의학박사 학위논문

당뇨 환자에서 기계학습을 이용한 생리학적 지표 및 위험요인이 심혈관계 예후에 미치는 영향에 대한 검증

Validation of Physiologic Indices and Risk Factors for Cardiovascular Outcomes in Patients with Diabetes Mellitus: A Machine-Learning Based Approach

2020년 8월

서울대학교 대학원

의학과 내과학 전공

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지도교수 구 본 권

이 논문을 의학박사 학위논문으로 제출함

2020년 5월

서울대학교 대학원

의학과 내과학 전공

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2020년 7월

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Validation of Physiologic Indices and Risk Factors for Cardiovascular Outcomes in Patients with Diabetes Mellitus: A Machine-Learning Based Approach

By Jinlong Zhang

A thesis submitted in partial fulfillment of the requirement for the degree of Doctor of Philosophy in Medicine (Internal Medicine)

in Seoul National University, Seoul, Korea

June 2020

Doctoral Committee

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학 번	2017-39235
연 락 처	010-7440-1237

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Abstract

Validation of Physiologic Indices and Risk Factors for Cardiovascular Outcomes in Patients with Diabetes Mellitus: A Machine-Learning Based Approach

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Background and Objectives:

Current European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines recommend fractional flow reserve (FFR) measurement as a standard invasive method to identify the ischemia-causing coronary lesions. However, patients after therapeutic procedures still suffer adverse cardiovascular events even after deferral of revascularization according to FFR, potentially due to the presence of microvascular dysfunction that may cause ischemia or foster the progression of obstructive disease. Coronary microvascular dysfunction (CMD) is more frequently observed in patients with diabetes mellitus (DM) and is a major

determinant of long-term adverse outcome. Since comprehensive physiologic assessment enables the evaluation of microvascular function which could not be fully demonstrated by angiography, we sought to investigate the prognostic implication of invasive physiologic index-defined CMD in patients with DM and coronary artery disease (part I). Increasing evidence showed that machine learning can provide tools to assist physicians during diagnosis and treatment of diverse clinical conditions, including myocardial infarction. Therefore, we sought to study using machine learning algorithms with an expanded sample size, to validate the physiologic indices and find out the valuable risk factors for cardiovascular outcomes in patients with DM and coronary artery disease (part II).

Methods:

Part 1: Two hundred and eighty-three patients with available FFR and index of microcirculatory resistance (IMR) were selected from the 3V FFR-FRIENDS study. Patients were classified according to the presence of DM and CMD into group A (DM-, CMD-), group B (DM-, CMD+), group C (DM+, CMD-), and group D (DM+, CMD+). Primary outcome was a major adverse cardiac event (MACE, a composite of cardiac death, myocardial infarction and ischemia-driven revascularization) at 2 years. Part 2: Seven hundred and fourteen patients (235 patients with DM) with deferred coronary revascularization according to FFR (>0.80) were included. This registry hitherto is the biggest cohort whose patients were fully assessed by comprehensive physiologic indices. Comprehensive physiologic evaluation, including coronary flow reserve (CFR), IMR and FFR, was performed at the time of revascularization deferral. The median values of CFR (2.88), FFR (0.88) and IMR (17.85) were used to classify high or low CFR, FFR, and IMR groups.

Information gains of variables with 5,000-permutation resampling, minimal depth and Boruta algorithms were used for feature selection. Furthermore, prognostic models were compared using c-index. In this part, patient-oriented composite outcome (POCO) at 5 years, including all-cause death, any myocardial infarction, and any revascularization, was the primary outcome.

Results:

Part 1: DM population showed significantly higher risk of MACE compared with non-DM population (HR 4.88, 95% CI 1.54-15.48, p=0.003). MACE at 2-year among four groups were 2.2%, 2.0%, 7.0%, and 18.5%, respectively. Group D showed significantly higher risk of MACE compared with group A (HR 8.98, 95% CI 2.15-37.41, p=0.003). The multivariable regression analysis showed the presence of DM and CMD was an independent predictor of 2-year MACE (HR 11.24, 95% CI 2.53-49.88, p=0.002) and integrating CMD into a model with DM increased discriminant ability (C-index 0.683 vs. 0.710, p=0.010, integrated discrimination improvement 0.015, p=0.040). Part 2: Compared with non-DM population, DM population showed a higher risk of POCO at 5 years (HR 2.49, 95% CI 1.64-3.78, p<0.001). Low CFR group had a higher risk of POCO than high CFR group (HR 3.22, 95% CI 1.74-5.97, p<0.001) only in DM population. In contrast, CFR values could not differentiate the risk of POCO in non-DM population. There was a significant interaction between CFR and the presence of DM regarding the risk of POCO (interaction p=0.025). Independent predictors of POCO at 5 years were low CFR and family history of coronary artery disease in DM population, and percent diameter stenosis and multi-vessel disease in non-DM population. Among all angiographic and physiologic parameters, CFR showed the highest information gain.

In DM population, CFR, consistently, was the most important feature followed by Age and FFR using “Minimal Depth” algorithm. Moreover, CFR was the valuable features to predict POCO using “Boruta” algorithm in DM population. In DM population, adding clinical risk factors (c-index 0.75 0.65-0.85, p=0.500) or clinical risk factors and invasive parameters together (c-index 0.75, 95%CI 0.65-0.85, p=0.535) into features from Boruta (c-index 0.73, 95% CI 0.63-0.83) did not show a better discriminant ability.

Conclusions:

The patients with DM and CMD were associated with increased risk of cardiovascular events. Integration of CMD improved risk stratification to predict the occurrence of MACE. The importance of risk factors for cardiovascular outcomes is different according to the presence of DM. CFR consistently was the important prognostic factor in patients with DM regardless of methods. Machine learning could help find out the most effective combination with acceptable numbers of features for better outcome prediction.

Keywords: Coronary artery disease, diabetes mellitus, coronary microvascular dysfunction, coronary flow reserve, fractional flow reserve, index of microcirculatory resistance, machine learning.

Student Number: 2017-39235

Contents

Abbreviations

CFR = coronary flow reserve

CI = confidence interval

CMD = coronary microvascular dysfunction

DM = diabetes mellitus

FFR = fractional flow reserve

HR = hazard ratio

IMR = index of microcirculatory resistance

MACE = major adverse cardiac event

PCI = percutaneous coronary intervention

POCO = patient-oriented composite outcome

Introduction

The presence of myocardial ischemia is the most important prognostic factor in patients with coronary artery disease. Current European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines recommend fractional flow reserve (FFR) measurement as a standard invasive method to identify the ischemia-causing coronary lesions.[1] It has been reported that the clinical outcomes of FFR-guided percutaneous coronary intervention (PCI) are better than those of angiography-guided PCI.[2-4] However, patients still suffer adverse cardiovascular events even after deferral of revascularization according to FFR, potentially due to the presence of microvascular dysfunction that may cause ischemia or foster the progression of obstructive disease.[2,5] Comprehensive physiologic assessment enables the evaluation of microvascular function which could not be fully demonstrated by angiography. Awareness of the existence of concealed mechanisms of coronary dysfunction could lead to closer patient surveillance and to specific treatments which, eventually, could result in better patient outcomes.[2,5] Therefore, identifying patients at higher risk of future adverse cardiovascular events is a clinically important issue, even after physiology-guided revascularization strategy.

The presence of diabetes mellitus (DM) is strongly associated with CAD and increases the risk of cardiovascular events.[6,7] Previous studies demonstrated that patients with DM were more likely to have multi-vessel disease and diffuse disease in small vessels,[8,9] and were associated with plaque vulnerability with more significant atherosclerotic burden with lipid-rich plaques.[10] In addition, coronary microvascular dysfunction (CMD), which can be defined by physiologic indices, is more frequently observed in patients with DM and[11,12] is a major determinant of long

term outcome in this patient population.[13] However, the prognostic implication of DM with or without CMD in patients has not been clarified. Moreover, prognostic value of physiologic indices and other risk factors in patients with DM and coronary artery disease has not been well investigated.

