture-free survival function between the three groups of the BMD status variable was tested for statistical significance, using the unstratified and stratified log-rank when each of the databases was used.

- HRs per SD reduction in total hip BMD, obtained using unadjusted and multivariable-adjusted Cox PH regression analyses, were compared for when the T-score variable was calculated based on either database.

3.10 Description of Key Analytical Methods

Analysis of receiver operating characteristic (ROC) curve. When the binary outcome of interest depends on time, such as that of time to event (survival) data, one should consider a ROC curve analysis that allows the outcome to vary, when the predictive ability of a continuous biomarker-T-score variable in this study is to be evaluated. For this reason, a choice was made to use the *stroccurve* package developed by Cattaneo , Malighetti and Spinelli (112), which allows the estimation of time-dependent ROC curves, taking into account that events occur at different time points and that observations could possibly be censored.

Survival analysis. This analysis consists of the group of statistical methods utilized when the outcome is time until a given event occurs. Accordingly, it focuses on event rates rather than proportions, which increases statistical power, allows the analysis of unequal observation times, and allows covariates to vary over time (113).

As Sainani described (112), the focus of survival analysis is the "survival function," denoted as S(t), which is the probability that the event of interest did not occur until a specific time point (t). In the survival function (Equation 1), the probability is 1 (100% survival probability), when (t)=0, and the median survival time is where 50% probability of survival is reached.

$$S(t) = P(T > t) = 1 - F(t) \qquad \textit{equation 1}$$

T: Time-to-event random variable

t: A specific point in time

P (T > t): Probability of the event not occurring until time (t)

F (t): Cumulative distribution function

The incidence rate for the entire follow-up period can be calculated by dividing the number of events that occurred during this period by the total number of observations. When the incidence rate at a specific point in the follow-up time is of interest, the instantaneous rate (the hazard) at time (t) is calculated. The hazard function h(t) is used to calculate the hazard at any time point, and it describes how fast S(t) declines with time (114).

Kaplan-Meier (KM) product limit approach. This method is used to estimate the survival distribution S(t), which entails the formation of a series of time intervals, where one death per interval occurs, and the beginning of each interval is marked by that death (115). The estimate obtained is the product of a series of estimated conditional probabilities S(t) (survival probabilities conditional on surviving past a given time) (115). This method is of value when the comparison between groups in terms of survival probabilities at a given time is intended, where they could be estimated separately, using the KM estimator, and then compared. This method is non-parametric.

The log-rank and the stratified log-rank tests. The log-rank test, the most popular method to compare survival between groups for the entire follow-up time, tests the null hypothesis that the populations being compared are equal in their probability of a given event at any time point. For each event time point, the observed number of events within each group and the expected number-under the null hypothesis-are calculated (116). The log-rank test uses a non-parametric method.

The stratified log-rank test uses the same statistical method as the log-rank test. However, it considers the difference in the prognostic (potentially confounding) factors

between two or more groups when data is stratified according to the levels of the prognostic factors.

Cox proportional hazards (PH) model. The Cox PH model (117), a semi-parametric method, is the widely used multivariable regression analysis technique for survival data in medical research. It evaluates the relationship between the incidence of the event of interest, represented by the hazard function h(t), and a group of covariates. Mathematically, the Cox model is written as shown in equation 2, where h(t) depends on the group of p covariates (x_1, x_2,…., x_p), and (b_1, b_2,…., b_p), represent the respective coefficients. The magnitude of the coefficient represents the effect a covariate has on h(t). The baseline hazard (h0) represents the hazard when all x_i are equal to zero, and it may be estimated after fitting the model without any prior assumptions for its distribution. The exponent of a given coefficient provides the hazard ratio (HR) for the corresponding variable (118).

$$h(t)= h0(t)\times\exp (b_1x_1+b_2x_2+\ldots..b_px_p) \qquad \textit{equation 2}$$

The multiplicative action of covariates on the hazard provides an essential assumption for the Cox model (the proportional hazards assumption): the hazard in one group is a constant multiple of that of the other group(s). This also indirectly entails that the survival curves for the groups being compared do not cross (118).

The KM estimator, the log-rank test, and the Cox model, are considered to be among the best approaches to handle censored data, which are all based on the likelihood function estimation (119).

Cox PH model diagnostics. These include assessment of the proportional hazards assumption, non-linearity test for continuous variables, outliers, influential observations and the overall goodness of fit of the model, and they are described as

follows:

- **The proportional hazards assumption assessment:** A number of approaches were used to assess the proportional hazards assumption:
    - **Incorporation of a time-dependent covariate.** This was done by introducing a time-varying covariate by creating an interaction term between time (or a function of time) and the time-static variable. The Wald or the likelihood ratio test statistics were used to compare the model that assumes no violation and the one with the incorporated time-dependent covariate (120).
    - **The log-log (ln-(ln)) of S(t) visual approach:** Given that S(t) is the exponential form of the hazard ratio, and the hazard function is the exponential form of the covariate, taking the logarithm of the survival function twice, transform it into a linear functional form. The transformed survival functions become parallel during the observation period, and accordingly, if the curves for the groups being compared were parallel, then this indicates that the HR does not change during this period (120).
    - **The goodness of fit (GOF) approach:** This approach compares survival function values of what is observed in reality with those estimated from the data, and the test provides a p-value, making this approach less subjective than a visual assessment. The test utilizes Shoenfeld residuals, which represent the difference between covariates observed in reality and those estimated by a Cox PH model; accordingly, the calculation of these residuals incorporates all the covariates of the

model. Violation of the proportionality assumption is suspected when the residuals show a relationship with time (120).

- **Non-linearity test for the continuous covariates in the Cox PH model:** To evaluate the assumption of the linear form of a given continuous covariate which is introduced in the Cox PH model, the martingale residuals were plotted on the Y-axis against the covariate in the X-axis, the plot acquired should be horizontal with no angling for the assumption to be upheld (121).

- **Outliers and influential observations:** The deviance residuals of the Cox PH model, which is a transformation of the Martingale residuals, is plotted against the linear predictor, $\beta^{\wedge} X_i$, where the residuals are normally distributed with a censoring rate less than 20%, and not normally distributed but symmetrical with a censoring rate more than 40%. Outliers were identified by their deviance residuals' absolute values that were too large (122). Observations may be evaluated for their influence on the regression coefficients or for their overall influence (122). Given that our sample size was large, and several covariates were considered, the overall influence evaluation was chosen for assessment. This was done using the likelihood displacement approach, where the likelihood displacement values, representing the magnitude of change in the likelihood of the model if a given observation were to be omitted (122), were obtained.

- **The overall goodness of fit of the Cox PH model:** To assess if the Cox PH model fits the data well, Cox-Snell residuals were examined to verify if they exhibit a standard censored exponential distribution with a hazard ratio=1. This was done by estimating the cumulative hazard function, based on the KM or the Neslon-Aalen estimators, utilizing Cox Snell residuals as the time variable, together with the data censoring indicator variable. If the data fitted the model,

the plot of the cumulative hazard against Cox-Snell residuals should follow a straight line with a slope of 1(123).

3.11 Ethical Considerations

As all data were extracted from HER, individual consents were not required from the study participants. Ethical approvals for the study protocol, were obtained from Qatar University Institutional Review Board (QU-IRB 1373-E/20) and HMC Medical Research Center (MRC-01-19-299).

3.12 Research Reporting

The reporting of this study follows the guidelines of The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for reporting observational studies (124). The reporting of survival analysis results is in line with the assessment items established by Xiaoyan Zhu and colleagues for evaluating the quality of reporting of survival analysis in articles published in Chinese oncology journals in 2013 (125).

Chapter 4: Results

A flowchart of patients' inclusion and exclusion is shown in Figure 1. A total of 705 patients were analyzed. Patient characteristics at baseline for the overall cohort and stratified by gender are provided in Table 5. The median follow-up time for the overall group was 31.03 months (IQR=12.05 months) with a minimum and maximum follow-up times of 0.01 and 58.62 months, respectively. The sample was predominated by female patients (84.96%) and by the Qatari nationals (42.84%). The mean age for all patients was 63.54±8.93 years. Female patients had a higher average BMI (31.95±6.61 kg/m^2) and a slightly lower average total hip BMD (0.77±0.14 g/cm^2), as compared to male patients (BMI=28.90±4.32 kg/m^2, BMD=0.78±0.15 g/cm^2). Diabetes and hyperlipidemia were highly prevalent among the overall cohort, with a respective prevalence of 47.66% and 58.16%. CKD was more prevalent among male patients (26.42%), as were organ transplants (20.75%) and corticosteroids use (37.74%). 16.60% of the overall cohort experienced a previous fracture before baseline, while 17.59% suffered from cancer of any type. Specifically, breast cancer prevalence was 13.69% among females, and prostate cancer prevalence was 14.15% among males. Radiotherapy, chemotherapy and thyroxin treatments were more prevalent in female patients compared to the administration of immunosuppressants, which was more frequent in male patients. The distribution of other clinical factors and the use of medications that are associated with both osteoporosis and fragility fractures are provided as well (Table 5).

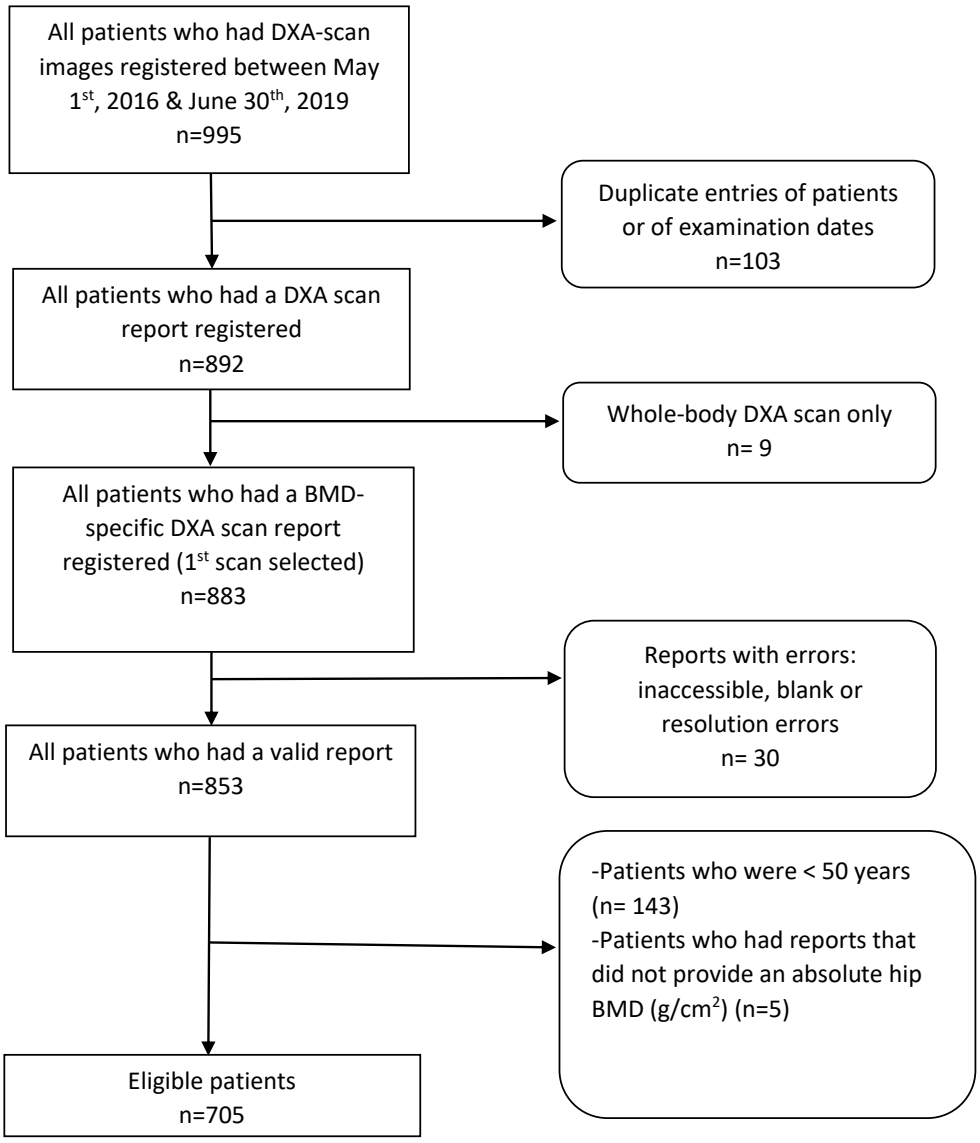

Figure 1. Flowchart for patient inclusion and exclusion.

Table 5. Characteristics of Patients at Baseline

Characteristic	Overall (n=705)	Men (n=106)	Women (n=599)
	Mean (SD)/n (%)		
Follow-up time (month) [a]	31.03 (12.05)	28.70 (15.15)	31.97 (11.51)
Demographics			
Age (year)	63.54 (8.93)	65.48 (9.04)	63.19 (8.87)
Qatari n (%)	302 (42.84)	32 (30.19)	270 (45.08)
Anthropometrics			
Height (cm)	157.50 (8.02)	168.01 (6.01)	155.64 (6.80)
Weight (kg)	78.04 (16.34)	81.62 (13.37)	77.40 (16.75)
BMI (kg/m^2)	31.49 (6.41)	28.90 (4.32)	31.95 (6.61)
Total hip BMD (g/cm^2)	0.78 (0.15)	0.85 (0.16)	0.77 (0.14)
Clinical n (%)			
Previous fracture	117 (16.60)	14 (13.21)	103(17.20)
DM	336 (47.66)	60 (56.60)	276 (46.08)
CADs	59 (8.37)	13 (12.26)	46 (7.68)
CKD [b]	62 (8.81)	28 (26.42)	34 (5.69)
Cancer	124 (17.59)	22 (20.75)	102 (17.03)
Breast	-	-	82 (13.69)
Prostate	-	15 (14.15)	-
Blood [c]	7 (0.99)	4 (3.77)	3 (0.50)
Hyperlipidemia	410 (58.16)	50 (47.17)	360 (60.10)
Rheumatoid arthritis	27 (3.83)	2 (1.89)	25 (4.17)
Organ transplant	32 (4.54)	22 (20.75)	10 (1.67)
Rheumatological/Auto-immune [d]	35 (4.96)	6 (5.66)	29 (4.84)
Neurological/Musculoskeletal	7 (0.99)	2 (1.89)	5 (0.83)
Treatment n (%)			
Corticosteroids [b]	113 (16.07)	40 (37.74)	73 (12.23)
Thyroxin [b]	130 (18.47)	6 (5.66)	124 (20.74)
Chemotherapy [b]	72 (10.23)	3 (2.83)	69 (11.54)
Radiotherapy [b]	94 (13.37)	12 (11.32)	82 (13.74)
Immunosuppressants [b]	44 (6.26)	18 (16.98)	26 (4.36)
Immunosuppressants with immunomodulators [b]	32 (4.55)	10 (9.43)	22 (3.69)
Diabetes medications [b]	329 (46.73)	56 (52.83)	273 (45.65)

[a] Presented as median (IQR)

[b] Number analyzed (n): CKD (n=704); corticosteroids (n=703); thyroxin (n=704); chemotherapy (n=704); radiotherapy (n=703); immunosuppressants (n=703); immunosuppressants with immunomodulators (n=703); diabetes medications (n=704). All missing values were within the women sub-groups.

[c] Blood cancers: Leukemia; lymphoma; multiple myeloma
[d] Include: Ankylosing spondylitis; polymyalgia rheumatica; systemic lupus erythematosus, polymyositis; gout; Sjogren's syndrome; Behcet's disease; sicca syndrome/lupus overlap disease; alopecia areata; psoriasis; anti-phospholipid syndrome; atopic dermatitis, myasthenia gravis.
Abbr. SD, standard deviation; BMI, body mass index; BMD, bone mineral density; DM, diabetes mellitus; CADs, coronary artery diseases; CKD, chronic kidney disease; IQR, interquartile range.

4.1 Fragility Fracture Cases and the Incidence Rate per 1000 Person-months in the Overall Cohort

A total of 34 patients experienced a fracture subsequent to the time of the scan. Figure 2 describes the distribution of these fractures according to the body region. The most prevalent fractures were at the foot and ankle regions (29%), followed by the wrist region (15%), whereas spinal compression fractures accounted for 12% of all fracture cases. Patients who sustained a fracture during follow-up were, on average, older (64.76±8.48 years), leaner (73.86±21.96 kgs), shorter (154.34±10.72 cms) and had lower average T-scores (-2.12±1.16) when compared to those who did not sustain a fracture (age= 63.48±8.95, weight= 78.25±16.00 kgs, height= 157.65±7.83 cms, T-score= 1.30±1.21). 88.24% of incident fracture cases were experienced by female patients. Fracture cases were more prevalent in the LBM group (47.06%), followed by the osteoporosis group (38.24%). For the 705 patients with 19,680.4 person-months at-risk of fracture, the estimated incidence rate of fragility fractures was 1.73 (95% CI= (1.23-2.42)), per 1000 person-months of follow-up, which is equivalent to 20.4 cases per 1000 person-years, or 2 cases per 100 persons per 1 year. Table 8 illustrates the age-specific and gender-specific incidence rates for the overall cohort and for the groups defined by BMD T-score classification. For the overall cohort, fracture rates increased with the increase in the 10-year increments in age, with the exception of the 80-and-above age group, which had relatively low rates of fragility fractures in general. Female

patients had higher overall rate (1.77 cases per 1000 person-months, (95% CI: (1.24-2.54)) as compared to male patients (1.45 cases per 1000 person-months, (95% CI: (0.54-3.86)) for the corresponding fracture cases of 30 (16,918.14 person-months) and 4 (2,762.27 person-months).

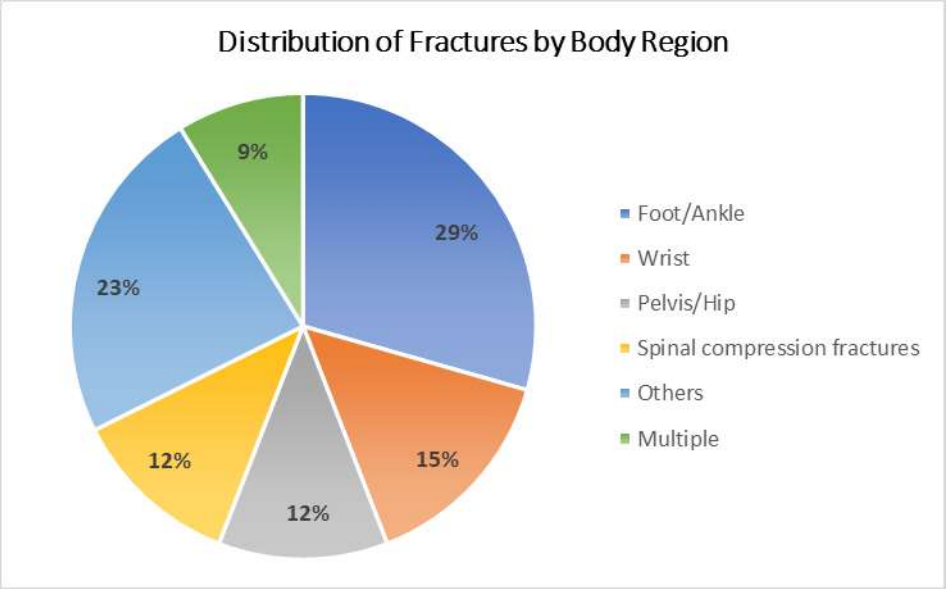

Figure 2. Distribution of fragility fractures by body region.

A KM curve illustrating the baseline incident fracture-free survival function for the cohort is shown in Figure 3. The estimated fracture-free survival probabilities for the overall cohort expressed here as percentages, at 1, 2 and 3 years and at 4 years or longer were 98.20% (95% CI = (96.85%-98.97%)), 96.34% (95% CI: (94.54%-97.56%)), 94.25% (95% CI: (91.87%-95.94%)), and 92.47% (95% CI: (88.58%-95.08%)), respectively. The wider CIs as time elapses are due to the decrease in sample size and number of events with time.

In general, survival was high, and a median survival time was not reached. The cumulative hazard of fragility fracture for the entire follow-up time (58.62 months/4.88 years), which takes into account the exponential decay in the study population, was

estimated to be 0.08 (95% CI= (0.05-0.12)) by the Nelson-Aalen estimator, which is one minus the overall survival probability at this time.

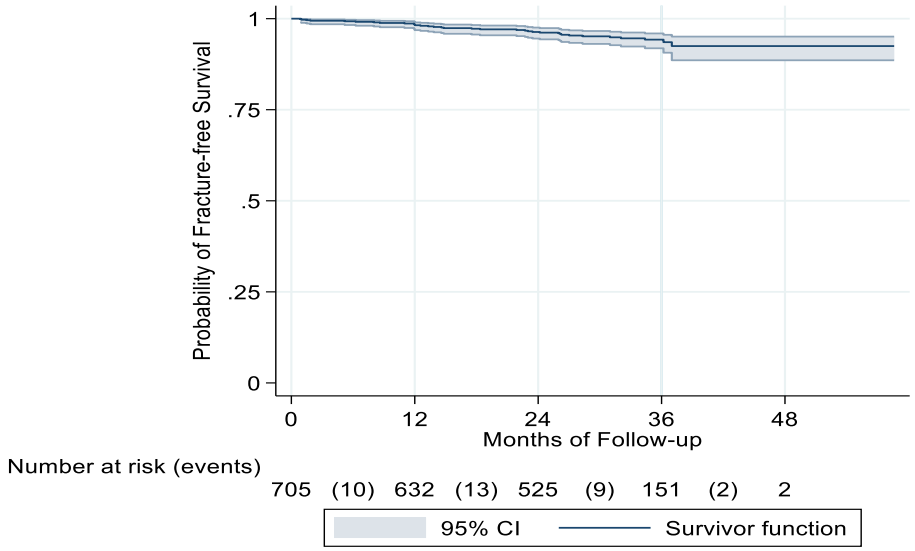

Figure 3. Kaplan-Meier plot of incident fracture-free survival in the study cohort.

4.2 Bone Mineral Density and Incident Fragility Fractures

The characteristics of the patients in each of the three groups classified according to their BMD status, which was based on total hip BMD T-score cutoffs, are illustrated in Table 6. Of the total sample, 36.88% were classified as having normal BMD, 47.09% as having LBM and 16.03% as having osteoporosis, with a mean total hip BMD in g/cm^2 of 0.93±0.09, 0.73±0.05 and 0.56±0.06, respectively. The mean T-score in the three arms of comparison is also provided (Table 6). On average, patients who have osteoporosis are older, shorter and leaner when compared to the other two groups. The trends of decreasing height, weight and BMI and increasing age, from the normal BMD group to the osteoporosis group, were observed. Female patients and Qatari patients predominated in the three arms of comparison. With regards to the other internationally validated factors for fragility fractures, a previous fragility fracture and

rheumatoid arthritis were more prevalent in the osteoporosis group, whereas corticosteroid use was more prevalent in the normal BMD group. The median follow-up time was comparable among the three groups. The distribution of other factors that are associated with fragility fractures is also provided (Table 6).

Table 6. Characteristics of Patients According to Total Hip BMD Status [a], (N=705)

Characteristic	Osteoporosis (n=113)	Low Bone Mass (n=332)	Normal (n=260)
	Mean (SD)/n (%)		
Follow-up time (months) [b]	29.0 (14.38)	30.0 (11.36)	32.3 (10.81)
Total hip BMD			
BMD (g/cm^2)	0.56 (0.06)	0 .73 (0.05)	0.93 (0.09)
T-score	-3.11 (0.51)	-1.73 (0.40)	-0.08 (0.76)
Demographics			
Age (years)	69.1 (9.9)	63.8 (8.2)	60.8 (8.2)
Female	105 (92.9%)	291 (87.7%)	203 (78.1%)
Qatari	55 (48.7%)	149 (44.9%)	98 (37.7%)
Anthropometrics			
Height (cm)	154.1 (8.5)	156.8 (7.2)	159.9 (8.2)
Weight (kg)	70.1 (16.1)	75.5 (15.1)	84.7 (15.6)
BMI (kg/m^2)	29.6 (6.7)	30.8 (6.2)	33.2 (6.2)
Clinical n (%)			
Previous fracture	41 (36.3)	53 (16.0)	23 (8.9)
Rheumatoid arthritis	8 (7.1)	14 (4.2)	5 (1.9)
DM	53 (46.9)	151 (45.5)	132 (50.8)
CADs	10 (8.9)	26 (7.8)	23 (8.9)
CKD [c]	6 (5.3)	27(8.2)	29 (11.2)
Cancer	15 (13.3)	53 (16.0)	56 (21.5)
Breast [c]	10 (8.8)	34 (10.2)	38 (14.6)
Prostate [c]	2 (1.8)	5 (1.5)	8 (3.1)
Blood [d]	0.0 (0.0)	3 (0.9)	4 (1.5)
Hyperlipidemia	66 (58.4)	195 (58.7)	149 (57.3)
Organ transplant	1 (0.9)	13 (3.9)	18 (6.9)
Rheumatological/Auto-immune [e]	2 (1.8)	16 (4.8)	17 (6.5)
Neurological/Musculoskeletal	2 (1.8)	2 (0.6)	3 (1.2)

Characteristic	Osteoporosis	Low Bone Mass	Normal
Treatment n (%)			
Corticosteroids [c]	11 (9.7)	48 (14.5)	54 (20.9)
Thyroxin [c]	23 (20.4)	64 (19.3)	43 (16.6)
Chemotherapy [c]	12 (10.6)	26 (7.8)	34 (13.1)
Radiotherapy [c]	12 (10.6)	38 (11.5)	44 (17.0)
Immunosuppressants [c]	6 (5.3)	19 (5.7)	19 (7.3)
Immunosuppressants with immunomodulators [c]	0.0 (0.0)	16 (4.8)	16 (6.2)
Diabetes medications [c]	46 (40.7)	147 (44.3)	136 (52.5)

[a] Categories were based on the WHO classification according to total hip T-scores. Calculated hip T-scores were based on the young normal mean hip BMD of 0.942 ± 0.122 g/cm^2.
[b] Presented as median (IQR)
[c] Number of missing values in variables within BMD groups: CKD (1 in LBM); corticosteroids (1 in LBM & 1 in Normal BMD); thyroxin (1 in normal BMD); chemotherapy (1 in normal BMD); radiotherapy (1 in LBM & 1 in Normal BMD); immunosuppressants (1 in LBM & 1 in Normal BMD), immunosuppressants with immunomodulators (1 in LBM & 1 in Normal BMD); diabetes medications (1 in normal BMD). All missing values are within the women sub-groups. The number analyzed for breast cancer and prostate cancer is based on at-risk female and male groups, respectively.
[d] Blood cancers: Leukemia; lymphoma; multiple myeloma
[e] Include: Ankylosing spondylitis; polymyalgia rheumatica; systemic lupus erythematosus, polymyositis; gout; Sjogren's syndrome; Behcet's disease; sicca syndrome/lupus overlap disease; alopecia areata; psoriasis; anti-phospholipid syndrome; atopic dermatitis, myasthenia gravis.
Abbr. BMI: Body Mass Index; DM: Diabetes Miletus; CADs: Coronary Artery Diseases; CKD: Chronic Kidney Disease; IQR, interquartile range

4.2.1 Incidence Rate of Fragility Fracture per 1000 Person-months

The incidence rate was higher in the osteoporosis group, followed by the LBM group when compared to the normal group, as illustrated in Table 7. The number of patients, the number of fracture cases, and the time at risk of incident fracture in each group are also provided in Table 7. The number of fracture cases was highest in the LBM group, followed by the osteoporosis group and then the normal group. However, around 85% of the cases occurred in the two former groups. The fracture rate ratio in osteoporotic patients as compared to the rest of the cohort was 3.31 (95% CI: (1.52-6.92)), and the rate difference per 1000 person-months was 2.93 cases (95% CI: (0.58-

5.27)). The trend seen with increasing rates in the direction towards osteoporosis was found to be statistically significant using the Mantel-Haenszel-type method for stratified rate ratios (rate ratio: 2.54 (95% CI: (1.57-4.11), chi^2=14.28, P-value=0.0002). The rate ratio estimate reported here is an approximation to the rate ratio for one level change in the categorical BMD status variable.

Table 8 illustrates the age-specific and the gender-specific incidence rates for the overall cohort and for the groups defined by BMD T-score classification. Overall, the highest rates were found among patients in their seventies in the osteoporosis group. The trend of increasing incidence rates, from the normal BMD group to the osteoporosis group, was observed among patients in their sixties and seventies. Patients who are eighty or older had relatively lower rates of fragility fracture in general. Female patients had higher fracture rates as compared to male patients in the osteoporosis and normal BMD group; however, the reverse was observed in the LBM group.

Table 7. Incidence Rates per 1000 Person-months of Fragility Fractures for the Overall Cohort and Stratified by BMD Status

BMD status	No. of patients	No. of cases	Person-time at risk	Incidence rate (95% CI)
Normal	260	5	7,346.5	0.68 (0.28-1.64)
LBM	332	16	9,233.74	1.73 (1.06-2.83)
Osteoporosis	113	13	3,100.15	4.19 (2.43-7.22)
Total	705	34	19,680.41	1.73 (1.23-2.42)

Abbr. BMD, bone mineral density; CI, confidence interval; LBM, low bone mass

Table 8. Age-specific and Gender-specific Incidence Rates per 1000 Person-months of Fragility Fractures for the Overall Cohort and Stratified by BMD Status [a]

Category	Cases (person-month) [b]	Osteoporosis	Low Bone Mass	Normal	Total
Age group (years)		Rate (95% CI)			
50-59	10 (7,310.66)	2.05 (0.29-14.54)	2.14 (1.02-4.49)	0.56 (0.14-2.25)	1.37 (0.74-2.54)
60-69	13 (7,573.91)	5.34 (2.40-11.89)	1.36 (0.57-3.26)	0.72 (0.18-2.89)	1.72 (1.00-2.96)
70-79	10 (3,556.16)	6.80 (3.05-15.13)	1.60 (0.51-4.95)	1.26 (0.18-8.94)	2.81 (1.51-5.23)
80+	1 (1,239.68)	0.00	2.50 (0.35-17.72)	0.00	0.81 (0.11-5.73)
Gender					
Women	30 (16,918.14)	4.13 (2.34-7.27)	1.69 (1.00-2.86)	0.70 (0.26-1.86)	1.77 (1.24-2.54)
Men	4 (2,762.27)	5.21 (0.73-37.00)	2.08 (0.52-8.33)	0.62 (0.09-4.41)	1.45 (0.54-3.86)

[a] BMD status is defined according to the WHO T-score-based classification scheme; calculated hip T-scores were based on the young normal mean hip BMD of 0.942±0.122 g/cm^2.

[b] Number of cases and person-months for the entire subgroup.

Abbr. CI: Confidence Interval

4.2.2 Kaplan-Meier Curves and Incident Fracture-free Survival Probabilities

KM curves of the estimated incident fracture-free survival of the three groups classified according to total-hip BMD T-scores are depicted together in Figure 4 and separately, with their range of 95% CIs in Figure 5.

In the normal group, survival probability was 100% for one year, 99.53% (95% CI: (96.71%-99.93%)) and 97.66% (95% CI: (93.80%-99.13%)) at two and three years, respectively. The minimum survival probability was at 3.5 years, and it was 95.49% (95% CI: (87.27%-98.45%)).

In the LBM group, survival was 98.09% (95% CI: (95.79%-99.14%)) for one year. At two, three and four years and beyond, survival probabilities were, 97.08% (95% CI: (94.45%-98.47%)), 94.07% (95% CI: (90.11%-96.47%)), and 91.72% (95% CI: (84.22-95.74%)), respectively.

As for the osteoporosis group, 94.46% (95% CI: (88.08%-97.47%)) of patients survived up until one year, and survival probabilities dropped at two years and beyond to 87.00% (95% CI: (78.58%, 92.27%)). Overall, the cumulative survival rates at 1 and 2 years were lower in the osteoporosis group, followed by the LBM group as compared to the normal group. However, survival probabilities at these time points were much lower in the osteoporosis group, relative to the other groups. At 95% level of confidence, the estimates for the osteoporosis group is less precise relative to the other groups due to the smaller group size as indicated by the wider CIs of the estimated probabilities for the osteoporosis group depicted in Figure 5. Alternatively, the Nelson-Aalen cumulative hazard curves for the three groups are provided in Figure 6, where the cumulative hazard of fractures is highest in the osteoporosis group, followed by the

LBM group and then the normal BMD group.

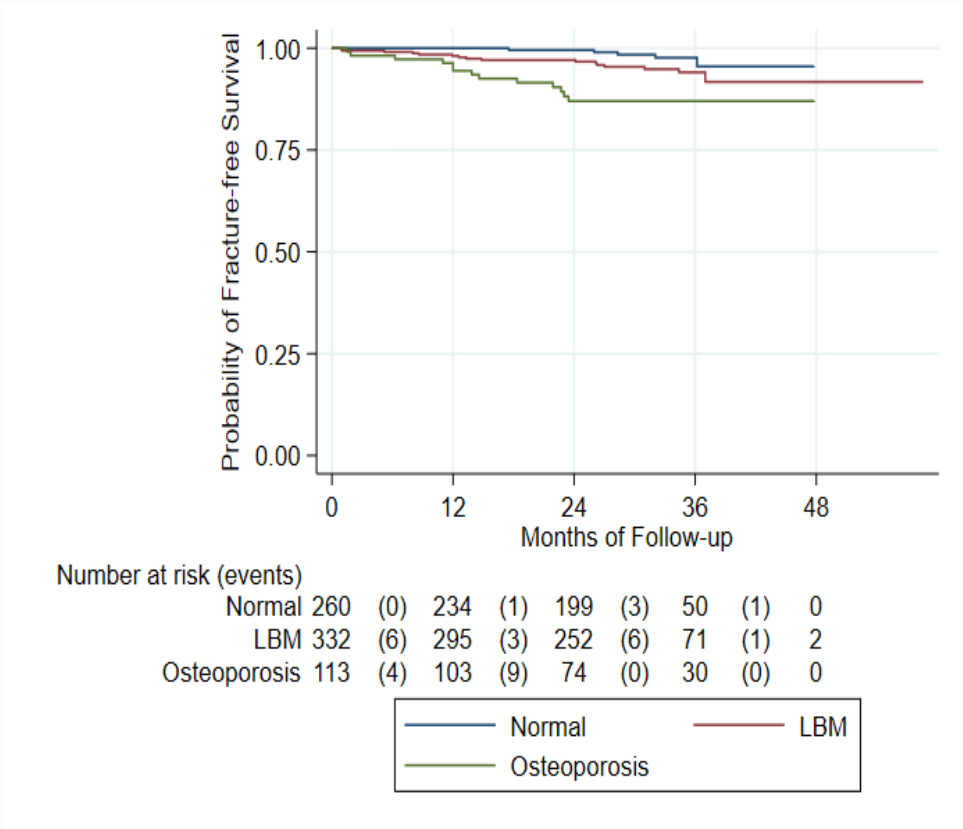

Figure 4. Kaplan-Meier curves of incident fracture-free survival for the groups categorized according to BMD status.

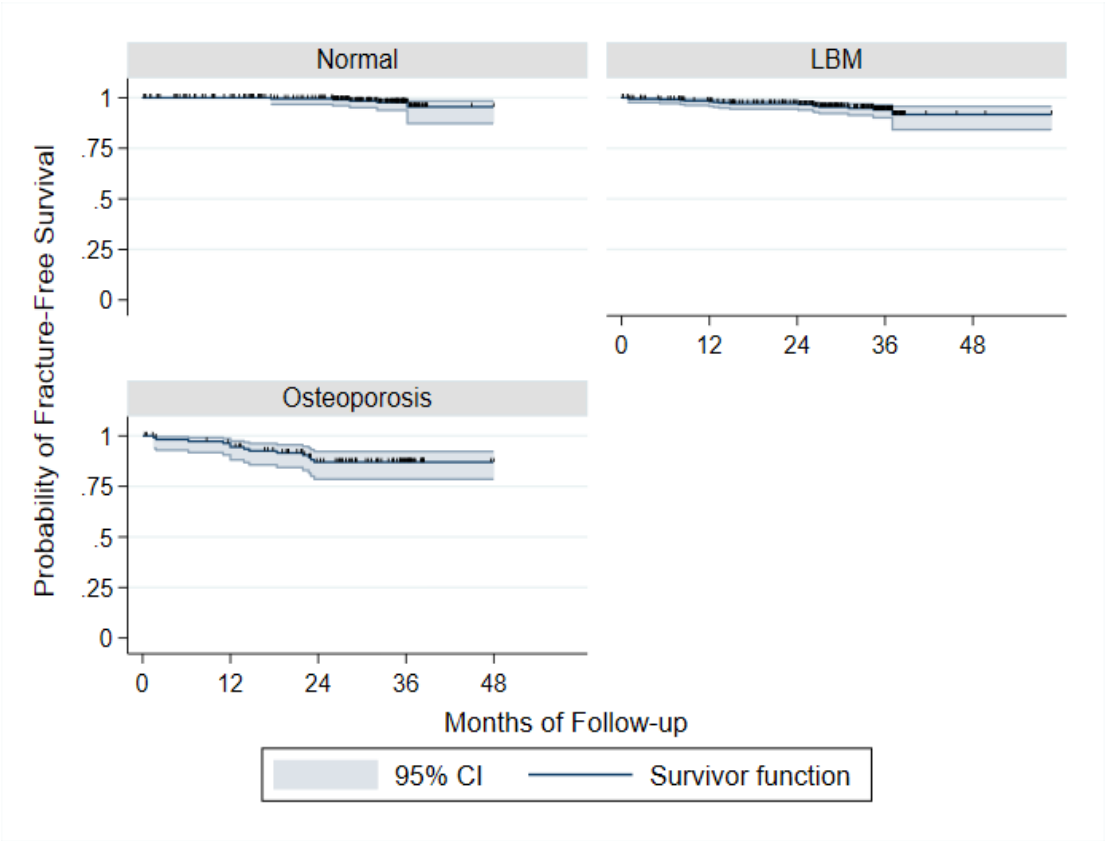

Figure 5. Kaplan-Meier curves of incident fracture-free survival for each of the groups categorized according to BMD status and the bands of the 95% confidence intervals.

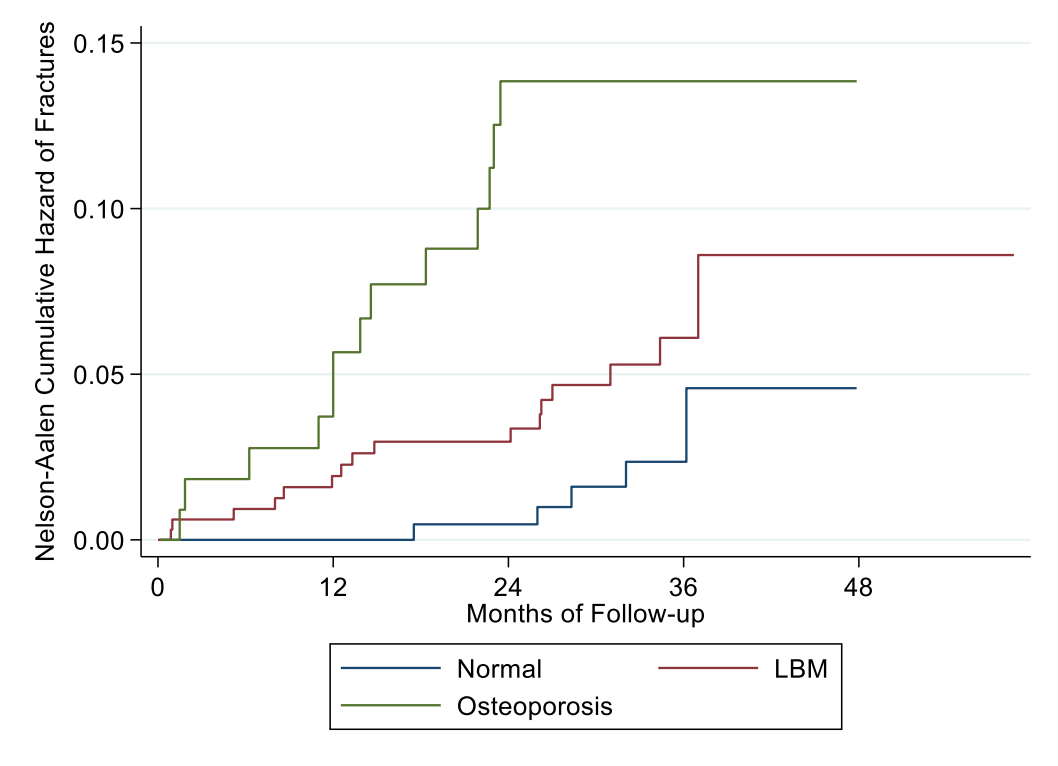

Figure 6. Nelson-Aalen cumulative hazards curves of incident fragility fractures in the groups categorized according to BMD status.