Machine learning, an application of artificial intelligence, is the study of computer algorithms that can analyze clinical information and provide tools to assist physicians during diagnosis and treatment of diverse clinical conditions. Conventional statistical method exists within a mathematical framework and make certain probabilistic assumptions about the data generation process. In contrast, machine learning approach makes no assumptions about the data generating process and learns relationships from the data itself.[14] Furthermore, it becomes an increasing trend of published work in the combined field of medicine and data science.[14,15]

The main aim of our study is to investigate the prognostic implication of invasive physiologic index-defined CMD in patients with DM and coronary artery disease. Furthermore, with an expanded sample size, we went on to validate the physiologic indices and find out the valuable risk factors for cardiovascular outcomes using machine learning algorithm in patients with DM and coronary artery disease.

Part 1

Methods

Study Design and Patient Selection

The study was sub-study of 3V FFR-FRIENDS study (3-vessel fractional flow reserve for the assessment of total stenosis burden and its clinical impact in patients with coronary artery disease, NCT01621438), which was international multi-center prospective study recruiting patients from 11 centers in 3 countries (Korea, China, and Japan) between November 2011 and March 2014.[16] Patients who had >30% stenosis in a major epicardial coronary artery by visual estimation and underwent FFR measurement in all major coronary arteries were included. The exclusion criteria were patients with depressed left ventricular systolic function (ejection fraction <35%), acute ST-elevation myocardial infarction within 72 hours, previous coronary artery bypass graft surgery, chronic renal disease, abnormal epicardial coronary flow (TIMI flow <3), or planned coronary artery bypass graft surgery after diagnostic angiography.

The current study was performed to evaluate clinical outcomes of patients according to the presence of DM and CMD, which was assessed by using IMR. Among the main study cohort, 284 patients with 458 lesions who underwent IMR measurement were selected for the current analysis. The study protocol was approved by the Institutional Review Board or Ethics Committee at each center and was conducted following the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Angiographic Analysis and Quantitative Coronary Angiography

Coronary angiography was performed using standard techniques. Angiographic views were obtained after intracoronary nitrate administration (100 or 200 μg). Quantitative coronary angiography was analyzed at a core laboratory (Seoul National University Hospital) in a blinded fashion with validated software (CAAS II, Pie Medical System, Maastricht, The Netherlands). The minimum lumen diameter, reference vessel size, percent diameter stenosis, and lesion length were quantified.

FFR and IMR Measurements

FFR and IMR measurements were performed after diagnostic angiography. Briefly, coronary angiography was performed using a 5-7 Fr guide catheter without side holes. FFR and IMR were measured with standardized protocol among the participating centers using a pressure-temperature sensor guide wire (St. Jude Medical, St. Paul, MN, USA).

The pressure sensor was positioned at the distal segment of target vessel, and intracoronary nitrate (100 or 200 μg) was administered before FFR and IMR measurements. To induce hyperemia, continuous intravenous infusion of adenosine or adenosine triphosphate was used. Hyperemic proximal aortic pressure (Pa) and distal arterial pressure (Pd) were obtained during sustained hyperemia, and FFR was calculated by means of Pd/Pa during hyperemia. According IMR measurement, resting mean transit time was obtained by injecting 4 ml saline at room temperature for 3 times, and hyperemic mean transit time was measured during sustained

hyperemia. The IMR was calculated by Pd × mean transit time during hyperemia.[16,17] PCI was recommended as the current guideline for lesions with FFR ≤0.80. Pre-PCI FFR and IMR values were used in this study.

Cut-off Values and Classification of Patients

CMD was defined as IMR values ≥25U. Study population was classified according to the presence of DM and CMD: group A, non-DM with non-CMD; group B, non-DM with CMD; group C, DM with non-CMD; group D, DM with CMD.

Patient Follow-Up, Outcome Measurements, and Clinical Events Adjudication

The patients were followed up at outpatient clinic visits or by telephone. All events were adjudicated by an independent clinical events committee unaware of clinical, angiographic, and physiologic data. The primary outcome was a major adverse cardiac event (MACE), including cardiac death, vessel-related myocardial infarction, and vessel-related ischemia-driven revascularization during 2-year follow-up. The individual components of MACE were also analyzed. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of MI.[18] All deaths were considered cardiac, unless an undisputable non-cardiac cause was present. Ischemia-driven revascularization was defined as a revascularization procedure with at least one of the following: (1) recurrence of angina, (2) positive non-invasive test and (3) positive invasive

physiologic test.

Statistical Analysis

Categorical variables were presented as frequency and percentage. Continuous variables (normal distribution) were presented as mean and standard deviation or median and interquartile range (non-normal distribution). Chi-squared (or Fisher exact test) and Student`s t test were used to evaluate the differences among two groups at baseline. Chi-squared (or Fisher exact test) and ANOVA (or Kruskal–Wallis test for non-normal distribution) were used to evaluate the differences among four groups at baseline. Multiple comparisons were performed using Tukey's Multiple Comparison Test. A multivariate Cox proportional-hazard regression model was used to calculate hazard ratio (HR) and 95% confidence interval (CI) to estimate the relative risks of the incidence of 2-year MACE. Additive prognostic implication of IMR in addition to DM was evaluated using Harrell's C-index comparison as well as relative integrated discrimination improvement.

All probability values were two-sided and p values <0.05 were considered statistically significant. The SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA) and R 3.2.3 (R Corporation, USA) statistical packages were used for statistical analyses.

Results

Characteristics of patients and target vessels

Table 1 shows baseline patient and lesion characteristics among 4 groups, classified according to the presence of DM and CMD. Among total patients, mean %DS was 36.76±15.12% and median FFR was 0.88 (Q1-Q3 0.80-0.94). Of 283 patients, 47.4% had non-DM and non-CMD (group A), 18.0% had non-DM and CMD (group B), 25.1% had DM and non-CMD (group C), and 9.5% had DM and CMD (group D). The distribution of most cardiovascular risk factors and clinical presentation was similar among all groups, except that the proportion of hypertension and hyperlipidemia. The Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery score of group B was significantly lower than other groups, while mean reference diameter of group B was higher than other groups. The 3-vessel FFR showed no significant difference among 4 groups (2.71 vs. 2.76 vs. 2.73 vs. 2.68, overall p=0.135). Significant different rate of positive FFR (34.3% vs. 13.7% vs. 21.1% vs. 33.3%, overall p=0.019) and rate of those without PCI were shown among 4 groups (20.9% vs. 3.9% vs. 12.7% vs. 7.4%, overall p=0.016) mostly due to group A and group B. The comparisons of baseline clinical characteristics according to DM or CMD are presented in Table 4.

Clinical Outcomes According to Presence of DM and CMD

At 2 years of follow-up, DM patients had significantly higher risk of MACE (HR 4.88, 95% CI 1.54-15.48, p=0.003), compared with non-DM patients. The significant difference in MACE was mainly driven by higher risk of ischemia-driven revascularization in DM patients (HR 3.87, 95% CI 0.97-15.37, p=0.039), compared with non-DM patients (Figure 1).

Among the four groups, classified according to the presence of DM and CMD,

the cumulative incidence of MACE was 2.2%, 2.0%, 7.0%, and 18.5% for groups A, B, C, and D, respectively (p=0.006). Only group D showed significantly higher risk of MACE, compared with other groups (Table 2 and Figure 2). The significant difference in the risk of MACE was mainly driven by ischemia-driven revascularization. The incidence of death, cardiac death and MI was not different among 4 groups (Table 2).