4.2.3 The Log-rank Test

The results obtained from the log-rank test are illustrated in Table 9. The difference in fracture-free survival among the three BMD status groups was statistically significant (chi^2=15.60, degrees of freedom (df)=2, p<0.0001), and so was the trend in the survival (chi^2= 14.29, df=1, p<0.0001) as obtained by the log-rank test of trend. The distributions of survival probabilities of the different categories of the internationally validated risk factors, namely, age, gender, BMI, previous fracture, corticosteroid use and rheumatoid arthritis, were not found to be statistically significantly different (p-value>0.05). However, when the test of equality of survival functions among the three BMD groups was stratified according to the aforementioned factors, survival among the three groups was statistically significantly different (p-value<0.05). This suggests that the association between BMD status and time-to-incident fragility fracture persists

even after accounting for these potentially confounding factors.

Table 9. Log-rank Test of Equality of Survival Distributions Among the Groups Categorized According to their BMD Status [a]

Log-rank test	Chi-square [b]	P-value
Non-stratified test	15.6	<0.001
Stratified test		
Age group	15.72	<0.001
Gender	15.34	<0.001
BMI category	10.85	0.004
Previous fracture	19.27	<0.001
Corticosteroid use	16.67	<0.001
Rheumatoid arthritis	15.72	<0.001

[a] Categories were based on the WHO classification according to total hip T-scores. Calculated hip T-scores were based on the young normal mean hip BMD of 0.942 (SD 0.122) g/cm^2.
[b] Degrees of freedom for the Chi-square=2
Abbr. BMD, bone mineral density; BMI, body mass index

4.2.4 Cox Proportional Hazards Regression Analysis

The results of the Cox PH regression analyses of time-to-incident fracture on total hip BMD and the internationally validated clinical risk factors of fragility fracture are presented in Table 10, which illustrates the risk estimates of incident fragility fracture obtained by these analyses (Numbered 1-6), namely, the HRs along with their 95% CIs. The Wald test p-value denoting the statistical significance of the coefficient of the estimated total hip BMD T-score parameter in each of these analyses is also provided (Table 10). Total hip T-score variable-upon which the categorized BMD status variable was based-was considered in these analyses, and accordingly, relative risk is expressed here as the hazard ratio of incident fragility fracture, per SD reduction in total hip BMD from the young normal (negative T-scores). The number of patients included in each of the performed analyses, out of the 705 patients representing the total

sample, is provided as well (Table 10).

In the unadjusted analysis (analysis No.1), where only the relative hazard of incident fracture per 1 SD reduction in BMD was considered, the rise in risk (hazard ratio) of incident fragility fracture per SD reduction in total hip BMD was 1.82. The result is statistically significant (95% CI: ((1.34-2.48)), p-value<0.001). The results of a series of adjustment analyses (analyses No. 2-6), where BMD T-score was considered along with one or a combination of the internationally validated risk factors for fragility fractures, which were listed earlier, are tabulated as well (Table 10). Adjusting for both age and gender had a positive effect on the relative hazard (HR: 1.93, 95% CI: (1.37-2.71)), p-value<0.001), where age contributed the large majority of this effect. Adding previous fracture variable to the adjustment analysis that controlled for age, gender and BMI, yielded a 20% increase in the relative hazard (HR: 2.19, 95% CI: (1.51-3.17), p-value<0.001), compared to that of the unadjusted model. The relative risk of fracture barely changed per SD change in BMD when the adjustment included the remaining factors, namely, rheumatoid arthritis and corticosteroid use. All the results were statistically significant based on the CIs that do not contain the null value of equal risks, which equals 1. The results agree with those obtained by the log-rank test presented earlier, indicating that control for these potentially confounding factors does not nullify the association between BMD and time-to-incident fracture; however, it appears to decrease the magnitude of the association.

Testing for the interaction between total hip BMD T-score and each of the included variables in the model containing all variables (analysis No. 6 in Table 10), using the Wald test, revealed statistically non-significant results (p-value>0.05) for the corresponding variables' coefficients. Also, when the considered theory-driven interactions between age and previous fracture and between BMI and gender were

tested, the coefficients did not achieve statistical significance. According to analysis No. 6, when adjusting for age, gender, BMI, previous fracture, corticosteroids use and rheumatoid arthritis, the risk of sustaining an incident fragility fracture (the hazard) rises by a factor of 2.22 for every SD reduction in total hip BMD from the young normal. This result is statistically significant as indicated by the 95% CI (1.53-3.21), that do not include the null value of 1 and the p-value that is less than 0.05. Worth mentioning here is the unexpected result of the regression of time-to-incident fracture on the previous fracture variable adjusted for all other factors in the model, which showed that the hazard of incident fragility fracture is 62% lower in patients who experienced a fragility fracture before the start of follow-up (HR=0.38), compared to those who did not, suggesting a survival benefit for the former group. However, this result was statistically non-significant (95% CI: (0.13-1.12), p-value=0.081).

Table 10. Risk Estimates of Incident Fragility Fracture Expressed as HRs per SD Reduction in Total Hip BMD [a]

Analysis No. [b]	Analysis	HR	95% CI	P-value [c]
1	Unadjusted	1.82	(1.34-2.48)	<0.001
2	Adjusted for age	1.91	(1.36-2.68)	<0.001
3	Adjusted for age and gender	1.93	(1.37-2.71)	<0.001
4	Adjusted for age, gender and BMI	1.99	(1.39-2.83)	<0.001
5	Adjusted for age, gender, BMI and previous fracture	2.19	(1.51-3.17)	<0.001
6	Adjusted for age, gender, BMI, previous fracture, corticosteroid use and rheumatoid arthritis	2.22	(1.53-3.21)	<0.001

[a] T-scores were based on the young normal mean hip BMD of 0.942 (SD 0.122) g/cm^2.
[b] Analysis is performed for all 705 patients in analyses No. 1-5 and for 703 patients in analysis No. 6
[c] P-value of the Wald test of significance of the coefficient (not shown) of the BMD T-score variable for each model presented

Abbr. HR, hazard ratio; SD, standard deviation; CI, confidence interval; BMD, bone mineral density; BMI, body mass index

4.2.5 Cox Proportional Hazards Regression Model Diagnostics

The assumptions of a Cox PH model were evaluated for the multivariable model relating time-to-incident fragility fracture with BMD and the other internationally validated risk factors for fragility fractures (analysis No.6, table 10).

Proportional hazards assumption. The assumption mandates that the relative hazard of the groups being compared is independent of time. For this purpose, investigating the violation of this assumption was considered for the variables included in the fitted Cox PH model. The approaches presented below vary between statistical tests and graphical diagnostics, and they assess the model as a whole and the individual variables included in the model. The results of these methods are as follows:

1. Examination of the KM curves: As shown in Figure 4, when considering the categorized variable into groups defined by T-scores instead of the continuous one entered in the model, the curves for the three groups (normal, LBM and osteoporosis) do not cross for the entire follow-up time. At around 24 months of follow-up, the curve for the osteoporosis group plateaus while the curves for the other two arms of comparison drop afterward.
2. Incorporation of time-dependent covariates in the model: The coefficient of the time-dependent covariate for the T-score variable was significant (p-value= 0.015), while those of the other covariates included in the model were not significant. Hence, the assumption of proportionality did not hold for the T-score variable according to this test.
3. Schoenfeld and Scaled Schoenfeld residuals: The assumption was tested for the model as a whole, using Schoenfeld and Scaled Schoenfeld residuals. The

results obtained indicate that the null hypothesis of the test, that is, proportionality holds, cannot be rejected (chi^2=11.44, df=7, p-value=0.120). This suggests that residuals of the fitted model and time-to-incident fracture are independent of each other, and no violation of proportionality assumption is assumed. When considering each variable separately, the test was only significant for the T-score variable (*Rho*=0.399, Chi^2=6.88, df= 1, p-value= 0.009). Figure 7 illustrates the relationship between the corresponding set of scaled Schoenfeld residuals with time. The smoothing spline fit of the plot represented by the solid line seems to deviate slightly from the horizontal axis centered about zero. Hence, no major violation of the assumption is observed graphically.

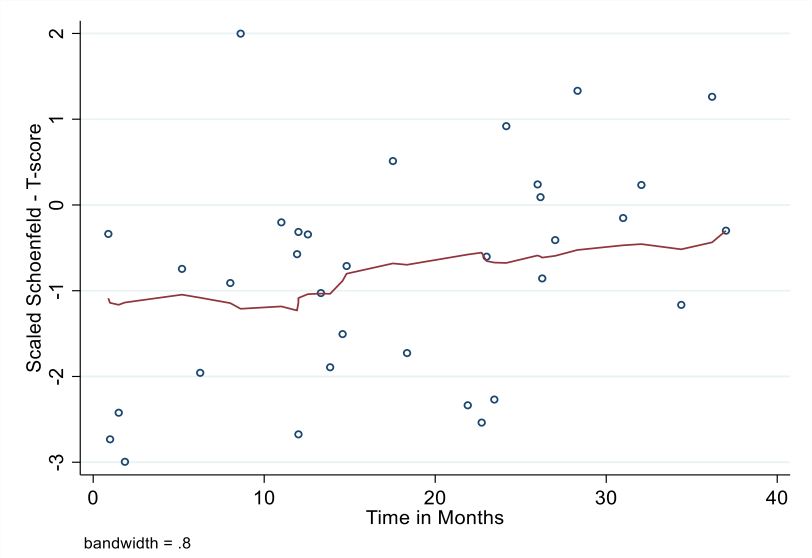

Figure 7. Individual scaled Schoenfeld residuals test of proportional hazards assumption for the T-score variable.

4. The log-log plot of survival: To further investigate the variable T-score, another graphical examination of the assumption was performed by plotting the natural

log of the estimated survival probabilities-taken twice-for the three groups defined by the T-score variable against the natural log of time; the log(-log(S(t)) vs. log(t), as illustrated in Figure 8. The curves for the osteoporosis and the LBM categories are reasonably parallel, whereas the normal category curve does not show the same parallelism with the other two categories.

Overall, the proportional hazards assumption was upheld for the model as a whole. However, the T-score variable seems to violate this assumption.

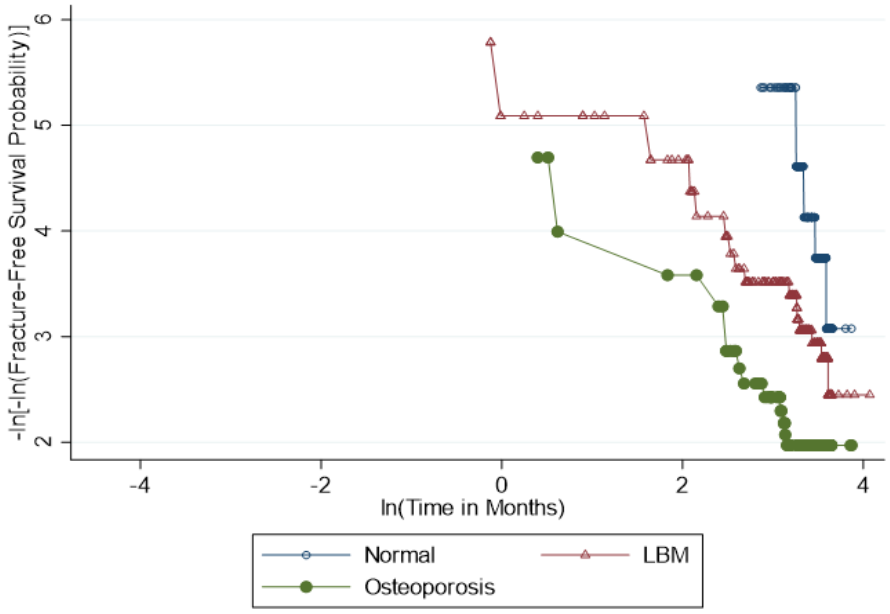

Figure 8. Proportional hazards assumption evaluation for the categorized BMD status variable: A log-log plot of fracture-free estimated survival against the log of time in months.

Assessing outliers. This was done by plotting the standardized form of Martingale residuals, namely, deviance residuals of the model versus the linear predictor, as illustrated in Figure 9. Censored observations are represented as clumps of deviance residuals near 0, and all residuals should fall within 1 and -1 SDs, for the observations to not be considered as outliers. The residuals identified 34 potential

outliers (residuals falling above 1 SD).

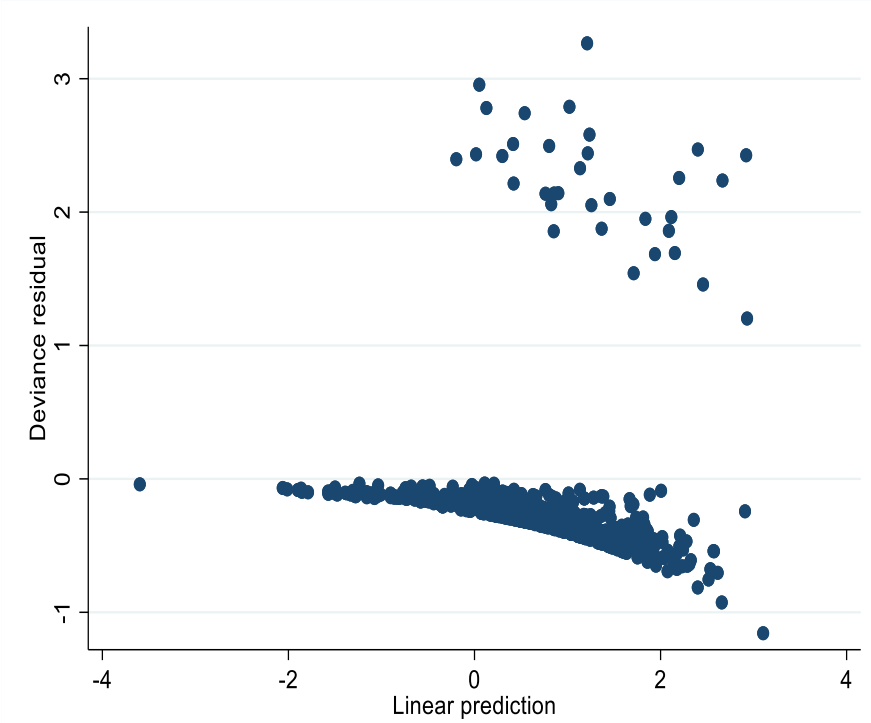

Figure 9. A plot of deviance residuals of the BMD multivariable-adjusted Cox model against linear predictions to investigate the presence of potential outliers.

Assessing influential observations. The plot of the likelihood displacement values against time is shown in Figure 10; the points represent observations labeled by the corresponding observation number. Observations No. 639 and No. 403 seem to be influential with a likelihood displacement value of 1.293 and 1.053, respectively. The first one is a diabetic female patient who has rheumatoid arthritis, previous fracture history and did sustain fracture at 12 months of follow-up time, and the second is a diabetic female who is morbidly obese (BMI: 66.22 Kg/m^2) and who sustained fracture very early in follow-up time. The likelihood displacement values listed here would represent the respective amount of increase in twice the log of the likelihood of the model if these observations were to be omitted.

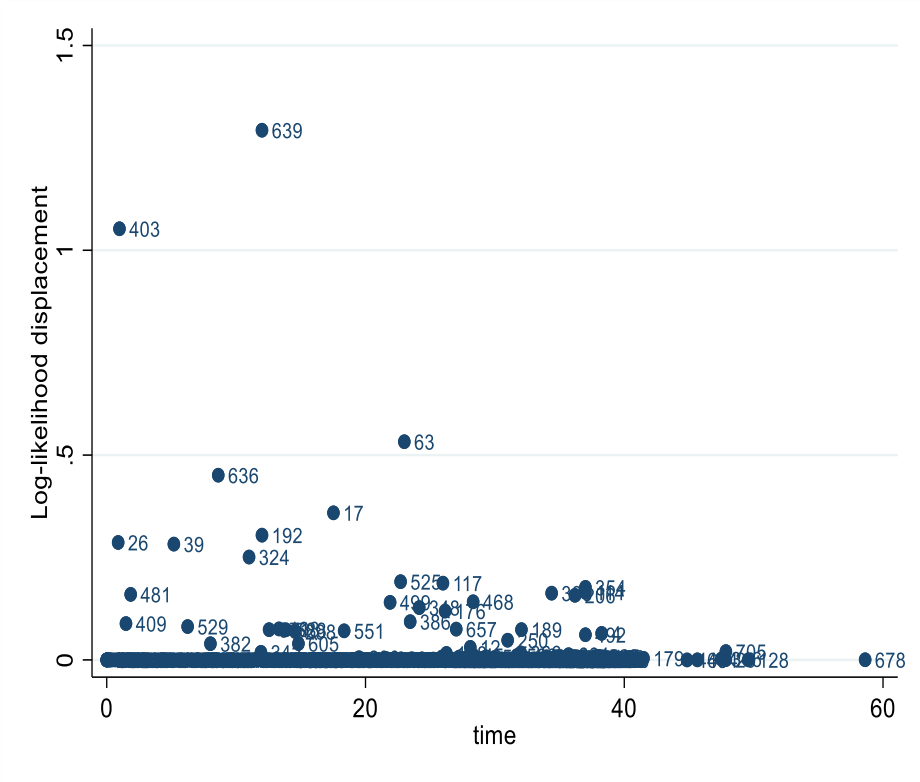

Figure 10. Displacement in the likelihood of the multivariable-adjusted Cox proportional hazards model, obtained by regression of time-to-incident fragility fracture on BMD T-score.

Non-linearity test. This was done by plotting the Martingale residuals on the Y-axis against the continuous covariates on the X-axis to detect nonlinearity or, in other words, to assess the functional form of a continuous covariate. The resulting plots for age, T-score and BMI variables (not shown) were fairly horizontal and not angling. Thus, the linearity assumption for these variables is upheld.

The goodness of fit of the model. The fit of the model was assessed by examining the Cox-Snell residuals. Figure 11 illustrates the graphing of the Nelson-Aalen cumulative hazard function, and the Cox-Snell created variable. The hazard function follows the 45-degree line. The wiggling at large values of time is not unusual with censored data and does not warrant concern. The result indicates that the hazard

approximates an exponential distribution with a hazard rate of one and we conclude that the model fits the data well.

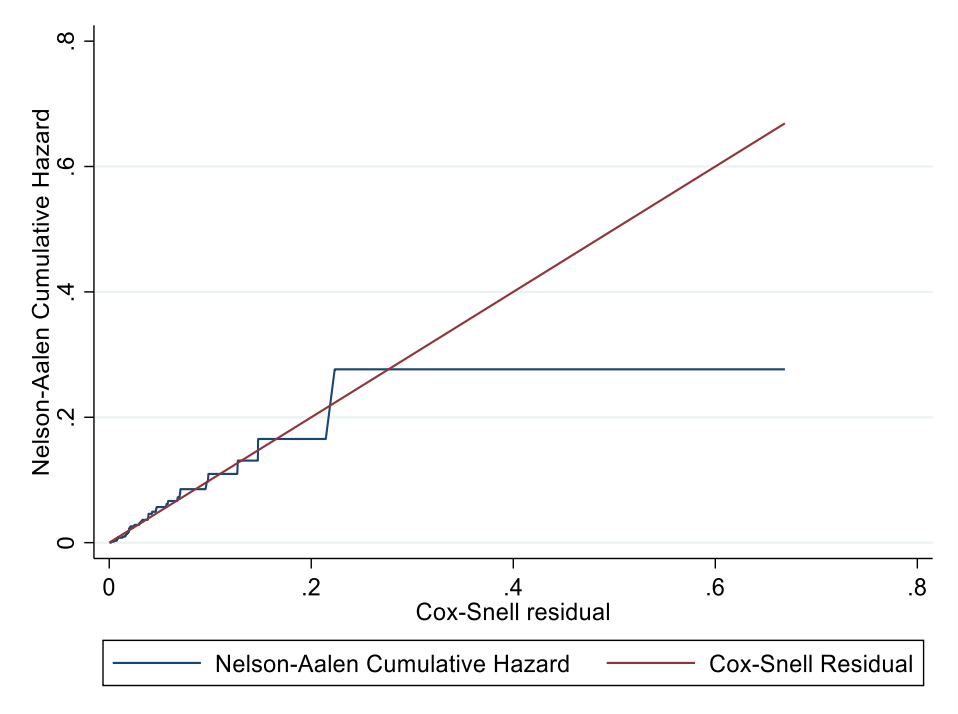

Figure 11. The goodness of fit of the multivariable-adjusted Cox proportional hazards model, obtained by regression of time-to-incident fragility fracture on total hip BMD T-score, using the Cox-Snell residuals.