Prognostic Implication of CMD in Addition to DM

A multivariate model showed that DM was an independent predictor of MACE. When CMD and DM was included as one of the covariates, the presence of DM and CMD (group D) was the most powerful independent predictor for MACE (HR 11.24, 95% CI 2.53-49.88, p=0.002) (Table 3). In addition, integration of CMD into prediction model with DM for 2-year MACE showed significantly improved discriminant function (C-index 0.683 vs. 0.710, p=0.010) and reclassification ability (relative integrated discrimination improvement 0.015, p=0.040). When we put CFR into the model instead of IMR, consistently improvement of c-index was shown (0.025, 0.683 vs 0.708, p=0.046). However, there was rarely integrated discrimination improvement (0.01, p=0.359).

Part 2

Methods

Study Population

The study population was from the International Collaboration of Comprehensive Physiologic Assessment Registry which included patient-level data of 3 registries from 5 university hospitals in Korea, Tsuchiura Kyodo General Hospital (Ibaraki, Japan), and Hospital Clinico San Carlos (Madrid, Spain).[5,19-22] All enrolled patients underwent comprehensive coronary physiologic evaluations (FFR, CFR and IMR) during coronary angiography, and all registries shared the same exclusion criteria. FFR was measured in intermediate stenosis to identify hemodynamic significance and CFR and IMR were measured as a part of routine clinical practice and for research purposes. Exclusion criteria were hemodynamic instability, left ventricular dysfunction and a culprit lesion of acute coronary syndrome. Finally, the International Collaboration of Comprehensive Physiologic Assessment Registry included a total of 1,397 patients with 1,694 vessels. This registry hitherto is the biggest cohort whose patients were fully assessed by comprehensive physiologic indices. According to the purpose of this study, 714 patients with 988 vessels with deferred coronary revascularization according to FFR (>0.80) were included. In patients with multi-vessel interrogations, a representative vessel was defined as the one with the lowest FFR value. The study protocol was approved by the ethics committee at each participating center and was conducted according to the principals of the Declaration of Helsinki. All patients provided written informed consent. The study protocol was registered at clinicaltrials.gov

(NCT03690713).

Invasive Coronary Angiography and Measurement of Physiologic Indices

Invasive coronary angiography was performed utilizing standard techniques. Briefly, all angiograms were acquired after administration of intracoronary nitrate (100 or 200ug).

Quantitative coronary analysis was performed at each core laboratory of included registries using a validated software program. Reference vessel diameter, MLD, %DS and lesion length were evaluated. Coronary physiologic indices were measured following diagnostic angiography.[19] After engagement of a guide catheter, a pressure/temperature-sensor guide wire (Abbott Vascular, St. Paul, MN, USA) was calibrated and equalized to aortic pressure. Then, it was positioned at the distal part of a coronary artery. During maximal hyperemia, FFR was acquired and was defined as the lowest value of mean hyperemic distal coronary to aortic pressure. CFR was calculated as a ratio of resting Tmn to hyperemic Tmn. To obtain Tmn, 3 injections of room-temperature saline were performed, and thermodilution curves were acquired in both resting and hyperemic state. Hyperemic state was induced with administration of intravenous adenosine (140 μg/kg/min). Pressure wire pull-back was performed after every measurement to check the presence of pressure drift. IMR was calculated as distal coronary artery pressure × Tmn during hyperemia, and all IMR values were adjusted to the expected collateral support using Yong's formula (Pa × Tmn × ([1.35 × Pd/Pa] − 0.32).[17]

Data Collection, Clinical Outcomes, and Classification of Patients

Data collection was performed using a standardized form of a spreadsheet with standardized definitions of variables. Clinical, angiographic, and physiologic data of the enrolled patients were recorded at the time of the index procedure using this form. Clinical outcome data were collected by outpatient clinic visits or telephone call. Baseline characteristics including age, sex, body mass index, conventional risk factors (including hypertension, DM, dyslipidemia, current smoking, prior history of myocardial infarction and revascularization, family history of CAD), left ventricular ejection fraction (%) and the presence of multivessel disease were obtained. Body mass index was defined as weight (kg)/height (m^2). Hypertension was defined as systolic blood pressure more than 140 mmHg, diastolic blood pressure more than 90 mmHg, previous history of hypertension, or the use of antihypertensive medications. DM was defined as fasting glucose more than 126 mg/dL, previous history of DM or the use of DM medications. Dyslipidemia was defined as low-density lipoprotein cholesterol more than 160 mg/dL, previous history of dyslipidemia, or the use of lipid lowering medications. Current smoker was defined if a patient had smoked regularly within past 12 months. Left ventricular ejection fraction was measured by M-mode echocardiographic estimation to evaluate systolic function and multivessel disease was defined as having at least 2 major epicardial coronary arteries with the presence of greater than 50% luminal narrowing. All data were requested of the principal investigators of each registry to be sent to Seoul National University Hospital, Korea. All submitted data were double-checked by a

central monitoring team at Seoul National University Hospital, Korea.

The primary outcome was the patient-oriented composite outcome (POCO) at 5 years, including all-cause death, any myocardial infarction, and any revascularization. All clinical outcomes followed the definitions of the Academic Research Consortium, including the addendum to the definition of myocardial infarction.[23,24]

All patients were grouped according to the values of CFR, FFR, and IMR in a representative vessel. The median values of CFR (2.88), FFR (0.88) and IMR (17.85) were used to classify high or low CFR, FFR and IMR groups, respectively.

Statistical Analysis

The categorical variable was described as a number and relative frequency and the continuous variable as mean and standard deviation. The Student's t-test was performed to compare continuous variables. Kaplan-Meier analysis was used to calculate the cumulative incidence of clinical outcomes, and a log-rank test was used to evaluate the group differences. Cox proportional hazard regression model was used to calculate the HR and 95% CI. In addition, multivariate Cox proportional hazard regression models were used to identify independent predictors of POCO according to the presence of DM. The covariates that were considered clinically reliable or were associated with clinical outcomes (univariate analysis, p value < 0.1) were included in the models. In addition, the locally-weighted scatterplot smoothing regression line was used to explore the prognostic value of CFR. All p values were 2-sided, and $p<0.05$ was considered statistically significant. The statistical package

R, version 3.4.3 (R Foundation for Statistical Computing) was used for statistical analysis.

Machine learning

In order to build a reasonable machine learning model, data visualization was performed via Histogram, Density Plot and Whisker Plot for univariate distribution and Correlation Plot, Scatter Plot matrix Plot and Density Plots by Class for multivariate correlation. Missing data will be checked on missingness map.

Random survival forest is one of the most popular techniques used in data mining or machine learning. A binary tree is a decision tool that uses a binary tree-like graph or model of decisions and their possible consequences. It is a flowchart like structure where each node represents a decision (based on a selected variable) and the two branches of the node represent the outcome of the test (Figure 3). The process of Random Survival Forest method is started with bootstrapping samples from the data. Each bootstrap sample excludes one-third of the data, called out-of-bag data, and a binary survival tree is made from each bootstrap sample by the repeated splitting of tree nodes starting from the root node. At each node, randomly selected variables from the data are used to split the nodes by maximizing the survival difference between daughter nodes (maximizing cumulative hazard function at that node). The tree is fully grown until each terminal node has at least one unique outcome. The trees are grown 3,000 times in this study. Then, cumulative hazard function for each tree is calculated, and an ensemble hazard function is obtained by averaging over all trees.