4.2.6 Adjusted Incident Fragility Fracture-free Survival Curves

The adjusted fracture-free survival curves of two pairs of covariate patterns were chosen to be plotted for the sake of comparison as follows:

Covariate patterns pair No. 1. Figure 12 compares the adjusted fracture-free curve of a 70 years old female patient with a T-score value of -3 (falls into the osteoporosis category) and who has a BMI value of 20 kg/m^2 (which falls in the average category) with that of another female patient, with similar age and BMI values but has a T-score of -2 (falls in the LBM category), adjusting for the other respective explanatory variables in the model, namely; a history of previous fracture, rheumatoid

arthritis and the use of corticosteroids. As shown in the graph, the adjusted survival probability is higher for the patient who has LBM than the one who has osteoporosis.

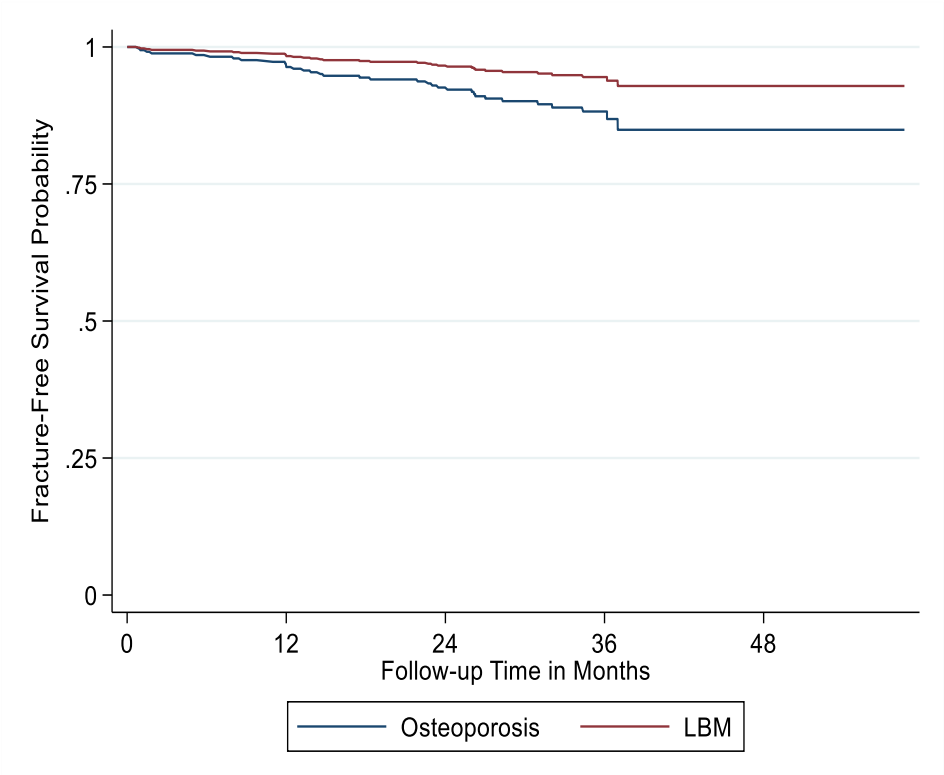

Figure 12. Adjusted survival curves obtained from the multivariable-adjusted Cox proportional hazards regression of time-to-incident fragility fracture on total hip BMD T-score: Covariates pattern pair No. 1.

Covariate patterns pair No. 2. Figure 13 compares the adjusted fracture-free survival curve of a female patient with a T-score value of -3 (falls into the osteoporosis category) and who has a previous fragility fracture before baseline, with that of another female patient, with a similar T-score, but does not have a history of fragility fracture, adjusting for the other respective explanatory variables in the model, namely; age, BMI, rheumatoid arthritis and the use of corticosteroids. As shown in the graph, the adjusted survival probability is higher for the patient who has a history of a fracture.

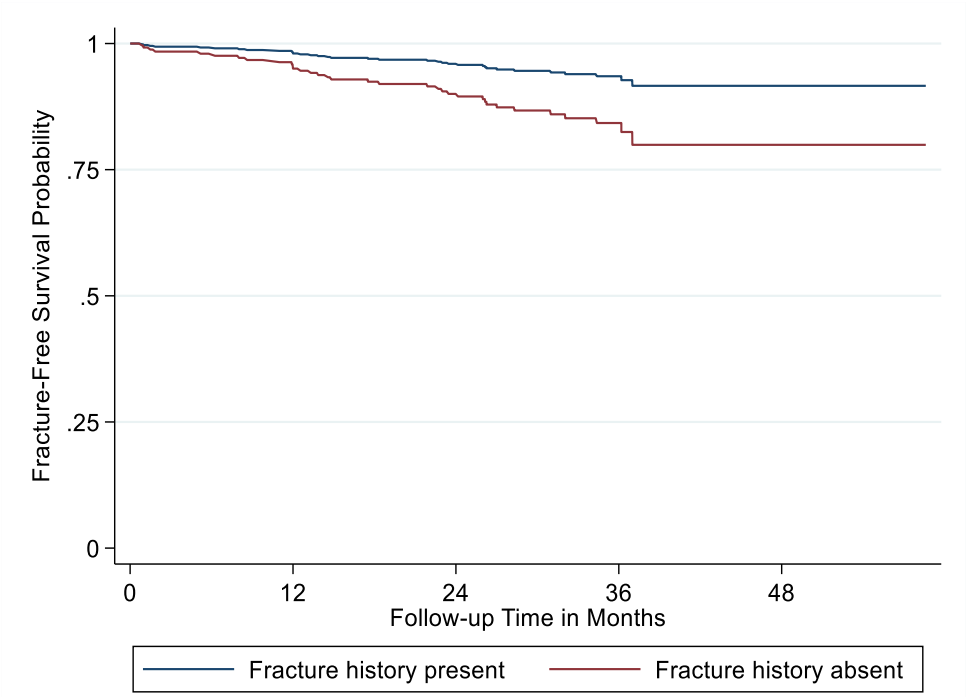

Figure 13. Adjusted survival curves obtained from the multivariable-adjusted Cox proportional hazards regression of time-to-incident fragility fracture on total hip BMD T-score: Covariates pattern pair No. 2.

4.3 Diabetes Mellitus and Incident Fragility Fractures

A comparison of the characteristics of patients included in this analysis (N=705) between the groups defined by the diagnosis of diabetes, namely, the diabetic (47.66%) and the non-diabetic (52.34%) groups, is provided in Table 11.

Overall, and on average, diabetic patients were followed for about the same time as non-diabetic patients. The diabetic patients were heavier (80.46±17.71 kgs), on average, and had a slightly higher average BMI (32.64±7.07 kg/m^2) when compared to the other group (weight=75.82±14.66 kgs, BMI=30.43±5.53 kg/m^2). On average, there were no marked differences between the two groups in terms of age, height, gender distribution (female gender predominance in both arms), or in terms of their BMD measurements, T-scores or the prevalence of osteoporosis. The large majority (92.84%) of diabetic patients received treatment for diabetes (either insulin or oral hypoglycemic

drugs) and a small proportion of the non-diabetic group received one of the oral drugs to treat conditions such as obesity. Nearly half (52.38%) of diabetic patients were Qatari. The use of corticosteroids, thyroxin and immunosuppressants was higher in the diabetic group, whereas receiving chemotherapy and radiotherapy was higher in the non-diabetic group owing to the fact that cancer in general-including breast cancer in women-was more prevalent in the latter group. Previous fracture and organ transplant cases, CKD, CADs and hyperlipidemia, were more encountered in the diabetic group.

Table 11. Characteristics of Patients by the Diagnosis of Diabetes

Characteristic	No Diabetes (n=369)	Diabetes (n=336)
	Mean (SD)/n (%)	
Follow-up time [a]	30.63 (11.28)	32.65 (13.13)
Demographics		
Age (years)	62.37 (8.97)	64.80 (8.71)
Female	323 (87.53 %)	276 (82.14%)
Qatari	126 (34.15%)	176 (52.38%)
Anthropometrics		
Height (cm)	157.83 (7.41)	157.12 (8.62)
Weight (kg)	75.82 (14.66)	80.46 (17.71)
BMI (kg/m^2)	30.43 (5.53)	32.64 (7.07)
Total hip BMD		
Absolute (g/cm^2)	0.77 (0.14)	0.78 (0.15)
T-score [b]	-1.39 (1.14)	-1.29 (1.29)
Osteoporosis [c]	60 (16.26%)	53 (15.77%)

Characteristic	No Diabetes	Diabetes
Treatment		
Diabetes medications	18 (4.88%)	311 (92.84%)
Corticosteroids	53 (14.36%)	60 (17.96 %)
Thyroxin	59 (15.99%)	71 (21.19%)
Chemotherapy	53 (14.36%)	19 (5.67%)
Radiotherapy	66 (17.89%)	28 (8.38 %)
Immunosuppressants	17 (4.61%)	27 (8.08%)
Immunosuppressants with immunomodulators	15 (4.07%)	17 (5.09%)
Clinical conditions		
Previous fragility fracture	54 (14.63%)	63 (18.75%)
CADs	14 (3.79%)	45 (13.39%)
CKD	13 (3.52%)	49 (14.63%)
Hypothyroidism	60 (16.3%)	70 (20.83%)
Cancer	82 (22.22 %)	42 (12.50%)
Breast	57 (15.44%)	25 (7.44%)
Prostate	5 (1.36%)	10 (2.98%)
Blood [d]	7 (1.89%)	0 (0.00%)
Hyperlipidemia	182 (49.32%)	228 (67.86%)
Rheumatoid arthritis	13 (3.52%)	14 (4.17%)
Organ transplant	5 (1.36%)	27 (8.03%)
Rheumatological/Auto-immune [e]	20 (5.42)	15 (4.46%)
Neurological/Musculoskeletal	5 (1.36%)	2 (0.60%)

[a] Presented as median (IQR)
[b] Calculated total hip T-scores were based on the young normal mean hip BMD of 0.942±0.122 g/cm^2.
[c] Classified as having osteoporosis based on the WHO definition as having a T-score≤-2.5
[d] Blood Cancers: Leukemia; lymphoma; multiple myeloma
[e] Include: Ankylosing spondylitis; polymyalgia rheumatica; systemic lupus erythematosus, polymyositis; gout; Sjogren's syndrome; Behcet's disease; sicca syndrome/lupus overlap disease; alopecia areata; psoriasis; anti-phospholipid syndrome; atopic dermatitis, myasthenia gravis
Abbr. SD, standard deviation; BMI, Body Mass Index; BMD, bone mineral density; CAD, coronary artery diseases; CKD, chronic kidney disease; IQR, interquartile range

4.3.1 Incidence Rate of Fragility Fracture per 1000 Person-months

Table 12 illustrates the incidence rates of fragility fractures for the diabetic and the non-diabetic groups, in addition to the rates stratified by age and gender within each

group. Of the 34 fragility fracture cases observed in the overall group, 19 of these cases were observed in the diabetic group as compared to 15 cases in the non-diabetic group.

The incidence rate per 1000 person-months was approximately 50% higher in the diabetic group (2.01 cases, 95% CI: (1.28-3.16)), compared to that in the non-diabetic group (1.46 cases, 95% CI: (0.88-2.43)). The incidence rate difference per 1000 person-month was 0.55 cases (95% CI: (-0.62-1.72)) and the rate ratio was 1.37 (95% CI: (0.66-2.91)). With regards to age, the highest frequencies of fracture cases were observed in diabetic patients in their sixties, whereas non-diabetic patients aged 80 and older did not sustain any fracture. Fracture rate, however, was highest in non-diabetic patients in their seventies (3.68 cases per 1000 person-months, 95% CI= (1.65-8.19)). This group of patients had more fracture cases than their counterparts in the diabetic group with relatively comparable person-months of fracture-free observation. With the exception of this age group, fracture rates were consistently higher within age groups of the diabetic arm, compared to the rates within their counterparts in the non-diabetic arm. The incremental nature of rate with age was observed from fifty to sixty-nine years in the diabetic arm and from fifty to seventy-nine years in the non-diabetic arm. The rates were markedly low in patients who are eighty years of age and older, regardless of the group they are assigned to. Gender-specific rates were higher in the diabetic group, and female patients had overall higher rates than male patients.

Overall, person-months at risk of fracture were comparable between the diabetic and the non-diabetic groups in general and among age and gender subgroups of the two arms of comparison, with the exception of the 50-59 years age groups and female patients in the two arms of comparison, which was higher in the non-diabetic arm in both exceptions.

Table 12. Incidence Rates per 1000 Person-months of Fragility Fractures by Diabetes Diagnosis and Stratified by Age Groups and Gender

	Cases	Person-months at risk	Incidence rate (95% CI)
Diabetic	19	9,437.08	2.01 (1.28-3.16)
Age group			
50-59	5	2,691.21	1.86 (0.77-4.46)
60-69	9	4,216.63	2.13 (1.11-4.10)
70-79	4	1,925.49	2.08 (0.78-5.54)
80+	1	603.74	1.66 (0.23-11.76)
Gender			
Women	16	7,800.73	2.05 (1.26-3.35)
Men	3	1,636.35	1.83 (0.59-5.68)
Non-diabetic	15	10,243.33	1.46 (0.88-2.43)
Age group			
50-59	5	4,619.44	1.08 (0.45-2.60)
60-69	4	3,357.29	1.19 (0.45-3.17)
70-79	6	1,630.67	3.68 (1.65-8.19)
80+	0	635.93	0 (-)
Gender			
Women	14	9,117.41	1.54 (0.91-2.59)
Men	1	1,125.92	0.89 (0.13- 6.31)

Appr. CI, confidence interval

4.3.2 Kaplan-Meier Curves and Incident Fracture-free Survival Probabilities

KM curves showing the comparison of incident fracture-free survival estimates between the two groups classified according to the diagnosis of diabetes are provided in Figure 14.

Using the non-parametric KM method in the estimation of incident fracture-free survivorship, it was found that, in the non-diabetic group, survival proportion was 99.70% (95% CI: (97.89%-99.96)) for one year and then dropped to 97.47% (95% CI: (94.99%-98.73%)) and to 94.59% (95% CI: (90.80%-96.85%)) at two and three years, respectively. At 3.5 years, the minimum fracture-free probability was reached with a

proportion of fracture-free patients equivalent to 93.07% (95% CI: 87.55%-96.19%)).

By comparison, fracture-free survivorship estimates in the diabetic group at 1, 2 and 3 years, in this order was: 96.56% (95% CI: (93.87%-98.08%)), 95.12% (95% CI: (92.03%-97.04%)) and 93.76% (95% CI: (90.21%-96.06%)). Minimum fracture-free probability was reached at 3.5 years, with a proportion of fracture-free patients equivalent to 91.89% (95%CI: (85.86%-95.42%)). According to these results and as shown in Figure 14, fracture-free survivorship was high in both groups (stays close to a probability of 1), and specifically higher in the non-diabetic group. In other words, the cumulative fracture probability was higher in the diabetic group.

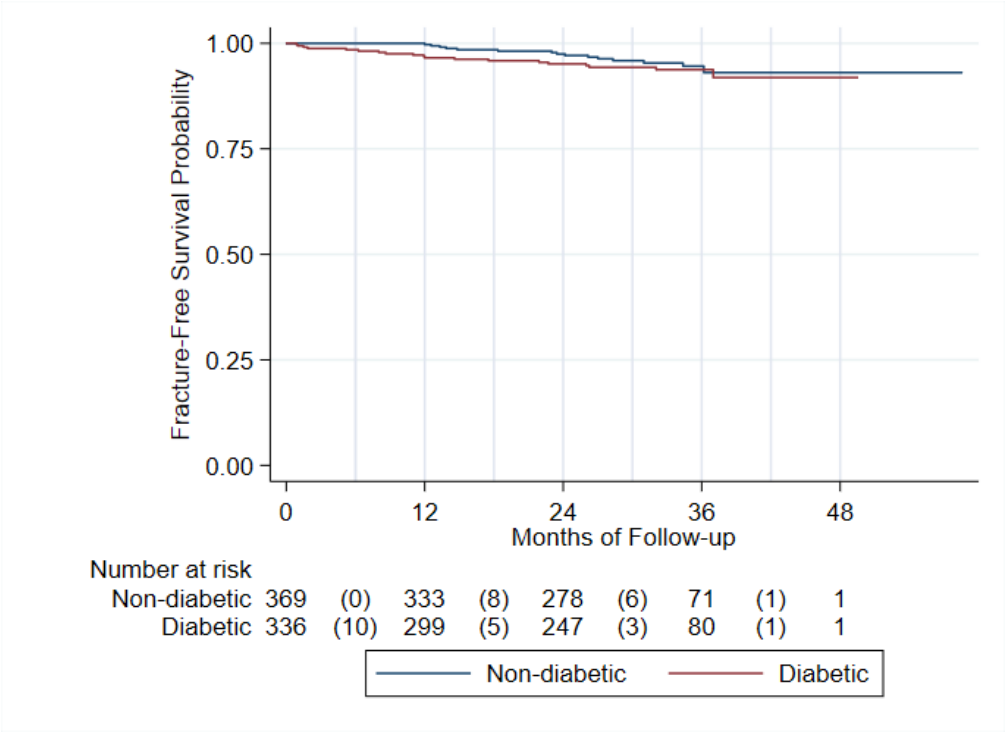

Figure 14. Kaplan-Meier curves of incident fracture-free survival for diabetic and non-diabetic patients.

4.3.3 The Log-rank Test

The difference in incident fracture-free survival distribution between diabetic and non-diabetic patients was evaluated, using the log-rank test of equality in survival

distributions. Results of this test when the comparison was made between the two groups with no stratification made by any other variable are presented in Table 13. The table also illustrates the comparison made by stratifying each group by the levels of diabetes treatment and by the levels of each of the internationally validated risk factors. The latter approach aids our investigation of the confounding properties of these factors to the relationship between diabetes and fracture-free survivorship. The log-rank test results of equality of survival in the levels of the clinical risk factors were reported earlier in section 4.2.3.

As presented in Table 13, survival distributions of the two groups were not found to be statistically significantly different (Chi^2=0.8, df=1, p-value=0.372), i.e., the fracture-free survival was not associated with being diabetic or non-diabetic. The survival curves graphed in Figure 14 do not show much separation, which is consistent with the non-significant findings reported here. Similar results were obtained by the stratified tests by the aforementioned risk factors (Table 13), where statistical significance was not reached to reject the null hypothesis of the equality of survival. Statistically, the survival distributions of the diabetic and non-diabetic groups were not different according to the levels of these potential confounders. The result of the test, stratified by diabetes treatment level, was statistically significant (chi^2= 4.84, df=1, p-value=0.028), suggesting that survival between diabetic and non-diabetic patients is influenced by whether patients were treated for diabetes or not. However, the latter result is most likely biased due to the non-homogenous distribution of diabetes treatment between diabetic and non-diabetic patients (92.84% of diabetic patients were on diabetic treatment before baseline as opposed to 4.88% of non-diabetic patients).

Table 13. Log-rank Test of Equality of Survival Distributions of the Diabetic and the Non-diabetic Study Groups

Log-rank test	Chi-square	P-value
Non-stratified test	0.8	0.372
Stratified test		
Age group	0.5	0.478
Gender	0.91	0.341
BMD category [b]	1.18	0.277
BMI category	1.25	0.264
Previous fracture	0.81	0.368
Corticosteroid use	0.78	0.378
Rheumatoid arthritis	0.78	0.378
Diabetes treatment	4.84	0.028

[a] Degrees of freedom for the Chi-square test=1
[b] Categories were based on the WHO classification using T-scores. Hip T-scores were based on the young normal mean hip BMD of 0.942 (SD 0.122) g/cm^2.
Abbr. BMD, bone mineral density; BMI, body mass index

4.3.4 Cox Proportional Hazards Regression Analysis

Survival analysis is extended here to relate the main predictor (diabetes status) and other risk factors, considered simultaneously, to survival time using Cox PH regression analysis. Table 14 illustrates the results for the univariate analysis, analysis No. 1-where only the relative hazard of fracture between diabetic and non-diabetic groups was considered-and the results of different analyses where diabetes status was considered along with one or a combination of the internationally validated risk factors for fragility fractures, which were listed earlier.

The results are expressed in HRs and their 95% CIs. The Wald test p-value for the significance of the coefficients of diabetes status variable corresponding to each analysis is also provided. The non-diabetic group was chosen as a reference in this comparison (the denominator in HR), and accordingly, HR is represented here as the risk of fragility fracture in the diabetic group compared to that in the non-diabetic group.

In the unadjusted analysis, the instantaneous risk of sustaining a new fragility fracture in the diabetic group is 1.36 times the risk in the non-diabetic group, given that patients survived up until a given time point. The result is not statistically significant (95% CI: (0.69-2.68), p-value=0.374). Adjusting for both age and gender had a negative effect on the relative hazard (HR=1.33, 95% CI: (0.67-2.64), p-value=0.415), whereas adding BMI to the adjustment analysis noticeably increased the relative hazard (HR=1.40, 95% CI: (0.70-2.82), p-value=0.342). The relative risk of fracture barely changed when the total hip BMD T-score variable was added to the risk set.

Testing for interactions between diabetes status and each of the included variables in the model containing all variables (analysis No. 6 in Table 14) using the Wald test, with the exception for the interaction with rheumatoid arthritis, revealed statistically non-significant results for the corresponding variables' coefficients. As for rheumatoid arthritis and diabetes treatment, the coefficients for their interaction with diabetes status were inestimable due to the low number of events in corresponding strata after adjustment. Upon adjustment for age, gender, BMI, BMD T-score, previous fracture, corticosteroids use and rheumatoid arthritis (analysis No. 6), the risk of sustaining a new fragility fracture (the hazard) is 1.44 times higher in the diabetic group as compared to the non-diabetic group. However, this result is not statistically significant as indicated by the 95% CI (0.71-2.93) that includes the null value of 1, indicating that hazards are not statistically significantly different between the diabetic and the non-diabetic groups.

Table 14. HRs for Incident Fragility Fracture for Being Diabetic Compared to not Being Diabetic

Analysis No. [a]	Analysis	HR	95% CI	P-value [b]
1	Unadjusted	1.36	(0.69-2.68)	0.374
2	Adjusted for age	1.31	(0.66-2.60)	0.435
3	Adjusted for age and gender	1.33	(0.67-2.64)	0.415
4	Adjusted for age, gender and BMI	1.40	(0.70-2.82)	0.342
5	Adjusted for age, gender, BMI and BMD T-score [c]	1.41	(0.70-2.84)	0.337
6	Adjusted for age, gender, BMI, BMD T-score, previous fracture, corticosteroids use and rheumatoid arthritis	1.44	(0.71-2.93)	0.314

[a] Analysis is performed for all 705 patients in analyses No. 1-5 and for 703 patients in analysis No. 6
[b] P-value of the Wald test of significance of the coefficient (not shown) of the diabetes status variable for each model presented
[c] Hip T-scores were based on the young normal mean hip BMD of 0.942 (SD=0.122) g/cm^2.
Abbr. HR, hazard ratio; CI, confidence interval; BMD, bone mineral density; BMI, body mass index

4.3.5 Cox Proportional Hazards Regression Analysis Diagnostics

Proportional hazards assumption. Proportional hazards models assume that the relative hazard of the groups being compared is independent of time. For this purpose, investigating the violation of this assumption was considered for the variables included in the fitted Cox PH model (analysis No. 6 in Table 14). The approaches presented below vary between statistical tests and graphical diagnostics, and they assess the model as a whole and the individual variables included in the model.

1. Examination of the KM curves: As shown in Figure 14, the estimated KM curves for the two groups (diabetic and non-diabetic) do not cross for the entire follow-up time, except at the very end where the estimation of survival

probabilities is based on very low numbers.

2. Incorporation of time-dependent covariates in the model: When time-dependent covariates were incorporated in the model of the adjusted analysis No. 6 (Table 14) for all the predictors in the model, the interaction between all covariates and time was not significant (Wald test p-value>0.05), with the exception for the main predictor; diabetes status and for the T-score variable, which their interaction with time was significant (Wald test p-values: 0.026 and 0.019, respectively). Hence, the assumption of proportionality did not hold for the diabetes status and the T-score variables.
3. Schoenfeld and scaled Schoenfeld residuals: Testing if the assumption for the whole model in analysis No. 6 in Table 14, with the covariates specified, using Schoenfeld and scaled Schoenfeld residuals, which were calculated using all explanatory variables included in the model, revealed that the null hypothesis of the global test-that proportionality holds-was to be rejected (Chi^2=18.72, df=8, p-value=0.016). The test indicates that residuals and time seem to be dependent on each other, and violation of proportionality assumption is assumed. When considering each individual covariate, the test was only significant for the diabetes status (*Rho*=-0.457, Chi^2=7.27, Chi^2 d.f.: 1, p-value: 0.007) and BMD T-score (*Rho*= 0.396, Chi^2: 6.67, Chi^2 df=1, p-value=0.010) variables. The result of the examination of the plots of these residuals for the significant variables from the test is provided in Figures 15 and 16. Figure 15 illustrates the plotting of the scaled Schoenfeld residuals of the variable diabetes status against time. Ideally, the smoothed line should follow the horizontal reference line at Y-axis value=0. However, the residuals curve seems to deviate slightly from the reference line, suggesting that the residuals of the variable

diabetes status were possibly associated with time. In general, the variable diabetes status seems to violate the proportionality assumption. Figure 16 illustrates the evaluation of the assumption using the same approach for the variable T-score. The curve for the residuals does not have a slope of zero, also indicating a degree of violation of the assumption.

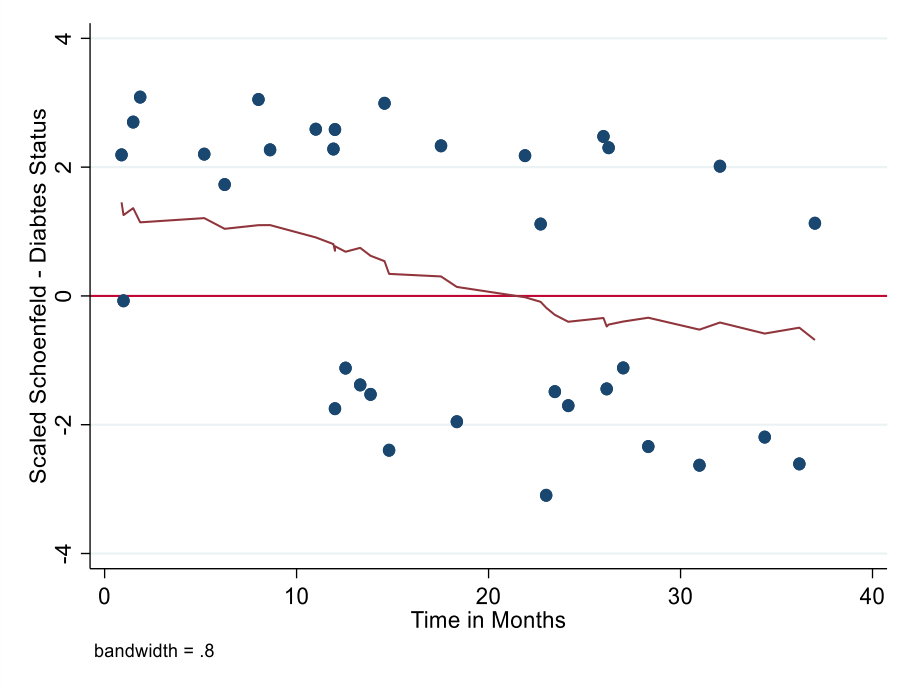

Figure 15. Test of the proportional hazards assumption for the diabetes status variable by plotting scaled Schoenfeld residuals versus time.

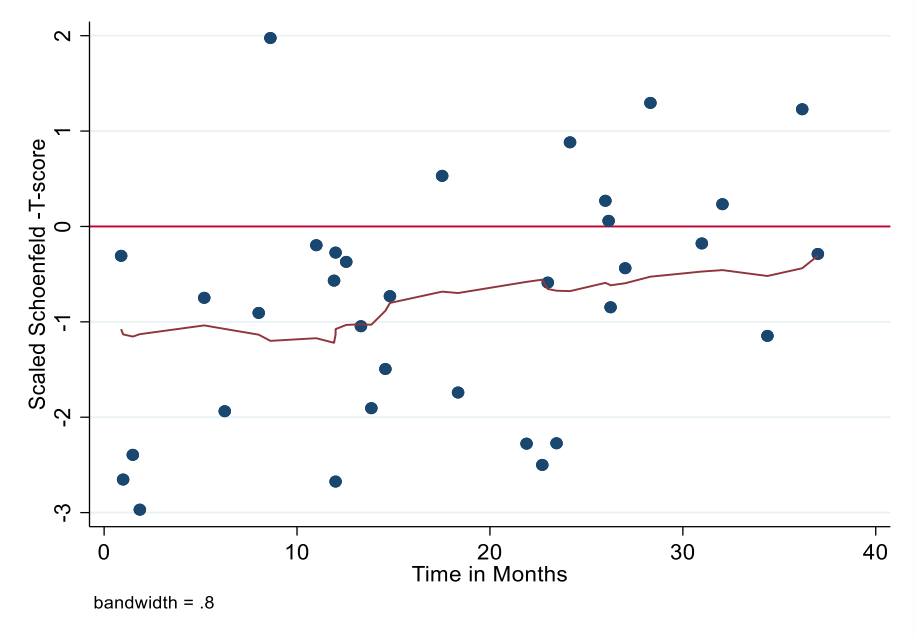

Figure 16. Test of the proportional hazards assumption for the T-score variable in the Cox model that contains diabetes status as the main exposure using scaled Schoenfeld residuals.

4. The log-log plot of survival.: To further investigate the variables diabetes status and BMD T-score, a graphical examination of the assumption was performed for the two variables with **no adjustment** of other factors by plotting the natural log of an estimated survival probability taken twice against the natural log of time; the log(-log(S(t))) vs. log(t). The categorical variable derived from the T-score continuous variable was considered for this approach for appropriateness, as illustrated earlier in Figure 8. The curves for the osteoporosis and the LBM categories are reasonably parallel, whereas the normal category curve does not show the same parallelism with the other two categories. For the unadjusted diabetes status variable (Figure 17), the curves corresponding to each group cross near the end. Overall, the previously presented results indicate that the assumption of proportional hazards could not be fulfilled by the diabetes status and the T-score variables. However, this

violation does not seem to be major.

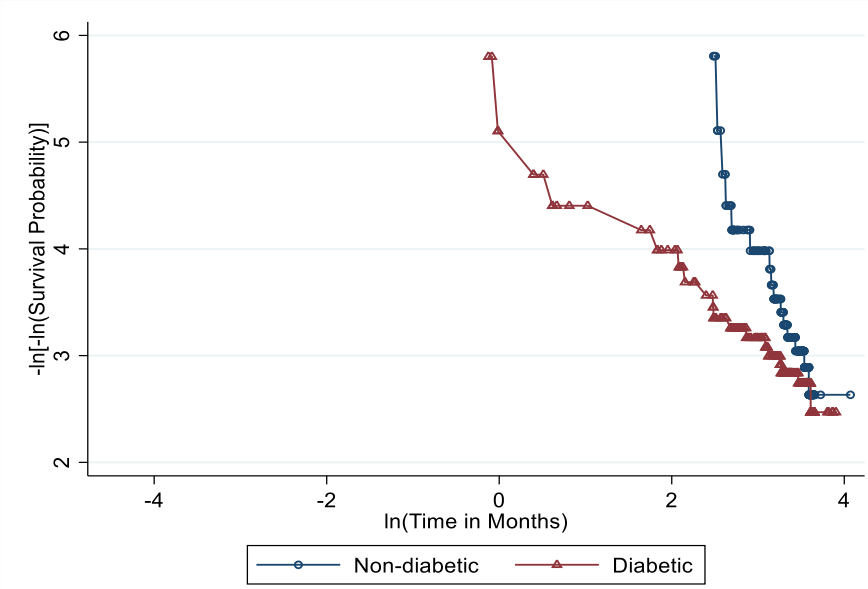

Figure 17. Proportional hazards assumption evaluation for the diabetes status variable using the log-log plot.

Assessing outliers. This was done by plotting the deviance residuals versus the linear predictor. Censored observations are represented as clumps of deviance residuals near 0, and most of the residuals had an SD of 1, as depicted in the graph in Figure 18. The positive values (>1 SD) represent patients that sustained the fracture too soon.

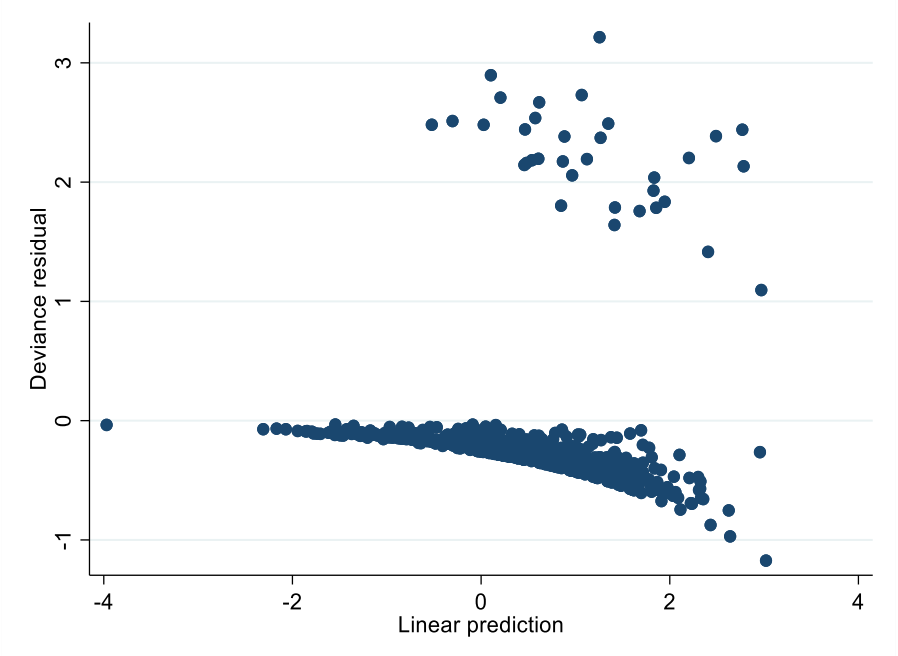

Figure 18. A plot of deviance residuals of the multivariable-adjusted Cox model, obtained by regression of time-to-incident fragility fracture on the diabetes status variable, against linear predictions to investigate the presence of potential outliers.

Assessing influential observations. The influence of a given subject on the coefficient vector of a model as a whole rather than individual variables coefficient was chosen to assess and measure the influence, given that the data is large and there are multiple regressors in the model. This was done using the likelihood displacement values. Figure 19 illustrates the plot of the likelihood displacement values against time, and the points are labeled by the corresponding observation number. Observations No. 639 and No. 403 seem to be influential with likelihood displacement values of 1.315 and 1.033, respectively. The first patient was a diabetic female patient who had rheumatoid arthritis, previous fracture history and did sustain fracture at 12 months of follow-up time, and the second is a diabetic female who was morbidly obese (BMI=66.22 kg/m^2) and who sustained fracture very early in follow-up time. The likelihood displacement values listed here would represent the respective amount of increase in twice the log of the likelihood of the model if these observations were to be

omitted.

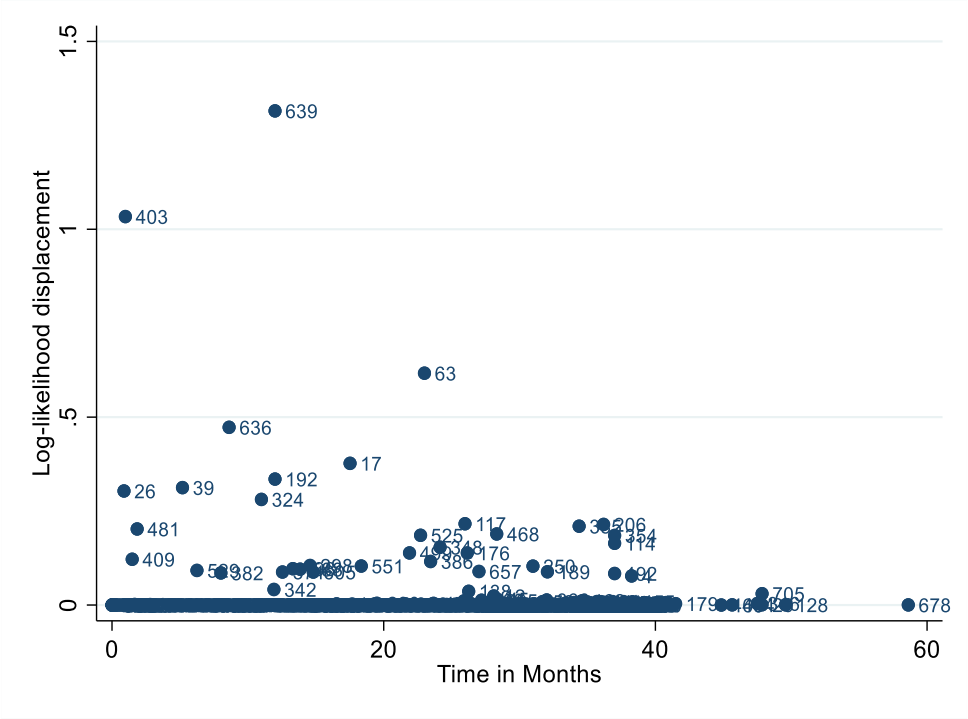

Figure 19. Displacement in the likelihood of the multivariable-adjusted Cox proportional hazards model, obtained by regression of time-to-incident fragility fracture on the diabetes status variable.

Non-linearity test. This was done by plotting the Martingale residuals on the Y-axis against the continuous covariates on the X-axis to detect nonlinearity or, in other words, to assess the functional form of a continuous covariate. The resulting plots for the variables of age, T-score and BMI (not shown) were fairly horizontal and not angling. Thus, the linearity assumption for these variables is upheld.

The goodness of fit of the model. The fit of the model was assessed by examining the Cox-Snell residuals. Figure 20 illustrates the graphing of the Nelson-Aalen cumulative hazard function and the Cox-Snell created variable. By comparing the hazard function to the diagonal line, it is shown that the hazard function follows the 45-degree line. The wiggling at large values of time is not unusual with censored data

and does not warrant concern. This indicates that it approximates an exponential distribution with a hazard rate of one, and we conclude that the model fits the data well.

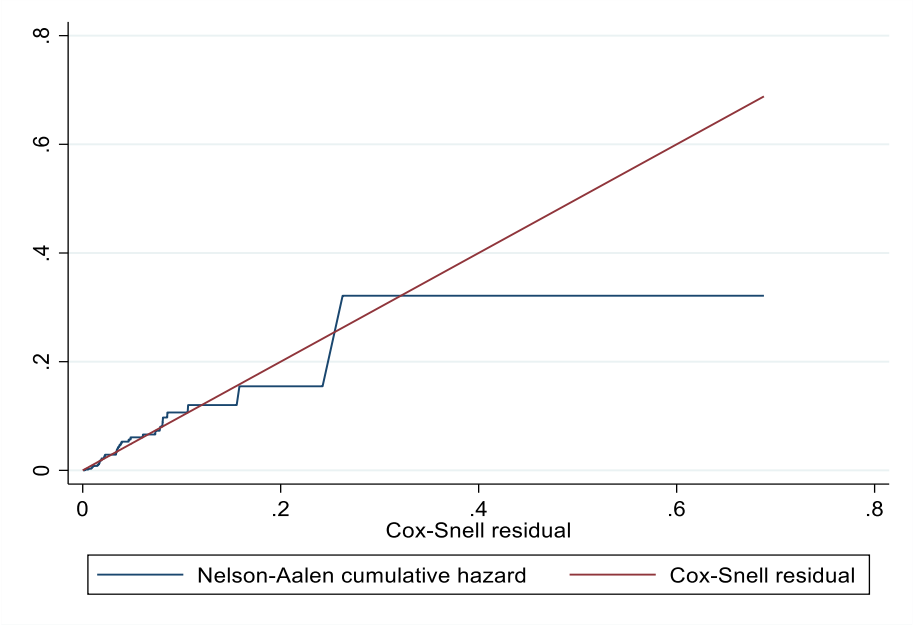

Figure 20. The goodness of fit of the multivariable-adjusted Cox proportional hazards model by regression of time-to-incident fragility fracture on the diabetes status variable using the Cox-Snell residuals.