Feature selection to identify the important predictors is based on the minimal

depth of variables. The minimal depth is the shortest distance from the root node to the root of the closest maximal subtree of the variable. A maximal subtree for the variable is the largest subtree whose root node splits on the variable. The smaller value of minimal depth means the more predictive value.

For evaluating the relative importance of covariates to predict POCO, information gains of variables with 5,000-permutation resampling method were calculated. Information gain presents the effect of the variable of interest, and is defined as the change of information entropy between before and after the variable given.[25] Entropy is a measure of the randomness of the distribution of data. Higher information gain means the covariate is more informative in classifying the outcome. The higher information gain means covariate has more importance in predicting the clinical outcome.

The "Boruta" algorithm was used for evaluating the importance of variables. The "Boruta" algorithm can provide a numerical ranking according to Z-score for input parameters in classification or regression of an outcome variable, and all input parameters are classified as important, or unimportant based on the comparison with random variables through 1 iteration. Firstly, it adds randomness to the given data set by creating shuffled copies (shadow features) of all feature. Then it trains random forest classifier on the data set and applies a feature importance (mean decrease accuracy) to evaluate the importance of each feature. At each iteration, it checks whether a real feature has a higher importance than the best of its shadow. Finally, the algorithm stops either when all features gets confirmed or rejected or reaches a specified limit of random forest runs. In the current study, 3,000 iterations of the Boruta algorithm were performed.

Results

Patient Characteristics

Among the 714 patients included in this study, 235 patients (32.9%) had DM. Baseline patient and lesion characteristics are presented in Table 5. Compared to patients without DM, DM patients were associated with older age (63.1±10.6 vs. 65.7±9.7 years, p=0.001), higher body mass index (24.6±3.4 vs. 25.4±4.3, p=0.027) and higher prevalence of hypertension (55.7% vs. 74.9%, p<0.001). Neither the clinical presentation nor the presence of multivessel disease was significantly different between the DM and non-DM populations.

Lesion Characteristics and Clinical Outcomes According to the Presence of DM

Anatomical lesion severity was not different among patients with or without DM (diameter stenosis 41.7±13.9 vs. 40.3±15.5 %, p=0.245; lesion length 11.4±7.4 vs. 11.6±7.2 mm, p=0.846). However, vessel reference diameter was smaller in patients with DM than those without DM (2.86±0.62 vs. 3.02±0.66, p=0.002) (Figure 4 and Table 5). In terms of physiological indices, DM patients showed lower CFR and FFR values than those without DM (CFR 2.90±1.22 vs. 3.15±1.26, p=0.011; FFR 0.88±0.05 vs. 0.89±0.05, p=0.012) (Figure 4 and Table 5). There was no significant difference in IMR between patients with and without DM (21.8±17.8 vs. 21.9±14.1, p=0.978) (Figure 5 and Table 5).

Compared with the non-DM population, the DM population showed a higher

risk of POCO at 5 years (6.9% vs. 17.4%, HR 2.49, 95% CI 1.64-3.78, p<0.001) (Figure 5 and Table 6). Higher risk of POCO in the DM population was mainly driven by higher risk of all-cause death (6.1% for patients with DM vs. 1.4% for patients without DM, HR 3.74, 95% CI 1.89-7.41, p<0.001) and any revascularization (12.0% for patients with DM vs. 5.5% for patients without DM, HR 2.15, 95% CI 1.39-3.32, p<0.001) (Table 6).

Clinical Outcomes According to Physiologic Indices and the Presence of DM

The relationship between physiological indices and long-term patient outcomes differed significantly between patients with and without DM.

In the DM population, the low CFR group had a higher risk of POCO than the high CFR group (24.1% vs. 8.1%, HR 3.22, 95% CI 1.74-5.97, p<0.001) (Figure 6 and Table 7). In contrast, low FFR or high IMR value showed only a trend toward higher risk of POCO (low FFR vs. high FFR groups 20.3% vs. 12.4%, HR 1.48, 95% CI 1.00-2.20, p=0.053; high IMR vs. low IMR groups 20.2% vs. 13.9%, HR 1.54, 95% CI 0.73-3.24, p=0.252).

In the non-DM population, CFR and FFR values could not differentiate the risk of POCO. The low CFR and low FFR groups showed comparable risk of POCO at 5 years with the high CFR and high FFR groups (the low CFR vs. high CFR groups 6.8% vs. 6.9%, HR 0.99, 95% CI 0.47-2.10, p=0.983; the low FFR vs. high FFR groups 7.1% vs. 6.6%, HR 1.05, 95% CI 0.61-1.79, p=0.862) (Figure 7 and Table 7). IMR showed a borderline association with a risk of POCO in the non-DM population (HR 2.08, 95% CI 1.00-4.31, p=0.050) (Figure 6 and Table 7).

When the CFR values were treated as a continuous variable, the risk of POCO at 5 years was significantly increased with decrease of CFR in the DM population (HR 1.71, 95% CI 1.39-2.11, p<0.001), but not in the non-DM population (HR 1.13, 95% CI 0.85-1.50, p=0.418) (Figure 7). There were no significant interactions between FFR or IMR values and the presence of DM for POCO (interaction p values = 0.353 for FFR and 0.163 for IMR against DM). However, there was a significant interaction between CFR values and the presence of DM (interaction p=0.025).

Independent Predictors using Cox-regression and Important variables using Machine Learning Algorithm

Independent predictors of POCO at 5 years were low CFR and family history of CAD in DM patients (Table 8). Among the angiographic and physiologic indices, CFR showed the highest information gain (0.027, 95% CI 0.010-0.044) (Figure 8). In contrast, %diameter stenosis and multi-vessel disease were independent predictors of POCO at 5 years in patients without DM (Table 8) and information gain of diameter stenosis (0.014, 95% CI 0.006-0.022) was the highest (Figure 8). Consistently, The most important feature for POCO using “Minimum Depth” algorithm was CFR in patients with DM and age in patients without DM. (Figure 9) Moreover, “Boruta” algorithm showed sex, CFR, age were valuable (more important than shadow variable) in patients with DM and reference diameter, sex, FFR, age, %DS, MLD were valuable in patients without DM (Figure 10).

Prognostic Models with Conventional Risk Factors or

Features Selected from Machine Learning in Patients with DM

As for the discriminant ability for POCO in patients with DM, the model with important features selected using minimal depth algorithm (CFR, age, FFR and % diameter stenosis; c-index 0.74, 95% CI 0.63-0.85, p=0.606) or using information gain algorithm (CFR, minimum lumen diameter, % diameter stenosis, age and sex; c-index 0.74, 95% CI 0.64-0.84, p=0.587) showed similar discriminant ability compared to that with features selected using Boruta algorithm (sex, CFR and Age; c-index 0.73, 95% CI 0.63 – 0.83) (Figure 11).

Moreover, adding clinical risk factors (acute coronary syndrome, hypertension, dyslipidemia and family history of coronary artery disease; c-index 0.75 0.65-0.85, p=0.500) or clinical risk factors and invasive parameters (%diameter stenosis, FFR, IMR) together (c-index 0.75, 95%CI 0.65-0.85, p=0.535) into features from Boruta did not show a better discriminant ability (Figure 12).