4.3.6 Adjusted Incident Fracture-free Survival Curves

Figure 21 highlights the relationship between diabetes and osteoporosis. Three adjusted fracture-free curves are presented here; a curve for a diabetic female who has a T-score value of zero (falls into the normal category of BMD), another for a diabetic female patient with a T-score value of -3 (falls into the osteoporosis category) and another who has a T-score value of -3, but does not suffer from diabetes. These curves are generated by adjusting for the other respective explanatory variables in the model, namely, age and BMI (by considering the mean of both variables) and history of previous fracture, rheumatoid arthritis and the use of corticosteroids (by considering the reference value). As shown in the graph, the adjusted survival probability is lowest

for the patient who was classified as having osteoporosis and was diabetic and highest in the patient who only had diabetes but was classified as having normal BMD. The combination of the two illnesses seems to add an additional risk of fracture, compared to when each of the illnesses is experienced alone. With that being said, having osteoporosis alone appears to have a larger effect on survival when compared to having diabetes alone, even after controlling for the other risk factors, as evident by the comparison of the green and the maroon curves.

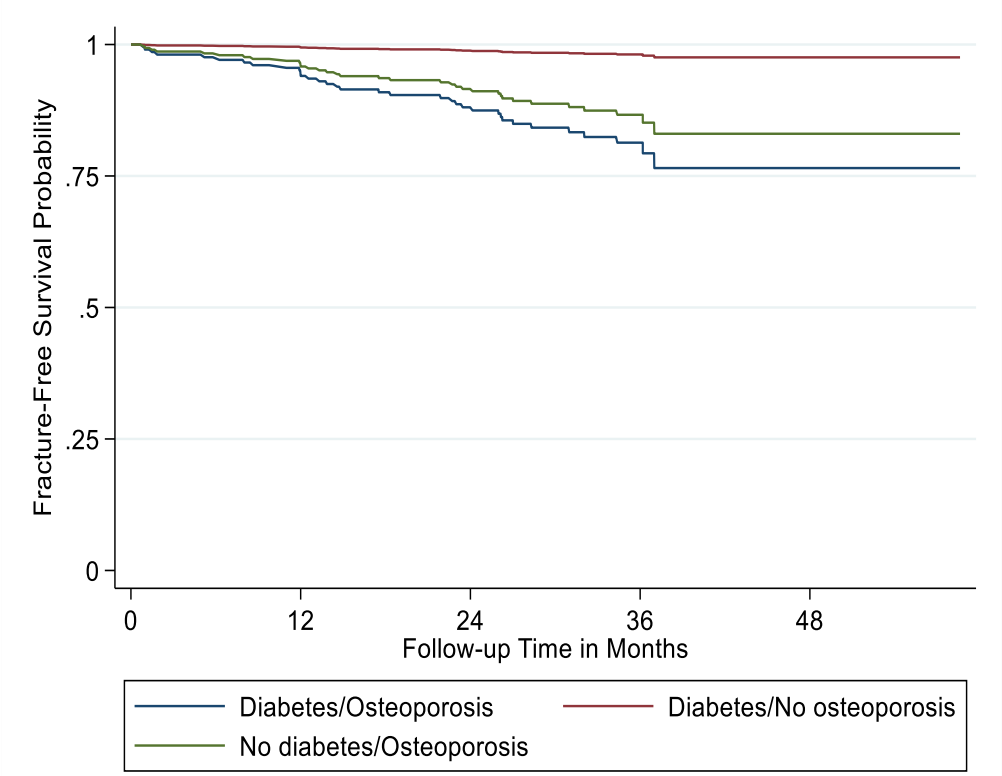

Figure 21. Multivariable-adjusted survival curves obtained from the Cox proportional hazards regression of time-to-incident fragility fracture on diabetes status.

4.4 Comparison of Fragility Fracture Risk Estimates between NHANES and Qatari Databases

A total of 270 patients were analyzed**.** The characteristics of patients at baseline are shown in Table 15. The Median follow-up time was 33.03 months (IQR=9.75), with

a minimum and maximum follow-up times of 1.00 and 58.62 months, respectively. The average BMI was 32.05 kg/m^2 (SD=6.87), which falls under the obese category. Few patients were diagnosed with rheumatoid arthritis (2.59%), whereas 18.52% of patients experienced fragility fracture before baseline. Eighteen patients experienced an incident fragility fracture during the follow-up time. Patients who sustained a fracture were slightly older on average (65.22 years) and had a higher average BMI (34.58 kg/m^2) than those who did not (63.53 years and 31.87 kg/m^2). Only 5.56% of patients who sustained an incident fracture have experienced a previous fracture before baseline. The overall incidence rate of fragility fractures in the study sample was 2.26 per 1000 person-months (95% CI: (1.42-3.58)), for a total of 7,970.79 person-months, denoting the total time at risk of fracture for the total sample.

Table 15. Characteristics of Patients at Baseline, (N=270)

Characteristic	Mean (SD)/n (%)
Follow-up time (months)[a]	33.03 (9.75)
Age (years)	63.64 (9.04)
Height (cm)	154.21 (6.90)
Weight (kg)	76.20 (17.03)
BMI (kg/m^2)	32.05 (6.87)
BMD (g/cm^2)	0.76 (0.15)
Previous Fracture	50 (18.52%)
Rheumatoid arthritis	7 (2.59%)
Corticosteroid use	34 (12.59%)

[a] Median (interquartile range) are presented
Abbr. SD, standard deviation; BMI, body mass index; BMD, bone mineral density

4.4.1 Total Hip BMD T-scores and the Incidence of Fragility Fractures

Table 16 illustrates the comparison between using each of the databases for the young normal total hip BMD reference population in obtaining total hip BMD T-scores and the effect of that on the prevalence of osteoporosis and LBM. The average T-score

of the total sample was lower when the Qatari database was used (-2.21±1.14) as compared to when the NHANES database was used (-1.52±1.21). The difference between the two means was statistically significant (two-tailed paired t-test p-value<0.001). When considering the three groups of BMD status, which are classified based on T-scores, nearly twice as many patients were classified as having osteoporosis when the Qatari database was used (41.85%) as when the NHANES database was used (20%). 44.44% of the study sample were classified as having LBM by the Qatari database, whereas 50% fell under the same category when the NHANES database was used. Overall, the use of the Qatari database yields more cases of osteoporosis and LMB combined. The agreement in classifying patients as having osteoporotic bone or as having non-osteoporotic bone between the two databases was 78.15% (kappa=0.52, p-value<0.001), suggesting that patients are classified differently 21.85% of the time into either osteoporosis or non-osteoporosis category when using the two different databases.

Table 16. T-scores and Proportion of Patients with Osteoporosis and LBM Using either NHANES or Qatari Databases, (N=270)

Total hip BMD	NHANES database	Qatari database
	Mean (SD)/n (%)	
T-score	-1.52 (1.21)	-2.21 (1.14)
Normal	81 (30%)	37 (13.70%)
LBM	135 (50%)	120 (44.44 %)
Osteoporotic	54 (20%)	113 (41.85%)

Abbr. NHANES, National Health and Nutrition Examination Survey; BMD, bone mineral density; SD, standard deviation; LBM, low bone mass

Incident fractures were more prevalent in the osteoporosis group when using the Qatari database and more prevalent in the LBM group when the NHANES database was used. Time at risk in person-month units within the osteoporosis, LBM and normal groups using both methods is provided in Table 17. The comparison of the incidence rates of fragility fracture among BMD groups (based on the dichotomized or the categorical T-score variable) classified according to each of the two databases is also provided (Table 17). Both classification approaches result in incidence rates that are higher in the patients who were identified, by the corresponding approach, as having osteoporotic bone, followed by those who were identified as having LBM. However, the rate in patients classified as having osteoporosis by using the NHANES database (4.62 cases per 1000 person-months, 95% CI= (2.20-9.70)) was higher than that when the classification of osteoporosis was based on the Qatari data (3.37 cases per 1000 person-months, 95% CI: (1.87-6.08)).

When comparing the incidence rate difference between the osteoporosis group and the rest of the cohort using the NHANES database and the Qatari database, the difference per 1000 person-months was 2.92 cases (95% CI: (-0.65-6.49), p-value=0.052) and 1.88 cases (95% CI: (-0.39-4.16), p-value=0.093), respectively. To interpret this in risk terms, patients classified as having osteoporosis compared to the rest of the cohort, had 2.92 additional cases and 1.88 additional cases of incident fractures per 1000 person-months when using the NHANES database and the Qatari database, respectively. The excess risk is higher in the former approach; however, these results did not reach statistical significance as evident by p-values and by the CIs that contain the null value of zero. The respective incidence rate ratios of the osteoporotic bone group to the non-osteoporotic bone group, using NHANES and Qatari databases, were 2.71 (95% CI: (0.89-7.67)) and 2.27 (95% CI: (0.80-6.89)).

Table 17 also illustrates the comparison between the two databases in terms of osteoporosis AF and PAF. 63% of incident fracture cases in the osteoporosis group could be attributed to having had osteoporosis (AF=0.63, 95% CI= (-0.12-0.87)), when the NHANES database was used, compared to 56% fracture cases when the Qatari data was used (AF=0.56, 95% CI= (-0.25-0.85)). PAF was 0.25 and 0.34, using the NHANES database and Qatari database, respectively. This translates into 25% of all fracture cases in the study population being attributable to having had osteoporosis when the NHANES data is used, compared to 34% when the Qatari data was used (CIs are inestimable).

Table 17. Incidence Rate per 1000 Person-months of Fragility Fractures Among BMD Groups, Osteoporosis Attributable Fraction (AF) and Population Attributable Fraction (PAF), Using NHANES and Qatari Databases

	NHANES database		Qatari database	
BMD status	Cases (person-month)	Rate (95% CI)	Cases (person-month)	Rate (95% CI)
Categorical BMD status				
Normal	3 (2397.13)	1.25 (0.40-3.88)	1 (1108.57)	0.90 (0.13-6.40)
LBM	8 (4059.87)	1.97 (0.99-3.94)	6 (3597.37)	1.67 (0.75-3.71)
Osteoporotic	7 (1513.79)	4.62 (2.20-9.70)	11 (3264.86)	3.37 (1.87-6.08)
Binary BMD status				
Non-osteoporotic	11 (6457.00)	1.70 (0.94-3.08)	7 (4705.94)	1.49 (0.71-3.12)
Osteoporotic	7 (1513.79)	4.62 (2.20-9.70)	11 (3264.86)	3.37 (1.87-6.08)
Osteoporosis AF & PAF	Proportion (95% CI)		Proportion (95% CI)	
AF [a]	0.63 (-0.12-0.87)		0.56 (-0.25-0.85)	
PAF [a]	0.25 (.) [b]		0.34 (.) [b]	

[a] Attributable fraction (AF) and population attributable fraction (PAF) are calculated based on the dichotomized total hip BMD T-score variable with a cutoff value≤-2.5 defining osteoporosis.
[b] Confidence intervals are inestimable
Abbr. NHANES, National Health and Nutrition Examination Survey; CI, confidence interval; BMD, bone mineral density; LBM, low bone mass; AF, attributable fraction; PAF, population attributable fraction.

Analysis of receiver operating characteristic (ROC) curve for detecting patients with incident fragility fractures using a T-score≤-2.5 revealed that the sensitivity for identifying patients with fragility fractures in the overall sample was 50% using the NHANES database compared with 23% using the Qatari database. On the other hand, specificity was also lower when using the Qatari database (60%) than when using the NHANES database (82%). The area under the ROC curve obtained from both analyses was similar.

4.4.2 Kaplan-Meier Curves and Incident Fracture-free Survival Probabilities

The rest of the analysis compares survival between the osteoporosis group and the rest of the cohort (grouped according to the dichotomized BMD status variable), using either database.

The comparison of the estimated survival probabilities between patients who were classified as having osteoporosis and those classified as not having osteoporosis by the NHANEs database and by the Qatari database is provided in Table 18. At any given follow-up time point, the probability of remaining fracture-free was lower in the osteoporotic bone group than in the non-osteoporotic group when either of the databases was used. However, survival probabilities were consistently higher when using the Qatari database, regardless of the caparison group and regardless of the time point chosen, with the exception for probabilities at 48 months, which are based on a very low number of observations in both groups, which accordingly could be overlooked. These results indicate that using NHANES yields a higher cumulative incidence rate of fragility fracture at any given time point. At 95% confidence level, estimates obtained in the osteoporotic bone group are more precise when the Qatari data was used, owing to the larger number of patients identified in this group when the Qatari data was used.

Table 18. Comparison of Incident Fracture-free Survival Probabilities at Specific Follow-up Timepoints Between Patients with Osteoporotic Bone and Patients with Non-osteoporotic Bone, Using NHANES or Qatari Databases

Follow-up time	Database	Osteoporotic	Non-osteoporotic
		Probability (95% CI)	
12 months	NHANES	0.943 (0.834-0.981)	0.995 (0.968-0.999)
	Qatari	0.964 (0.906-0.986)	1.000 (-)
24 months	NHANES	0.856 (0.721-0.929)	0.985 (0.956-0.995)
	Qatari	0.914 (0.841-0.954)	0.993 (0.953-0.999)
36 months	NHANES	0.856 (0.721-0.929)	0.944 (0.893-0.971)
	Qatari	0.892 (0.813-0.939)	0.952 (0.884-0.980)
48 months	NHANES	- [a]	0.897 (0.794-0.950)
	Qatari	- [a]	0.885 (0.739-0.952)

[a] Inestimable probabilities for the remaining single censored observation.
Abbr. NHANES, National Health and Nutrition Examination Survey; CI, confidence interval.

Figure 22 depicts the four estimated survival curves, two (blue and maroon) represent estimation utilizing the NHANES database and the other two (green and orange) represent estimation using the Qatari data. Overall survival is higher in the non-osteoporotic bone group as compared to the osteoporotic group using either database. Fracture-free survival was highest in the non-osteoporotic bone group (lowest fracture probability) using the Qatari data, and was lowest in the osteoporotic bone group (highest fracture probability) using the NHANES database. However, the difference visualized between the groups is larger with the NHANES database, suggesting that this database performs better in terms of separating the survival experience between the two groups. The Y-axis in Figure 22 shows a segment of the probability distribution to allow better visualization of curves.

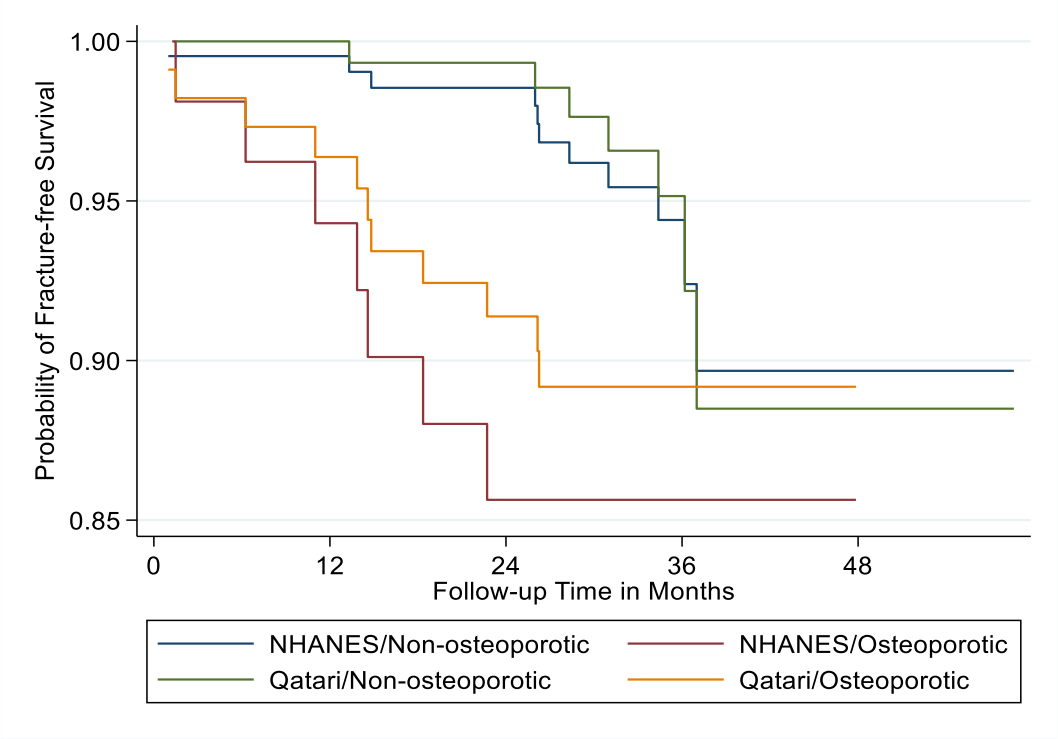

Figure 22. Kaplan-Meier curves of incident fracture-free survival for patients classified as having osteoporotic or non-osteoporotic bone using NHANES or Qatari databases.

4.4.3 The Log-rank Test

The overall test of equality of survival between the osteoporotic bone group and non-osteoporotic bone group yielded a statistically significant result obtained when using the NHANES database (chi^2=4.78, df=1, p-value=0.029) and a non-significant result upon use of the Qatari database (chi^2=3.01, df=1, p-value=0.083). This suggests that survival is statistically significantly different between the two arms of comparison when using the former database. The results from the log-rank test complement the conclusion based on the KM estimated survival probabilities. However, one should consider that all of the aforementioned results represent a crude analysis that overlooks the influence of the remaining risk factors of fragility fracture. The difference in survival among the groups of the other internationally validated risk factors, namely, age, BMI, previous fracture and corticosteroid use, was not statistically significant (p-value>0.05). As for rheumatoid arthritis, very few patients were diagnosed with the

disease in the subpopulation of Qatari women, which did not allow for proper comparison. The difference in survival between patients with osteoporotic bone and those without it, within the groups of the aforementioned risk factors and using the NHANES database was found to be statistically significant (p-value<0.05), suggesting that survival between the two arms of comparison remains different even after these factors are being controlled for.

4.4.5 Cox Proportional Hazards Regression Analysis

The results of the comparison between the NHANES and the Qatari databases in terms of fragility fracture risk estimation based on BMD, at any time point of follow-up with adjustment for the rest of the important risk factors, are provided in Table 19. Total hip T-score variable-upon which the dichotomized BMD status variable was based- was considered in these analyses, and accordingly, relative risk is expressed here as the hazard ratio of incident fragility fracture, per SD reduction in total hip BMD from the young normal (negative T-scores). The rheumatoid arthritis variable was not analyzed due to the very low number of cases, which does not allow estimation. The total sample of 270 patients with complete records was analyzed.

In the unadjusted analysis, the risk (the hazard) of sustaining a new fragility fracture increased by a factor of 1.67 (95% CI: (1.08-2.58), p-value=0.021), using NHANES database, and by a factor of 1.72 (95% CI: (1.09-2.72), p-value=0.021), using the Qatari data, per 1 SD reduction in total hip BMD from the young normal. The result is statistically significant. In general, adjusting for the other risk factors by adding one factor at a time to the previous model had a positive effect on the relative hazard, which was generally higher using the Qatari database, especially when the previous fracture variable was added with a nearly 20% and 30% increase in HR compared to the unadjusted model, using the NHANES database and the Qatari database, respectively.

The relative risk of fracture barely decreased per SD change in BMD from the reference value when the corticosteroid use variable was added to the risk set, using either of the databases. In general, risk estimates for fragility fracture obtained from analyses (both crude or adjusted) that are based on the NHANES data were consistently lower than those obtained upon the use of the Qatari database. However, this difference appears to be negligible, judging by the overlap between the 95% CI of each HR and its counterpart using the other database.

Testing for interactions between the total hip BMD T-score and each of the factors included in the model that adjust for all factors and for interaction between age and previous fragility fracture, using either of the databases, revealed statistically non-significant results for the corresponding interaction coefficient, indicated by the p-value that is more than 0.05. Accordingly, when age, BMI, previous fracture, and corticosteroid use were being controlled for, the risk of incident fragility fracture increases by 1.98-fold and by 2.06-fold, for every SD reduction in total hip BMD, using the NHANES database and the Qatari database, respectively.

Table 19. Risk Estimates of Incident Fragility Fracture Expressed as HRs per SD Reduction in Total Hip BMD (1 unit fall in T-scores) [a] Using NHANES or Qatari Databases

Analysis [b]	NHANES database		Qatari database	
	HR (95% CI)	P-value [c]	HR (95% CI)	P-value [c]
Unadjusted	1.67 (1.08-2.58)	0.021	1.72(1.09-2.72)	0.021
Adjusted for age	1.73 (1.05-2.85)	0.032	1.78 (1.05-3.03)	0.032
Adjusted for age and BMI	1.81 (1.12-2.94)	0.015	1.88 (1.13-3.13)	0.015
Adjusted for age, BMI and previous fracture	2.00 (1.22-3.30)	0.006	2.09 (1.23-3.53)	0.006
Adjusted for age, BMI, previous fracture and corticosteroids use	1.98 (1.20-3.28)	0.008	2.06 (1.21-3.51)	0.008

[a] Total hip BMD T-scores were based on the young normal mean hip BMD of 0.942 (SD=0.122) g/cm^2 using NHANES database and of 1.041 (SD=0.129) g/cm^2 using Qatari database.
[b] All analyses are performed on the total sample of 270 patients.
[c] P-value of the Wald test of significance of the coefficient (not shown) of the total hip BMD T-score variable for each model presented
Abbr. HR, hazard ratio; SD, standard deviation; BMD, bone mineral density; NHANES, National Health and Nutrition Examination Survey; CI, confidence interval; BMI, body mass index

4.4.6 Cox Proportional Hazards Regression Analysis Diagnostics

Evaluation of the proportional hazards assumption of the NHANES-based and the Qatari-based multivariable-adjusted models that included all covariates yielded the following results:

- Examination of the KM curves: As shown in Figure 22, the estimated KM curves for the two groups (osteoporotic bone and non-osteoporotic bone), based on either of the databases, do not cross for the majority of follow-up time.
- Incorporation of time-dependent covariates in the model: When time-dependent covariates were incorporated in the multivariable-adjusted model for all the predictors in the models based on either database, the interaction between all covariates and time was non-significant (Wald test p-value>0.05), with the exception for the main predictor; the T-score variable, that had a statistically significant interaction with time (Wald test p-value=0.012). Hence, the assumption of proportionality did not hold for the T-score variable.
- Schoenfeld and scaled Schoenfeld residuals: Based on either of the databases, the test of the assumption for the whole model, with the covariates specified, using Schoenfeld residuals-which are calculated using all explanatory variables included in the model-revealed that the null hypothesis of the global test, which is that proportionality holds, is rejected (Chi^2=11.56, df=5, p-value=0.041). The test indicates that residuals and time seem to be dependent on each other, and violation of the proportionality assumption is assumed. When considering each individual covariate, the test was only significant for the BMD T-score variable (*Rho*=0.691, Chi^2=9.69, Chi^2 df=1, p-value=0.002). The result indicates that the BMD T-score variable violates this assumption.

The goodness of fit of the NHANES-based and the Qatari-based multivariable-adjusted models was assessed by examining the Cox-Snell residuals. Figure 23 illustrates the graphing of the Nelson-Aalen cumulative hazard function and the generated Cox-Snell variable for the model based on the NHANES database. By comparing the hazard function to the diagonal line, the hazard function follows the 45-degree line for the major part of the plot but deviates slightly towards the end, suggesting that there is a lack of fit of the model to the data. Almost identical results were obtained for the model based on the Qatari data.

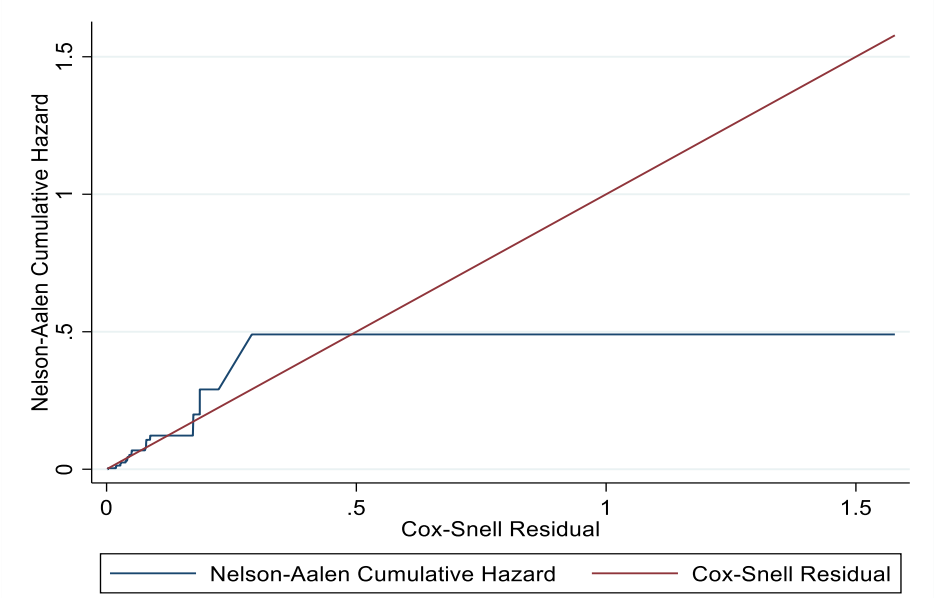

Figure 23. The goodness of fit of the NHANES-based multivariable-adjusted Cox proportional hazards model by using the Cox-Snell residuals.

Chapter 5: Discussion

This study focused on the occurrence and risk of fragility fractures among older patients who underwent DXA scans -requested by different medical disciplines at HMC and for an array of indications-to measure their BMD. The sample of 705 patients was composed mainly of Qatari nationals and female patients and with an average age of approximately 64. On average, the overall cohort BMI fell under the obese category, which was influenced by the mean BMI for the considerably larger proportion of female patients. DM and hyperlipidemia were highly prevalent, whereas cancer, corticosteroid use, previous fracture, and radio/chemotherapy accounted for significant proportions. This entails that this group of patients could be considered, in principle, as a high-risk group. Their representation of the population of community-dwelling individuals who are 50 years or older is limited. Concerning rheumatoid arthritis, it was more prevalent among female patients (4.17%) than among male patients (1.89%) with an approximate woman to man ratio of 2:1, consistent with the known pattern seen in women and men over 60 years old (126).

Male patients were included despite their lower representation than female patients, based on the fact that this demographic group does not receive much attention regarding osteoporosis as a health problem both locally and globally, judging by the amount of literature on osteoporosis dedicated to the two groups. The intent was to shed some light on men's experience in Qatar's population concerning osteoporosis and fragility fractures.

The mean absolute BMD was lower in female patients of the study cohort as compared to the BMD of Qatari or non-Qatari women who are 55 to 60 years old (1.10 ± 0.15 g/cm^2 and 1.06 ± 0.146 g/cm^2, respectively), reported in a cross-sectional study of Qatari and non-Qatari women selected from 9 geographically representative

primary health centers in Qatar, conducted between 2011 and 2012 (127). The study also reported a combined prevalence rate of osteoporosis and LBM among the population studied, of 4% by BMD measurements at the femur, unlike the findings of ours study, where the prevalence of osteoporosis and LBM among female patients was 17.53% and 48.58%, respectively. The difference in prevalence between the two studies is anticipated, given the difference in the population being studied.

Among male patients, on the other hand, the prevalence of osteoporosis and LBM was 7.55% and 38.68%, respectively. The percentages of Qatari male patients with osteoporosis and LBM was 3.13% and 43.75%, respectively, which were lower than what was reported in a study of Saudi Arabian men over 50 years who attended outpatient orthopedic and internal medicine departments (128), where the respective prevalence of osteoporosis and osteopenia was found to be 24.3% and 55.6%. The Saudi study reported that they classified osteoporosis and LBM based on the respective T-score cutoff values corresponding to $\leq$-2.5 and -1 to -2.5 SDs from the adult mean, unlike our study where a female reference was used for male and female patients alike. This may in part explain the higher prevalence rates in the Saudi study despite a similar setting to our study, given that the use of the endorsed female reference in obtaining BMD T-scores for men tends to diagnose more men as having normal BMD, compared to when a male reference is used (129).

5.1 Incidence Rate of Fragility Fractures

A small percentage of the overall cohort sustained a fragility fracture during the follow-up time (4.82%). Patients who sustained a fracture were mostly female and were older, leaner, and shorter, which is consistent with what was reported in the literature review about the factors that are associated with fragility fractures. The overall incidence rate of fractures for the study population was 1.7 cases per 1,000 person-months, which is equivalent to 20.4 cases per 1000 person-years, or 2 cases per 100

persons per 1 year. This means that the 1-year probability of sustaining a fragility fracture for a given patient is 0.2 or 2%. The rate was higher in female patients compared to male patients. These results were similar to those reported by the Rotterdam population-based cohort study of men and women who are 55 years and older, where the incidence rate of all non-vertebral fractures was 18.9 per 1000 person-years, and where women had higher incidence rates as well (130). According to our knowledge, data on the incidence of overall fragility fracture was non-existent in the EMR region. However, incidence rates of hip fractures were reported in several EMR countries, as indicated by the results of the Middle East and Africa regional audit that started in 2011, to assess the burden of osteoporosis in the region (131). It reported that the age-standardized rates of hip fractures, if available, varied according to gender and country, between 250 and 350 fracture cases per 100,000 persons per year for Lebanon, Kuwait, and Iran. Internationally speaking, the majority of encountered published results focused on the incidence of fragility fracture at a specific anatomical site, with hip fractures being the most studied. In our study, the overall number of fragility fractures was very low to allow for a meaningful estimation of the incidence rates of major osteoporotic fractures at different sites.

With regards to incidence rates of fractures in relation to age, the age-specific rates gradually increased from patients in their fifties up to patients in their seventies, which is expected, given that age-related bone loss, which starts in the fifth decade, is an ongoing process in the remaining lifespan (30). As for patients who are 80 and above, they had a relatively lower representation in the sample (6.24%), which is expected as well, given that the at-birth life expectancy in Qatar in 2018 was estimated to be 80 years (132). Moreover, patients in this age group are expected to be less mobile, reducing their risk of falls and, subsequently, their risk of fractures. Concerning gender-

specific rates, female patients had higher fracture rates than male patients in the osteoporosis group and the normal BMD group, as opposed to the LBM group, where men had higher rates by comparison. This again highlights the observation that more men will sustain fracture at higher T-scores, or even at normal T-score when a female reference rather than a male reference is used to obtain T-scores, and emphasize the need to have a more comprehensive approach in the evaluation of fracture risk in men, beyond that which rely solely on T-scores (129).

5.2 Bone Mineral Density and Incident Fragility Fractures

The group-specific incidence rate was higher in the osteoporosis group, followed by the LBM group. The comparison of fracture-free survival experience among the three groups, summarized by the graphical display of the corresponding KM curves, showed that, at all follow-up time points, there was a survival benefit for the normal BMD group, which was higher than that of the LBM and the osteoporosis groups. This difference in survival among the groups was statistically significant. The results mentioned so far are in line with what is known about the impact of having low bone density on an individual's risk of fragility fractures. This does not entail the absence of risk of fractures in individuals with normal BMD measurements; in fact, while the incidence rate was highest in the osteoporosis group-defined by a cutoff T-score value of≤-2.5-, fractures were more prevalent in the LBM category (47.06%). Similar results were found by the longitudinal, observational study of postmenopausal women in the US; the national osteoporosis risk assessment (NORA) (7), that reported a higher incidence rate but a lower prevalence in women with BMD T-scores of≤-2.5, as compared to women with BMD T-scores of≤-2.0. In fact, 82% of the NORA study participants with fractures had T-score values above -2.5. These results have important implications on the two fronts of clinical interventions and public health prevention. Clinically, if the intervention threshold was based solely on BMD measurement, a

significant proportion of fractures that potentially could be prevented will be sustained, creating a healthcare gap, and public health interventions that rely on BMD in identifying people with a high risk of fractures would be less successful. Hence, the incorporation of other factors in fragility fracture risk assessment is of great importance.

There is an abundance in the literature on the relation between BMD and fracture risk that dates back to the eighties. However, the results of many prospective studies indicate that for every SD reduction in BMD, fracture risk increases by 1.5 to 3 folds (5, 65). A meta-analysis of prospective cohort studies that were conducted approximately between the mid-eighties and the mid-nineties, which had baseline BMD measurements for the female participants of these studies, had the relative risk of fracture for 1 SD reduction in BMD-adjusted for age-as the main outcome (5). The obtained estimates-mainly by Cox PH or logistic regression-showed that the overall age-adjusted pooled estimate for all types of fractures was 1.5 (95% CI= (1.4-1.7)). This result was obtained for BMD measurements at calcaneus bone using ultrasound techniques. The estimate was 1.6 (95% CI= (1.4-1.8)) for measurement at the hip by techniques other than ultrasound (5). However, the obtained relative risk estimates for all fractures in individual studies included in the meta-analysis varied from 1.1 to 2.4. The authors reported that the choice of BMD measurement site was, in general, not associated with the ability to predict fractures. In addition, their findings showed that follow-up time was not associated with the main outcome. The findings of our study emphasize the consistency of BMD predictive ability of fracture risk, regardless of the ethnicity of the population being studied. Indeed, this predictive ability persisted even after controlling for factors that have a BMD-independent association with fragility fractures. The result obtained by our study (age-adjusted HR=1.91 (95% CI: (1.36-2.68)) is higher to some extent, relative to the pooled estimate reported by the meta-

analysis for all fractures. One possible explanation for this difference is that "all fractures" estimates reported from the different studies included represent estimates for different distributions of fractures sites. In our study, the combined group of fragility fractures are predominated by fractures of the foot/ankle and fractures of the wrist, while the included studies in the meta-analysis assessed different combinations of sites.

A point to consider here is that while the sample size in our study (705 patients) was considered large enough to obtain risk estimates that are reliable- which translates into enough power to detect significant covariates that influence fracture-free survival-, the power in survival analysis techniques depends on the number of events (133). This is especially problematic when the number of events is low (as in this study), and the incorporation of several covariates is intended. The results of simulation analyses suggest that the number of events for each covariate considered should be at least 10, and any number that is less than that warrants caution in the interpretation of the Cox PH model results (134). Considering the latter point, since 34 fracture cases were encountered during the follow-up period, the HR estimates for BMD adjusted for age and gender have more validity as compared to estimates from all the remaining models that incorporated additional covariates.

Our study found an unexpected result for the estimated HR of experiencing previous fragility fractures as compared to not experiencing them. This suggests a good prognosis in the former case, which contradicts what is known of the association between previous fractures and incident fractures. The analysis was based on four patients in the strata that contained event cases with previous fracture cases, as compared to 30 patients in the strata that contained event cases with no previous fractures, which resulted in bias in the estimate. Moreover, the fact that incident cases among patients who experienced previous fractures (3.42%) were less than incident

cases among patients who did not experience previous fractures (5.10%) may reflect, in part, differences in patients' and health care providers' attitudes and interventional efforts related to this health issue between the two groups of patients.

The findings from our study related to this section indicate that individuals who have osteoporosis sustain fragility fractures more quickly than individuals who do not have osteoporotic bone; however, the prevalence of fracture cases was highest in the LBM group. Additionally, the crude risk of fragility fractures increases by a factor of 1.82 (95% CI: (1.34-2.48)) for each SD reduction in total hip BMD from the young normal, and by approximately two folds when age is being controlled for.

5.3 Diabetes Mellitus and Incident Fragility Fractures

The incidence rate in the diabetic group was 2.01 per 1000 person-months (or 24.12 per 1000 person-years), and in the non-diabetic group was 1.46 per 1000 person-months (17.52 per 1000 person-years). Among female patients, the rates per 1000 person-years were 24.60 and 18.48 in the diabetic and the non-diabetic groups, respectively. Similar findings were reported in the study of osteoporotic fractures (SOF) (135), which is a US population-based prospective cohort study of women who are 65 years or older, where the rate per 1000 person-years of all-nonvertebral fractures was higher among insulin-treated (58.7) and non-insulin treated (43.4) diabetic women as compared to non-diabetic women (36.5). The fracture rates from the SOF study are higher in general as compared to our study, in part, due to the longer duration of follow-up in the former study (average follow-up of 9.4 years). A similar result was found with regard to vertebral fractures.

The fracture rate was higher in the diabetic group in the age groups 50-59 years and 60-69 years, as compared to the non-diabetic group, with an observed increase in fracture rate with increasing age, regardless of the comparison arm, which is consistent with the fact that increasing age poses a risk for fractures in general and in diabetic

patients specifically. However, non-diabetic patients in the age group 70-79 years had higher rates than their counterparts in the diabetic group. In fact, they had the highest rate in all groups. Analysis of the distribution of gender, osteoporosis, BMI, weight, previous fracture, and follow-up time revealed that these distributions were comparable in this age group in each of the diabetic and the non-diabetic arms. However, cancer and corticosteroid use were slightly more prevalent in the non-diabetic arm. The differential distribution of these two clinical factors or any other relevant factor that is unknown to us could explain this apparent observation.

There was a statistically significant yet small-in-magnitude fracture rate difference between the two arms of comparison, and the rate was 37% higher in the diabetic group relative to the non-diabetic group. These results are emphasized by the visualization of the KM curves for the two groups, where time-to-fracture was slightly lower in the diabetic group. The difference in the survival distribution of the two groups was statistically non-significant.

Diabetic and non-diabetic patients were similar in terms of average BMD and the prevalence of osteoporosis; however, diabetic patients were heavier and had a slightly higher BMI, which is consistent with what is known about that association between diabetes and obesity. In addition to obesity, hyperlipidemia and CADs were more prevalent in the diabetic group, representing the common association found in metabolic syndrome-or syndrome X-that is constituted by abdominal obesity, resistance to insulin, hyperlipidemia, and hypertension (136). CKD was more prevalent in the diabetic group, consistent with what is known about diabetes and its renal complications. On the other hand, caner, chemotherapy, and radiotherapy were more prevalent in the non-diabetic group. All of these factors are associated with fragility fractures to some degree, as previously delineated, and their unequal distribution might

potentially influence the risk estimates obtained by the performed Cox models. However, given the fact that we had a small number of events, we were only able to adjust for risk factors that are validated internationally with a non-BMD-dependent effect.

The evaluation of the risk of incident fragility fractures in diabetic patients relative to non-diabetic patients revealed that diabetic patients had 36% and 33% higher risk of sustaining a fragility fracture in the crude and in the age-and-gender adjusted analyses, respectively. Adjusting for BMI increased the relative hazard between the two groups (HR=1.40), which implies the protective role that BMI has in the occurrence of fractures that confounded the relationship between diabetes and incident fragility fractures. However, all of these results did not reach statistical significance. A similar relative risk estimate was reported among the men and women who are 55 years and older in the Rotterdam Study that assessed the association between diabetes and the risk of fractures (137). The reported gender-combined crude HR for non-vertebral fractures comparing diabetic to non-diabetic was 1.36 (95% CI: (1.10–1.67)). The risk analysis comparing insulin-treated diabetic women to non-diabetic women in the SOF study (138)-mentioned earlier in this section-reported an age-adjusted HR that equals 1.26 (95% CI: (0.56-2.82)), which is lower than the age-adjusted HR reported in our study (HR=1.31). Also, the risk of fractures in the diabetic group in the SOF study increased after adjusting for BMI and BMD, which is similar to the result reported here. The multivariable-adjusted analysis in the two studies was composed of different combination of covariates, as in the case of most observational studies, which deemed the comparison with our results from the multivariable-adjusted model inappropriate. In the EMR region, a Lebanese case-control study of men and women above 50 years, reported an association between diabetes and hip fractures in the bivariate analysis

(139).

The statistical non-significance for the estimates in our study could be attributed to the low number of events that did not allow for the estimation of a rather significant coefficient or could be due to a true lack of significance of the diabetes coefficient in the general population. Over 90% of all diabetic patients received treatment for the condition, rendering the investigation of a modifying effect of diabetes treatment in the association between DM and incident fragility fractures less relevant.

Worth mentioning here is that the observation that osteoporosis prevalence and average BMD measurements were comparable between the groups (slightly lower BMD measurements and higher osteoporosis prevalence in the non-diabetic group), and that the risk estimates from the Cox PH analysis did not significantly change after adjustment for BMD, suggest that there may be other mechanisms apart from the loss of bone density, by which diabetes affects bone health. In fact, it has been found that absolute BMD measurements measured by DXA are higher in diabetic patients as compared to those without diabetes; counterintuitively, fracture risk increases among the diabetic population (140). One possible explanation is that chronic hyperglycemia affects bone quality through certain underlying pathological mechanisms related to bone biology (141). Additionally, the tendency to fall is assumed to increase in diabetic patients owing to its complications related to loss of vision and peripheral neuropathies (142), such as those related to balance and gait. Moreover, while higher BMI and obesity, which are usually more observed in diabetic patients as observed in our study, are assumed to be protective against osteoporosis, they have a site-specific fracture risk that does not depend on bone loss at specific sites (143). For example, obese people have a lower risk of proximal femur and vertebral fractures and a higher risk of other fractures such as upper leg, proximal humerus and ankle fractures.