Discussion

This registry hitherto is the biggest cohort whose patients were fully assessed by comprehensive physiologic indices. The current study investigated the prognostic implication of invasive physiologic index-defined CMD, validated the physiologic indices and found out the valuable risk factors for cardiovascular outcomes in patients with DM and coronary artery disease. The main findings are as follows: 1) The DM population showed not only a higher risk of MACE at 2 years but a higher risk of POCO at 5 years than the non-DM population; 2) Patients with both DM and CMD were at increased risk of MACE and significantly improved discriminant

function and reclassification ability were observed when CMD were integrated into a prediction model with DM for 2-year MACE; 3) Low CFR value was associated with a higher risk of POCO at 5 years and was an independent predictor of POCO in the DM population but not in the non-DM population; 4) There were no significant interactions between FFR or IMR values and the presence of DM regarding the risk of POCO. However, there was significant interaction between CFR and the presence of DM. 5) In patients with DM, CFR was consistently an important index in predicting POCO regardless of methods. 6) Model with important features (age, sex, CFR) selected using machine learning showed a similar discriminant ability compared to model built by conventional factors (age, sex, CFR, acute coronary syndrome, hypertension, dyslipidemia, family history of coronary artery disease, %diameter stenosis, FFR and IMR).

Association Between Coronary Artery Disease and DM

DM is an important risk factor of CAD, and its prevalence is rapidly growing worldwide.[6,7] Patients with DM are more likely to have severe and diffuse vascular disease, multi-vessel disease, and microvascular dysfunction[9,11,26], which are poor prognostic factors in patients with CAD. The current guidelines recommend invasive physiologic index-guided coronary revascularization in patients without evidence of ischemia, and the indications for revascularization are not different between DM and non-DM populations.[27] In the current study, patient with DM had not only a significantly higher risk of MACE at 2 years but a significantly higher risk of POCO at 5 years than those without DM.

Prognostic Implication of CMD in Patients with DM

In the first part of our study, prognostic implications of CMD in diabetic patients who underwent comprehensive physiologic assessment was investigated. Coronary microvascular dysfunction is a wider category including abnormalities in microcirculatory resistance. It represents a spectrum from both the pathological and clinical viewpoint.[28] The presence of CMD is associated with an increased risk of clinical events.[29-32] There are several invasive and non-invasive diagnostic techniques to define CMD and IMR is a specific index to evaluate microvascular status in a cardiac catheterization laboratory. It is relatively independent from epicardial coronary stenosis and shows a good reproducibility.[33] A previous study showed that IMR >25 can be considered abnormal in a non-MI population[13], and Lee et al. demonstrated that the patients with high IMR and low CFR have the highest cumulative incidence of events including death, MI and revascularization.[5] Thus, the current study used the IMR cutoff value 25 to define CMD.[34]

In this study, the patients with DM and CMD (Group D) have significantly higher MACE compared to non-DM and non-CMD patients. In addition, only DM with CMD was an independent predictor of MACE, and the presence of DM and CMD has additional prognostic value. A similar result was published in a Doppler-derived coronary flow velocity reserve study. Cortigiani et al. investigated the prognostic implications in patients with type 2 diabetes with angiographically normal or near normal coronary arteries and preserved left ventricular function. The CMD conferred strong prognostic information which was predicting a nearly seven times higher hard-event compared to non-CMD group.[35] These results suggest that CMD is an important prognosticator in DM patients regardless of methods of

measurement.

Prognostic Factors in Patients with DM

In the second part of our study, population was extended from single country to three countries (Korea, Japan and Spain). To avoid the prognostic impact of PCI, we enrolled only deferred coronary lesions according to FFR > 0.80. Coronary physiology and the importance of prognostic factors can be different in the DM population, as DM affects various compartments of the coronary circulation system.[6] In the current study, different outcome predictors and valuable features were shown between DM and non-DM population. However, the results consistently showed CFR was a valuable feature in DM population. In previous study, the long term prognosis of patients with DM without obstructive coronary disease but impaired CFR has been shown to be poor, and similar to patients with DM and obstructive CAD.[13] In this context, the current study evaluated the characteristics and prognosis of deferred coronary lesions in the DM population, taking into account not only the functional relevance of epicardial coronary stenoses but also the subtended microcirculatory status.

Angiographic and Physiologic Features in Deferred Patients with DM

We investigated the impact of DM on deferred coronary lesions. The results showed that angiographic lesion severity, assessed by percent diameter stenosis and lesion length, was not different among patients with or without DM. However,

reference diameter and minimal lumen diameter in patients with DM were smaller than those in patients without DM. These results imply that there is a possibility of diffuse epicardial coronary disease in patients with DM, suggesting that deferred patients with DM might have a more extensive disease burden than those without DM. These results are in line with previous studies that the presence of DM was associated with more severe and diffuse CAD.[9] By physiologic assessment, CFR and FFR values were lower in DM patients. These angiographic and physiologic features seem to be the main factors for the higher risk of POCO in deferred coronary lesions in DM patients than in those without DM. In the current study, deferred patients with DM showed about 2.5-fold higher risk of POCO than those without DM, even though all patients had an FFR >0.8.

Considering the potential impact of DM on the coronary microvascular system, it is interesting that the IMR values were similar between DM and non-DM patients in our study. Although IMR reflects the microvascular state during the hyperemia,[34] not all aspects of microvascular dysfunction can be assessed by this index.[36] The direct relation between DM and IMR has been sparsely studied in a small number of patients.[37] In addition, several previous studies reported that DM was not an independent predictor of high IMR, and DM patients showed comparable level of IMR with non-DM patients.[5,38] The microvascular dysfunction in DM has been explained by endothelial dysfunction in not being able to increase the coronary flow when needed.[13,26,36] In this regard, our study results suggest that CFR can be a more appropriate index for evaluating microvascular dysfunction in DM patients without epicardial coronary stenosis.

Clinical Implications of Physiologic Indices for Revascularization Deferral in Patients with DM

Although patients with DM generally have a higher risk of cardiovascular events than those without, the risk was reported to be different according to anatomical and physiologic disease burden. Malik et al. reported that the risk of CAD ranged from 0.4% to 4% per year for annual CAD event rates, according to the amount of coronary artery calcium.[39] Murthy et al. investigated coronary vascular dysfunction in the DM population and reported that DM population without coronary artery disease and preserved CFR had a very low risk of cardiac death.[13] These studies suggest that DM carries a heterogeneous risk of CAD, thereby supporting the need for additional risk stratification in the DM population.

The current study demonstrated that CFR was the most important prognostic factor in the DM population after deferral of revascularization according to FFR. CFR showed the highest information gain and was an independent predictor for 5-year POCO in the DM population. Moreover, CFR was the most important feature using "Minimum Depth" algorithm and also was the valuable feature using "Boruta" algorithm in patients with DM rather than FFR and IMR. The predictive model with important features selected using machine learning showed a favorable discriminant ability.

There was a significant interaction between CFR values and the presence of DM regarding the risk of POCO, but not for FFR or IMR. Considering that DM affects various compartments of the coronary circulation system, it may be natural that CFR is better associated with the patients' outcomes than the other specific indices.[6] CFR reflects the status of both macrovascular and microvascular

compartments of coronary circulation and its capacity to respond to oxygen demand. Compared to the DM population, associations of coronary physiologic indices with future clinical outcomes and prognostic factors were different in the non-DM population. Our study results suggest that the association between coronary physiologic indices and clinical outcomes in deferred patients according to FFR can be different according to the presence of DM, thereby supporting the importance of CFR measurement in DM patients.

Important Features from Machine Learning Algorithm

Our study showed similar discriminant abilities using features from given three machine learning algorithms. Thereinto, Boruta algorithm provided us numerically least features (age, sex and CFR) among three algorithms. Moreover, adding clinical risk factors or clinical risk factors and invasive parameters together into the model made by features from Boruta did not make it more predictive although over 4 or more conventional risk factors had been added. This result implies that machine learning algorithm enables a minimization of feature numbers physicians should take care of when making cardiovascular outcomes in consideration, which called “dimension reduction”, unlike conventional statistic method.

Future Perspective

The implications of these findings merit further research, aimed to improve the safety of decision making on revascularization and, overall, to obtain better long-term clinical outcomes in patients with DM. On one hand, the presence of normal CFR in vessels with FFR>0.80 in patients with DM might reassure deferral of

revascularization. On the other, abnormal CFR values might foster implementation of tighter measures to control DM and cardiovascular risk factors. In the absence of studies supporting specific treatment for abnormal microcirculatory function in the DM population to modify prognosis, an abnormal CFR might indicate the presence of higher cardiovascular risk and, therefore, the need for closer patient surveillance. In addition, considering the diverse nature of microvascular dysfunctions, our study raises the need for thorough physiologic evaluation in other disease states, such as CAD with primary myocardial disease, to understand the state of microvascular circulation.

Increasing number of features about patient need to be considered for diagnosis, treatment and outcome prediction. In this regard, machine learning algorithm enables a minimization of feature and might help find out the most effective combination with acceptable numbers of features for daily practice.

Study Limitations

There were several limitations to be considered First, this study was not a randomized controlled trial and could not control all potential bias and confounding factors. Therefore, further studies are needed to validate the results of this study. Second, the information on true anatomical disease burden is not available as intravascular imaging was not performed. Third, although the same exclusion criteria were applied, there can be some heterogeneities in the patient population as this study consisted of 3 separate registries.

Conclusions

The patients with DM and CMD were associated with increased risk of cardiovascular events. Integration of CMD improved risk stratification to predict the occurrence of MACE. The importance of risk factors for cardiovascular outcomes is different according to the presence of DM. CFR consistently was the important prognostic factor in patients with DM regardless of methods. Machine learning could help find out the most effective combination with acceptable numbers of features for better outcome prediction.

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Table 1. Comparison of Clinical and lesion characteristics in 4 groups, classified according to diabetes mellitus and coronary microvascular disease

	Group A	Group B	Group C	Group D	P value
	NonDM and nonCMD	NonDM and CMD	DM and nonCMD	DM and CMD	
Per-patient analysis(n=283)	134(47.4)	51(18.0)	71(25.1)	27(9.5)	
General characteristics					
Age, years	61.04±9.88	61.16±10.55	63.38±10.26	64.22±8.70	0.237
Male	106(79.1)	35(68.6)	52(73.2)	22(81.5)	0.397
Cardiovascular risk factors					
Hypertension	77(57.5)	22(43.1)	51(71.8)	22(81.5)	0.001
Hyperlipidemia	75(56.0)	18(35.3)	47(66.2)	13(48.2)	0.007
Current smoker	38(28.4)	13(25.5)	17(23.9)	6(22.2)	0.863
Previous MI	6(4.5)	4(7.8)	4(5.6)	3(11.1)	0.547
Previous PCI/CABG	45(33.6)	14(27.5)	26(36.6)	10(37.0)	0.730
Clinical Presentation					

Stable angina	37(27.6)	16(31.4)	27(38.0)	8(29.6)	0.497
Unstable angina	18(13.4)	8(15.7)	10(14.1)	4(14.8)	0.983
NSTEMI	1(0.8)	1(2.0)	0	0	0.538
Syntax Score	10.5(6.0,16.0)†	6(2,11)§*‡	10(5,16)†	10(7,18)†	0.002
Coronary factors					
FFR ≤ 0.8	46(34.3) †	7(13.7) *	15(21.1)	9(33.3)	0.019
FFR ≤ 0.8 without PCI	28(20.9) †	2(3.9) *	9(12.7)	2(7.4)	0.016
3-vessel FFR	2.71(2.59,2.80)	2.76(2.65,2.81)	2.73(2.60,2.79)	2.68(2.57,2.82)	0.135
PCI performed	21(15.7)	7(13.7)	6(8.5)	7(25.9)	0.164
Per-vessel analysis (n=456)	234(51.3)	62(13.6)	125(27.4)	35(7.7)	
Quantitative coronary angiography					
Reference diameter	2.85±0.53†	3.16±0.69*‡	2.91±0.60†	2.99±0.72	0.004
Minimum lumen diameter	1.83±0.57†	2.08±0.62*‡	1.83±0.64†	1.78±0.64	0.017
Diameter stenosis	36.31±15.04	33.96±12.72	37.97±15.89	40.42±16.25	0.159
Lesion length	7.81(5.33,13.54)	8.69(5.71,13.38)	7.27(4.93,12.55)	8.48(5.58,16.59)	0.628

Coronary physiological parameters					
FFR(pre-PCI)	0.87(0.79,0.94)†	0.92(0.85,0.95)*	0.87(0.82,0.93)	0.88(0.76,0.93)	0.022
CFR	2.93±1.11	2.83±1.02	2.77±1.04	2.70±1.07	0.457
IMR	16.00(12.99,19.00)†§	32.40(28.00,38.06)*‡	16.33(12.74,20.00)†§	29.48(26.00,33.65)‡	<0.001

*: p<0.05 compared with group A; †: p<0.05 compared with group B; ‡: p<0.05 compared with group C; §: p<0.05 compared with group D. Abbreviations: CFR, coronary flow reserve; DM, diabetes mellitus; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; MI, myocardial infarction; PCI/CABG, percutaneous coronary intervention/ coronary artery bypass grafting; NSTEMI, non-ST segment elevation Myocardial Infarction.

Table 2. Clinical events in 4 groups, classified according to diabetes mellitus and microvascular disease

	Group A	Group B	Group C	Group D	P value*
	NonDM & NonCMD	NonDM & CMD	DM & NonCMD	DM and CMD	
Per-patient analysis (n=283)	134(47.4)	51(18.0)	71(25.1)	27(9.5)	
MACE	3(2.2)	1(2.0)	5(7.0)	5(18.5)	0.006
All cause death	2(1.5)	0(0)	2(2.8)	1(3.7)	0.398
Cardiac Death	1(0.8)	0(0)	2(2.8)	1(3.7)	0.166
MI	1(0.8)	0(0)	1(1.5)	0(0)	0.964
ID-Revascularization	2(1.5)	1(2.0)	3(4.2)	3(11.1)	0.041

Abbreviations: CMD, coronary microvascular dysfunction; DM, diabetes mellitus; ID-Revascularization, Ischemia-driven revascularization; MI, myocardial infarction.

Table 3. Independent predictors of MACE

	HR	95%CI	P value
Age	0.99	0.93-1.06	0.853
Male	1.53	0.25-9.39	0.645
Hypertension	0.49	0.16-1.49	0.208
Smoking	1.18	0.35-3.98	0.786
Hyperlipidemia	1.51	0.55-4.16	0.427
Syntax score	1.05	0.99-1.11	0.112
Diabetes	5.46	1.56-19.12	0.008
Diabetes mellitus and coronary microvascular dysfunction			
NonDM and nonCMD	Reference		
NonDM and CMD	1.04	0.11-9.58	0.974
DM and nonCMD	3.86	0.92-16.16	0.065
DM and CMD	11.24	2.53-49.88	0.002

Abbreviations: CMD, coronary microvascular dysfunction; DM, diabetes mellitus; MACE, , major adverse cardiac event (a composite of cardiac death, myocardial infarction and ischemia-driven revascularization).