According to the findings of our study related to this section, diabetic individuals sustain fractures more quickly than non-diabetic individuals over a span of nearly five years, and diabetes appears to be associated with an increased risk of fracture. However, the answer to whether this association represents a true relationship between diabetes and the risk of fragility fractures in the general population of older adults remains equivocal.

5.4 Comparing the Performance of the NHANES and the Qatari Databases in Relation to Fragility Fracture Risk Estimates

The secondary objective considered the effect of choosing a reference population with a similar ethnic background to the population under study (the Qatari database) as compared to a Caucasian reference population (the NHANES database) in obtaining BMD T-scores and the consequent classification of patients as having osteoporotic bone, on the risk of fragility fractures. Using the endorsed standard reference of a woman for men is reasonable so long the interest lies in fracture risk assessment since both genders have the same fracture risk for the same BMD. However, and as stated earlier, this practice tends to diagnose more men as having normal BMD, compared to when a male reference is used (129), owing to the fact that men, in general, have higher PBM than women. Our interest was in detecting fracture cases based on the diagnosis of patients as having osteoporotic bone, made by either of the databases. If we were to include men in the study, a proportion of male patients would potentially have been misclassified. This proportion would be different according to each database, and this will bias the results. In addition, this proportion in Qatari men is not known since there is no normative Qatari data available for men. Accordingly, Qatari male patients were excluded from the analysis.

The subpopulation of Qatari female patients was similar to the group of female patients in the overall cohort in terms of average age, height, weight, BMI, and absolute

BMD measurements. These attributes were also similar between the two groups, in the proportion that sustained a fragility fracture during follow-up time, with the exception of weight and BMI, which were higher in the proportion who experienced the fracture in the Qatari subgroup. The controversy of the role that BMI plays related to fracture risk has been reported before (144, 145), where dividing weight into its components of lean mass and fat mass complicates the association between BMI and fractures (145). Also, it has been suggested that the role of BMI in fracture risk is site-specific (146). However, no significant differences were found in the distribution of fracture sites between the two populations.

The analysis of the Qatari female subgroup revealed that the incidence rate was higher in patients with osteoporotic bone as compared to the rest of the cohort regardless of the database used. However, the rate difference was higher upon the use of the NHANES database, despite the fact that using the Qatari database identified more patients as having osteoporotic bone. These results are emphasized by the results of the ROC curve analysis, where the use of the NHANES database was proven to be more sensitive and more specific, which translates into a higher ability to capture all true fracture cases and less tendency to capture non-fracture cases. This makes the NHANES database superior to the Qatari database in terms of the overall capture of incident fracture cases. These results are mirrored by the result of the attributable fraction among the exposed-a very relevant measure in clinical settings-that was higher upon the use of the NHANES database. This implies that, among people who are diagnosed with osteoporosis, more fractures would be prevented or at least would be sustained less often-given ideal treatment-if the diagnosis was based on the NHANES database rather than the Qatari database.

Additionally, the probability of remaining fracture-free at different follow-up

time points was lower upon the use of the NHANES database, where the better separation of the survival experience of patients with osteoporotic bone from that of patients with non-osteoporotic bone was achieved. Conversely, the HR of fragility fractures for each SD reduction in BMD was higher, using the Qatari database. This is due to the fact that one SD reduction from the young normal is equal to 0.129 g/cm^2 using the Qatari database, which is larger than that of the NHANES database (0.122 g/cm^2). However, it is important to consider that HR is a relative measure and does not provide an estimate of the absolute risk of an individual (6).

Similar findings were reported by two Lebanese case-control studies that assessed the probabilities of hip and vertebral fractures (147, 148), using the NHANES database and a population-based database. The NHANES database was found to be more sensitive (45%), as compared to the Lebanese database (25%), in detecting prevalent hip fracture cases in the population of Lebanese elderly women. However, specificity was slightly higher using the Lebanese database (87% compared to 80% with the NHANES data). Similar findings were reported for vertebral fractures. Given the nature of the health outcome being assessed, that is, fragility fractures, sensitivity has greater importance than specificity.

The results from our analysis indicate that database selection influences the identification of fracture cases to a large extent and that the use of the NHANES database is superior to the use of the Qatari database in identifying elderly Qatari women who would sustain fragility fractures. However, it is important to consider that this comparative approach overestimates the role of BMD and underestimates the role of other important factors in fracture risk assessment, a fact that is evident by the low sensitivity obtained from the use of both databases.

It is also important to consider that the focus of our analysis was fracture risk,

which is reasonable, considering that fractures are what constitute the burden of osteoporosis and not osteoporosis itself. However, if the interest were to lie on the diagnosis of osteoporosis, which is less likely the case, the Qatari database would have been superior. This is due to the fact that the use of the NHANES database inherently underestimates osteoporosis, given that the comparison, in this case, is against the normal Caucasian BMD, which is lower than that of the normal Qatari BMD. This observation is mirrored in the result of the population attributable fraction, which was higher using the Qatari database. This implies that more fracture cases would be prevented in the overall population if osteoporosis were to be addressed in the general population, which poses a challenge given the silent nature of the disease.

5.5 Study Strengths

The study had shed light on fragility fractures in the elderly population of Qatar, which is one of the most significant outcomes related to osteoporosis. Additionally, the study assessed the status of osteoporosis and fragility fractures among the male population, a demographic group that receives less attention from the global and local body of research in these areas. Also, many methodological issues related to bias and confounding were addressed to allow for sound inferences. An example of attempting to avoid misclassification bias is that the establishment of the diagnosis of osteoporosis and LBM was based on BMD measurements obtained from DXA, which is the gold standard diagnostic tool. Additionally, BMD T-scores were derived from BMD measurement of the total hip, which is an adequately reliable site in terms of establishing the diagnosis of osteoporosis as well as predicting fracture risk. Also, T-scores were calculated utilizing a single standard reference population, accounting for the difference in the obtained BMD T-scores upon the use of different reference populations and across time. Moreover, data on a lot of important risk factors that are associated with either osteoporosis or diabetes and the increased risk of fractures was

obtained, and many of the internationally validated risk factors were analyzed for their potential confounding properties.

5.6 Study Limitations

There are several limitations to our study, which are to a larger extent due to the study nature being retrospective and relying on secondary data that was not documented for research purposes. For example, since the Cerner HER system was implemented at HMC around mid-2016, and the reporting of patient's clinical data was of lower quality before that time point, we made the decision to include patients who had DXA scans performed after that time point and not earlier. As a result, the average follow-up time for the overall cohort was relatively short (29 months), which did not allow for enough events to occur. Accordingly, we encountered a heavy rate of censoring, given that a small percentage of patients (4.82%) sustained a fragility fracture during their follow-up time. The remaining patients were right-censored at the time of their last encounter before the end-of-study date, which was arbitrarily and consistently set for the examination of the occurrence of fractures for all patients. Reasons for why "the last encounter date" for a given patient was sooner rather than later and vice versa, in relation to the end-of-study date, with the exception for patients who encountered death, could not be ascertained, given the retrospective nature of the study. These reasons could potentially be that patients are no longer residing in the country, they were not assigned for a next follow-up appointment, they were assigned for a next follow-up appointment, but they missed them, or any other unknown reason. Moreover, patients might still have had future encounters beyond the study time scope. Accordingly, we had to assume a non-informative censoring, where censoring times and survival times are not associated, to allow the utility of survival analysis methods that take into account censored times. However, the very high censoring rate, which represents a loss of information, is a potential source of bias in the study findings.

Death represents a competing risk for the incident fragility fractures, in the sense that patients who died before sustaining a fragility fracture during follow-up time are no longer considered at risk of sustaining fragility fractures and, accordingly, should no longer contribute to survival time passed their death. Competing risk events could potentially bias the estimation of risk if they were not considered in survival analysis. However, when the incidence of these events is small, the bias inflicted by overlooking them is also small (149). During follow-up, 11 patients had a documented death in their health records representing a small percentage (1.56%). These patients represent those who died in the state of Qatar. Presumably, some patients might have died abroad for any given reason, whom their proportion is not known. Accordingly, death was treated as a loss of follow-up, with the assumption that the overall incidence of death was small.

Power in survival analysis, as previously mentioned, is dependent on the number of events rather than the sample size. If the number of events per independent variable is less than 10, the estimated coefficients for these variables in the regression analysis becomes less accurate and less precise (150, 151). The fact that a small number of events occurred during follow-up potentially limits the validity of the estimates obtained by the multivariable-adjusted Cox models. It also limited the ability to assess fragility fractures according to their anatomical site, which subsequently limited the comparison of our findings with other studies that focused on a single site. Additionally, it limited the ability to stratify the Cox PH analysis by gender, which would have been ideal for estimating a gender-specific risk, allowing for proper comparison with other related studies.

A post hoc analysis of the sample size and the number of events required to reject the null hypothesis of the Cox PH model-that the regression coefficient equals zero-for the BMD T-score variable was performed. The following parameters were

used in the calculations for a two-sided hypothesis test: effect size (regression coefficient) =-0.601, squared multiple correlation coefficient (R^2) =0.2621, α=0.05, β=0.20, SD of T-scores=1.22 and event probability=0.048. The required sample size and event number to achieve 80% power were 412 and 20, respectively. The actual power given 34 events was 95%. The analysis was performed using the command "power cox" in Stata, which utilizes the method of Hsieh and Lavori (152).

Additionally, the PH assumption for the Cox models was violated for the T-score variable and the diabetes status variable according to the Shoenfeld residual test, which means that each of the variable's hazard ratio change with time. This may indicate that there is more than one estimate for each of the variable coefficient over time (153), which could lead to issues related to the accuracy of the obtained estimates. However, the PH assumption for the model based on the T-score variable, as a whole, was upheld, which may indicate that the violation by the T-score variable was corrected for by one or a combination of the other explanatory variables in the model. The KM curves for the groups of the two violating variables did not cross, suggesting that there's no major violation of this assumption. However, this method, as all other graphical methods, is subjective. On the other hand, the p-value of the Shoenfeld residual test depends on sample size, and for a large sample size, even a small violation of the assumption will be significant (non-proportionality might be overemphasized), and vice versa (120). Accordingly, we relied on both visual examinations and statistical tests to evaluate this assumption. In general, the violation was not major with the two variables, but it is more worrisome with the diabetes status variable. In cases of violation of the assumption, some methods can be used to account for this issue. Stratifying the Cox model by the violating variable is one example (120); however, since in both scenarios, the violating variable was the main exposure variable, this approach was not

considered. Another approach is to split follow-up time at certain points and obtain HRs specific to the time interval between time points; however, this approach does not provide a clinically meaningful interpretation of the risk estimate. One of the advantages of the Cox PH model is that it can accommodate time-varying predictors (113). Ideally, if we were able to collect BMD measurements at different time points of follow-up, then we would be able to estimate the HR by incorporating all measurements.

The significance of the PH assumption is debated; some emphasize its importance, while others consider that when the assumption is violated, HRs could represent the average effects during the follow-up time (154).

Bias, due to a decrease in the comparability among the groups being compared of the two exposure variables, BMD status and DM status, was inherent by choosing an internal comparison group(s). However, data on many of the risk factors and relevant characteristics of patients that could potentially influence the association between the main exposure variables and incident fragility fractures were collected and assessed for their differential distributions among the arms of comparison. As far as the adjustment of potential confounders, the small number of events impeded the adequate control of the many factors that are associated with the outcome. Accordingly, we limited our adjustment analyses to covariates that are internationally validated to have BMD independent risk via individual meta-analyses, yet some of these covariates were not attainable, which include smoking history, drinking alcohol, and family history of fractures.

Other important factors that were not attainable for collection due to lack or inconsistency of the information on the specific factor are those related to the risk of falls and the treatment with anti-osteoporotic drugs. Assessment of compliance to

treatments, in general, was challenged by the record-based nature of the study, especially in the case of anti-osteoporotic drugs that are commonly administered in an injectable form and in dosages that are separated by time. The lack of information about the use of anti-osteoporotic medication and factors related to the lifestyle such as physical inactivity and smoking poses a potential source of bias in our results regarding fracture rates and the gradient of risk of fragility fracture. This is given the assumption that subsequent to BMD testing, the attitudes of patients and their management are expected to differ in comparison to individuals whom their BMD statuses are not known.

Additionally, information on diabetes complications other than those collected, such as vision impairment and peripheral neuropathies that influence the risk of falls, were not consistently reported. With regards to vitamin D status, not all patients had measurements of serum vitamin D within three months around the BMD test. In a systematic review that assessed vitamin D insufficiency/deficiency in Qatar between 1980 and 2012, the estimated prevalence of low vitamin D was 90.4% (102). Thus, it is very likely, that the prevalence of low vitamin in our study sample was as high or even higher than the reported estimate.

Another limitation is that the distinction between type 1 and type 2 diabetes mellitus was not made due to inconsistent reporting. This could be in part due to the fact that the onset of type1 diabetes is in childhood and adolescence. However, given the fact that type 2 diabetes accounts for 95% of the incidence of diabetes (85), making type 1 diabetes far less prevalent, patients with documented diabetes in our study sample are most likely to be type 2 diabetics. Additionally, the duration of diabetes, which potentially modifies the effect of the disease on fragility fracture risk, could not be ascertained owing to poor reporting.

With regards to vertebral compression fractures, only symptomatic fractures were considered since the onset of vertebral fractures is usually not known; in fact, two-thirds of patients with these types of fractures have no symptoms, and they are discovered by chance (110). Accordingly, the number of these fractures in our study might be underestimated.

Information regarding menopause status for female participants could not be collected since it was not consistently reported in patients' records. However, the mean age of menopause among Qatari and Arab women was estimated to be 49.55±3.12 years in a cross-sectional study conducted in Qatar from July 2012 to March 2014 (155). Accordingly, female patients in our study are most likely to be perimenopausal or postmenopausal.

HMC is considered the main non-profit healthcare provider in Qatar, which has wide healthcare coverage, and Qatari nationals are covered by the national health insurance scheme. At HMC, there are four DXA scan machines distributed between Hamad Medical City, Rumailah Hospital, Women wellbeing Centre, and Bone and Joint Centre. Accordingly, the patients in this study sample represent the general population of Qatar in terms of healthcare access in general and access to DXA machines, specifically. However, the generalizability of the incidence rate of fragility fractures estimated in our study is only limited to older adults who undergo BMD testing since they represent people whom their BMD status is recognized, which will most likely influence patients' and health-care providers' attitudes. The generalizability of the obtained risk estimates for fragility fractures per SD reduction in BMD and according to diabetes status, to the general population of older adults in Qatar is limited, given that the study participants conducted DXA scan based on a prior indication and were not randomly selected from a representative population, which puts them at higher

risk compared to the general population and makes them more likely to represent individuals with a high risk of fragility fractures in the general population of older adults. Finally, with regards to our findings indicating the superiority of the NHANES database in identifying incident fragility fractures, there is no reason to suggest these results depend on the population being studied. Accordingly, these results could be generalized to the older adult women population of Qatar.

5.7 Research Implications and Future Recommendations

The study findings indicate that 2 out of 100 patients who have their BMD tested will sustain a fragility fracture per year following their test. This number is dependent on clinical intervention efforts directed toward preventing fragility fractures in these patients. The number of fragility fracture incident cases in this cohort, with known BMD statuses, reflects in part the effectiveness of clinical interventions, and it may or may not be dependent on the higher-risk nature of this study group. To better understand these issues, more prospective studies that are more representative of the general population of Qatar with the aim to quantify the burden of fragility fractures are required. Also, it was found that the incidence rate in male patients was not significantly different from that of female patients, which suggests that the risk of fractures between the two demographic groups is comparable and that men should receive a comparable amount of attention in terms of fracture risk evaluation.

Additionally, the result from this study indicates that the risk of fragility fractures increases by two folds per SD reduction in total hip BMD from the young normal, adjusting for age, which is consistent with the international risk estimates for fragility fractures. The results also indicate that total hip BMD predictive ability is comparable to that reported for femoral neck BMD. Despite the increased risk with lower BMD levels, incident fracture cases were higher in the LBM group, suggesting the important role of other risk factors for fragility fractures and shedding light on the

cost-effectiveness aspects of relying on BMD alone in fracture risk assessment.

Limited by the small number of fracture cases, we were not able to estimate, with greater validity, the effect of all collected risk factors on the relationship between BMD and incident fragility fractures. Accordingly, we recommend that more studies with a longer duration of follow-up assess the influence of these important factors more effectively. A similar recommendation is given regarding the assessment of the association between diabetes mellitus and the risk of fragility fracture, given that the lack of statistically significant association between diabetes and the risk of fragility fractures is potentially due to the reduced power of the test of hypothesis.

Despite the importance of considering other clinical risk factors for fragility fractures, the diagnosis of osteoporosis depends mainly on BMD and T-scores, which influence the decisions to initiate treatment. Accordingly, the choice of the database in the derivation of T-scores, which influence the diagnosis of osteoporosis and, consequently, the management of patients, is very relevant. The study findings indicate that selection of the NHANES database outperforms the selection of the Qatari database in terms of identifying patients with incident fragility fractures. Thus, our study findings validate the international guidelines for database selection (17, 18), which ultimately provide a common platform for the diagnosis of osteoporosis both globally and locally, avoid the different results obtained upon the use of different databases and enhance clinical intervention efforts.

Currently, there are no published guidelines in Qatar concerning the diagnosis of osteoporosis and the assessment of fragility fractures. However, the osteoporosis societies in the Gulf Cooperation Council (GCC) countries assembled recently to reach a consensus regarding the assessment and management of osteoporosis-related fractures among postmenopausal women, upon which region-specific guidance could

be formulated (156). One of the issues discussed was the importance of country-specific FRAX® and fracture liaison services. The FRAX® tool calculates the 10-year probability of hip fracture or major osteoporotic fractures, taking into account both fracture and death risks and incorporating an array of clinical risk factors (65). The adaptation of such a tool in Qatar will enhance fracture risk assessment efforts and will aid the formulation of guidelines related to the subject matter.

Chapter 6: Conclusions

Worldwide, osteoporosis constitutes a major public health problem, which is expected to increase in magnitude as the populations age. It is a silent disease until fractures occur, which lead to undesired outcomes in the affected individuals, including death. The epidemiological shift witnessed in recent years in the EMR region, with the continuous increase in life-expectancy, entails that the burden of osteoporosis and fragility fractures will continue to increase in this region. However, the evidence concerning the burden of osteoporosis in different demographic groups in the EMR region, in general, is sparse. Moreover, evidence related to the burden of fragility fractures and to their associated risk factors is even more scarce. Qatar is no exception to this rule.

In this study, the estimated incidence rate of fragility fractures that are sustained subsequent to BMD testing was 2 in 100 persons per year. The research findings indicate that the risk of fragility fractures, using the WHO BMD T-score cutoff values for the diagnosis of osteoporosis and LBM, is higher in people who are classified as having osteoporosis, followed by those who are classified as having LBM and then by those classified as having normal BMD. Additionally, the estimated crude BMD gradient of risk of fragility fractures was 1.82. These findings are in concordance with what is known internationally about BMD's high predictive ability for fracture risk.

Diabetes is highly prevalent in Qatar, and there is sufficient evidence in the literature suggesting an association between diabetes and the increased risk of fragility fractures. This potentially puts a significant proportion of the population of Qatar at a higher risk of fractures. The results of this study indicate that there is no statistically significant association. However, prospective studies with longer follow-up durations that permit the observation of an adequate number of fracture cases would allow the

proper estimation of the effects of both BMD and diabetes mellitus on the risk of fragility fractures with greater power.

Additionally, the use of the NHANES database as compared to the Qatari database in establishing the diagnosis of osteoporosis was found to be superior in terms of identifying patients with incident fragility fractures and would allow for a common platform between and within countries. It would also improve the management of patients.

Finally, the pathological process that ends with a fragility fracture is complex in nature, and it is the sum of certain attributes of the individuals, their clinical profile, and other factors relating to their environment. Moreover, there is no current policy that is globally accepted for population-based screening for osteoporosis; thus, a case-finding approach is recommended instead, where patients are identified when they sustain a fracture or by the identification of other risk factors (157). Accordingly, the incorporation of risk factors that are BMD-independent improves fracture risk assessment results.

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