Table 4. General characteristics of study population and target vessels according to presence of DM or CMD

	Total	Diabetes	Non-Diabetes	P value	CMD	Non-CMD	P value
Per-patient analysis	283	98(34.6)	185(65.4)		78(27.6)	205(72.4)	
General characteristics							
Age, yrs	61.95±10.02	63.61±9.82	61.08±10.04	0.043	62.22±10.00	61.85±10.05	0.785
Male	215(76.0)	74(75.5)	141(76.2)	0.895	57(73.1)	158(77.1)	0.482
Hypertension	172(60.8)	73(74.5)	99(53.5)	0.001	44(56.4)	128(62.4)	0.353
Hyperlipidemia	153(54.1)	60(61.2)	93(50.3)	0.079	31(39.7)	122(59.5)	0.003
Current smoker	74(26.2)	23(23.5)	51(27.6)	0.455	19(24.4)	55(26.8)	0.673
Previous MI	17(6.0)	7(7.1)	10(5.4)	0.558	7(9.0)	10(4.9)	0.195
Previous PCI/CABG	95(33.6)	36(36.7)	59(31.9)	0.412	24(30.8)	71(34.6)	0.538
CMD	78(27.6)	27(27.6)	51(27.6)	1.000	-	-	-
DM	98(34.6)	-	-	-	27(34.6)	71(34.6)	1.000
Clinical Presentation							
Stable angina	88(31.1)	35(35.7)	53(28.7)	0.222	24(30.8)	64(31.2)	0.942
Unstable angina	40(14.1)	14(14.3)	26(14.1)	0.958	12(15.4)	28(13.7)	0.871
NSTEMI[&]	2(0.7)	0	2(1.1)	0.546	1(1.3)	1(0.5)	0.476

SYNTAX score	10(5,16)	10(6,16)	10(4,15)	0.348	8(3,13)	10(6,16)	0.019
Coronary physiological parameters							
Highest IMR of all target vessels	19.29(14.82,25.83)	20.17(15.00,25.83)	19.00(14.40,25.22)	0.644	32.05(27.21,36.00)	16.97(13.00,20.02)	<0.001
FFR > 0.8	206(72.8)	74(75.5)	132(71.4)	0.454	62(79.5)	144(70.2)	0.118
Per-vessel analysis	456	160(35.1)	296(64.9)		97(21.3)	359(78.7)	
Quantitative coronary angiography							
Reference diameter	2.92±0.59	2.93±0.62	2.92±0.58	0.882	3.10±0.70	2.87±0.55	0.004
Minimum lumen diameter	1.86±0.61	1.82±0.64	1.88±0.59	0.263	1.97±0.64	1.83±0.60	0.035
Diameter stenosis	36.76±15.12	38.51±15.95	35.82±14.60	0.070	36.29±14.35	36.89±15.34	0.732
Lesion length	7.84(5.32,13.55)	7.76(5.16,13.95)	7.92(5.46,13.46)	0.957	8.53(5.71,14.10)	7.70(5.16,13.07)	0.283
Coronary physiological parameters							
FFR(pre-PCI)	0.88(0.80,0.94)	0.87(0.81,0.93)	0.88(0.79,0.95)	0.687	0.90(0.83,0.95)	0.87(0.79,0.94)	0.054
CFR	2.85±1.07	2.75±1.05	2.91±1.09	0.151	2.78±1.04	2.87±1.09	0.455
IMR	17.91(13.76,23.05)	18.17(13.55,23.00)	17.35(13.81,23.11)	0.767	31.00(27.20,35.60)	16.00(12.92,19.55)	<0.001

Values are n, N/n (%), mean ± SD, n (%), median (interquartile ranges). Abbreviations: CFR, coronary flow reserve; DM, diabetes mellitus; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; MI, myocardial infarction; PCI/CABG, percutaneous coronary intervention/ coronary artery bypass grafting; NSTEMI, non-ST segment elevation Myocardial Infarction.

Table 5. Baseline characteristics

	Total (n=714)	DM (n=235)	Non-DM (n=479)	p value
Patient characteristics				
Age, years	63.9±10.4	65.7±9.7	63.1±10.6	0.001
Male	516 (72.3)	178 (75.7)	338(70.6)	0.173
Body mass index, kg/m^2	24.9±3.7	25.4±4.3	24.6±3.4	0.027
Hypertension	443 (62.0)	176 (74.9)	267(55.7)	<0.001
SBP, mmHg	131.5±18.0	132.2±18.5	131.3±17.8	0.642
DBP, mmHg	79.4±9.8	78.7±10.0	79.6±9.7	0.431
Dyslipidemia	437 (61.2)	156 (66.4)	281(58.7)	0.056
Total cholesterol, mg/dL	163.9±36.5	158.0±34.1	166.8±37.4	0.004
LDL-C, mg/dL	92.7±29.4	85.8±25.6	96.1±30.6	<0.001
HDL-C, mg/dL	46.4±12.3	46.2±13.0	46.5±11.9	0.805
Current smoker	153 (21.4)	55 (23.4)	98(20.5)	0.421
Prior myocardial infarction	28 (3.9)	9 (8.2)	19(6.7)	0.779
Prior revascularization	131 (18.3)	42 (31.8)	89(26.7)	0.324
Family history of CAD	77 (10.8)	14 (6.6)	63(14.7)	0.004
Presentation with ACS	123 (17.2)	34 (14.5)	89(18.6)	0.207
LVEF, %	61.9±10.0	61.8±9.4	62.0±10.2	0.758
Multivessel disease	287 (40.2%)	103 (43.8%)	184 (38.4%)	0.192
Clinical Presentation				
STEMI	2 (0.3%)	1 (0.4%)	1 (0.2%)	0.747
UA/NSTEMI	87 (12.2%)	27 (11.4%)	60 (12.5%)	
Stable angina	625 (87.5%)	207 (88.1%)	418 (87.3%)	
Quantitative coronary angiography				
Reference vessel diameter, mm	2.96±0.65	2.86±0.62	3.02±0.66	0.002
Minimum lumen diameter, mm	1.78±0.60	1.68±0.55	1.82±0.62	0.004
Diameter stenosis, %	40.8±15.0	41.7±13.9	40.3±15.5	0.245
Lesion length, mm	11.5±7.3	11.4±7.4	11.6±7.2	0.846
Coronary flow reserve	3.07±1.25	2.90±1.22	3.15±1.26	0.011
Fractional flow reserve	0.88±0.05	0.88±0.05	0.89±0.05	0.012
Index of microcirculatory resistance	21.9±15.4	21.8±17.8	21.9±14.1	0.978
DM status				
HbA1c, %		7.1±1.1		
DM duration, year		9.1±9.3		
Oral hypoglycemic agent		188 (81.4%)		
Insulin		34 (14.2%)		

All values were presented as mean ± standard deviation or number (%). Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Table 6. Clinical outcomes according to the presence of diabetes mellitus

	DM population (n=235)	Non-DM population (n=479)	HR (95% CI)	p value*
POCO	31 (17.4%)	28 (6.9%)	2.49 (1.64-3.78)	<0.001
All-cause death	10 (6.1%)	6 (1.4%)	3.74 (1.89-7.41)	<0.001
Cardiac death	9 (5.5%)	3 (0.7%)	6.76 (1.65-27.75)	0.008
Myocardial infarction	4 (2.3%)	5 (1.2%)	1.74 (0.55-5.52)	0.345
Any revascularization	21 (12.0%)	22 (5.5%)	2.15 (1.39-3.32)	<0.001

*p values for univariate cox proportional hazard regression. Abbreviations: CI, confidence interval; DM, diabetes mellitus, HR, hazard ratio; POCO, patient-oriented composite outcome.

Table 7. Clinical outcomes according to coronary physiologic indices

DM population (n=235)				
	Low CFR	**High CFR**	**HR (95% CI)**	**p value***
POCO	25 (24.1%)	6 (8.1%)	3.22 (1.74-5.97)	<0.001
All-cause death	9 (10.1%)	1 (1.1%)	7.05 (1.22-40.93)	0.030
Cardiac death	8 (9.0%)	1 (1.1%)	6.26 (0.85-46.30)	0.073
Myocardial infarction	3 (2.4%)	1 (2.0%)	2.22 (0.53-9.27)	0.274
Any revascularization	16 (15.6%)	5 (7.1%)	2.46 (0.72-8.37)	0.151
	Low FFR	**High FFR**	**HR (95% CI)**	**p value***
POCO	22 (20.3%)	9 (12.4%)	1.48 (1.00-2.20)	0.053
All-cause death	6 (6.1%)	4 (6.1%)	0.91 (0.32-2.55)	0.855
Cardiac death	5 (5.1%)	4 (6.1%)	0.76 (0.30-1.93)	0.566
Myocardial infarction	3 (3.0%)	1 (1.2%)	1.83 (0.18-18.64)	0.612
Any revascularization	16 (15.6%)	5 (7.1%)	1.94 (0.97-3.90)	0.063
	High IMR	**Low IMR**	**HR (95% CI)**	**p value***
POCO	20 (20.2%)	11 (13.9%)	1.54 (0.73-3.24)	0.252
All-cause death	6 (6.1%)	4 (6.2%)	1.26 (0.39-4.12)	0.698
Cardiac death	5 (4.9%)	4 (6.2%)	1.05 (0.38-2.92)	0.921
Myocardial infarction	3 (3.2%)	1 (1.2%)	0.56 (0.42-15.73)	0.310
Any revascularization	14 (15.0%)	7 (8.2%)	1.70 (0.86-3.37)	0.126
Non-DM population (n=476)				
	Low CFR	**High CFR**	**HR (95% CI)**	**p value***
POCO	13 (6.8%)	15 (6.9%)	0.99 (0.47-2.10)	0.983
All-cause death	3 (1.5%)	3 (1.4%)	1.14 (0.19-6.72)	0.884
Cardiac death	2 (0.9%)	1 (0.4%)	2.28 (0.12-43.11)	0.582
Myocardial infarction	2 (1.1%)	3 (1.3%)	0.75 (0.19-2.94)	0.685
Any revascularization	10 (5.4%)	12 (5.6%)	0.95 (0.48-1.90)	0.894
	Low FFR	**High FFR**	**HR (95% CI)**	**p value***
POCO	15 (7.1%)	13 (6.6%)	1.05 (0.61-1.79)	0.862
All-cause death	2 (1.0%)	4 (1.9%)	0.45 (0.11-1.75)	0.248
Cardiac death	0 (0.0%)	3 (1.4%)	NA	NA
Myocardial infarction	2 (1.0%)	3 (1.5%)	0.59 (0.48-7.36)	0.685
Any revascularization	13 (6.2%)	9 (4.8%)	1.32 (0.96-1.81)	0.087
	High IMR	**Low IMR**	**HR (95% CI)**	**p value***

POCO	18 (9.4%)	10 (4.6%)	2.08 (1.00-4.31)	0.050
All-cause death	4 (2.1%)	2 (0.9%)	2.26 (0.53-9.66)	0.274
Cardiac death	2 (0.9%)	1 (0.4%)	2.23 (0.17-29.51)	0.543
Myocardial infarction	3 (1.5%)	2 (0.9%)	1.68 (0.60-4.74)	0.325
Any revascularization	14 (7.5%)	8 (3.8%)	2.03 (0.67-6.18)	0.213

*p values for univariate cox proportional hazard regression. Abbreviations: CFR, coronary flow reserve; CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio; IMR, index of microcirculatory resistance; NA, not available; POCO, patient-oriented composite outcome.

Table 8. Independent predictors of patient-oriented composite outcome according to the presence of diabetes mellitus

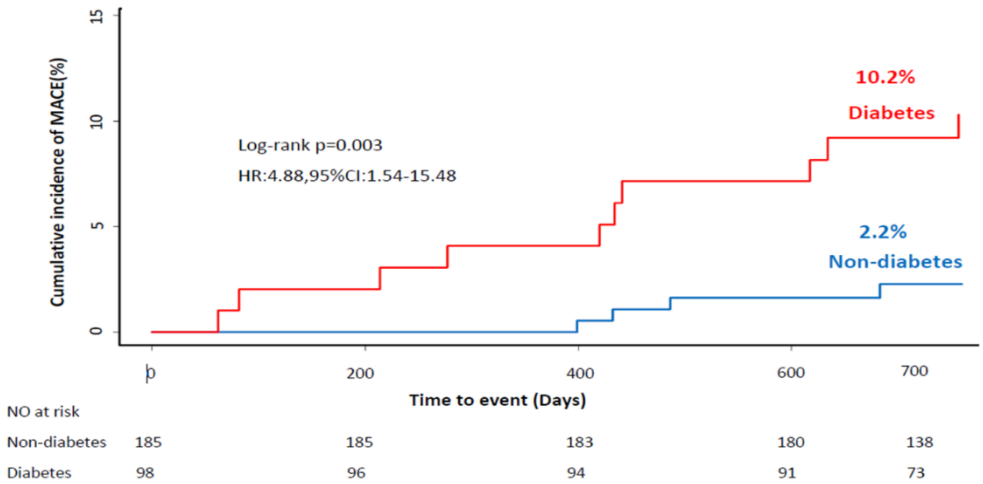
DM population		
Variables	**Adjusted HR (95% CI)**	**p value**
Low CFR*	3.49 (1.01-11.78)	0.048
Family history of CAD	8.23 (3.21-21.11)	<0.001
Non-DM population		
Variables	**Adjusted HR (95% CI)**	**p value**
% diameter stenosis	1.02 (1.00-1.03)	0.047
Multi-vessel disease	1.65 (1.01-2.69)	0.026

*Low CFR is defined as CFR value of < 2.88 (median value of CFR in this study population).

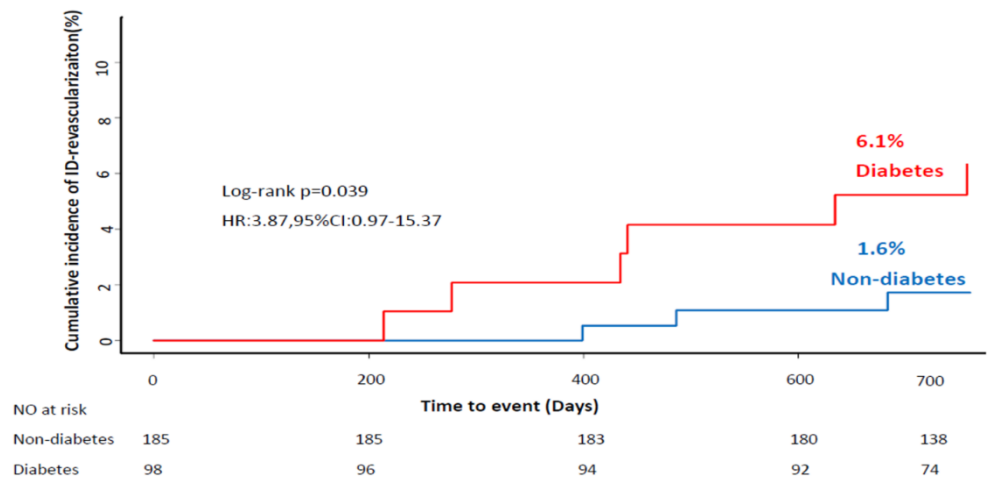
*The following risk factors were included in the multivariate Cox proportional hazard regression model: age, sex, hypertension, hypercholesterolemia, smoking, family history of CAD, previous myocardial infarction, previous revascularization, ejection fraction, clinical presentation, disease extent, lesion characteristics (lesion length, diameter stenosis, minimum lumen diameter, reference vessel diameter) and physiologic characteristics. Abbreviations: CAD, coronary artery disease; CFR, coronary flow reserve; CI, confidence interval; HR, hazard ratio.

Figure 1. Impact of DM on the cumulative incidence of MACE and ischemia-driven revascularization

(A) MACE

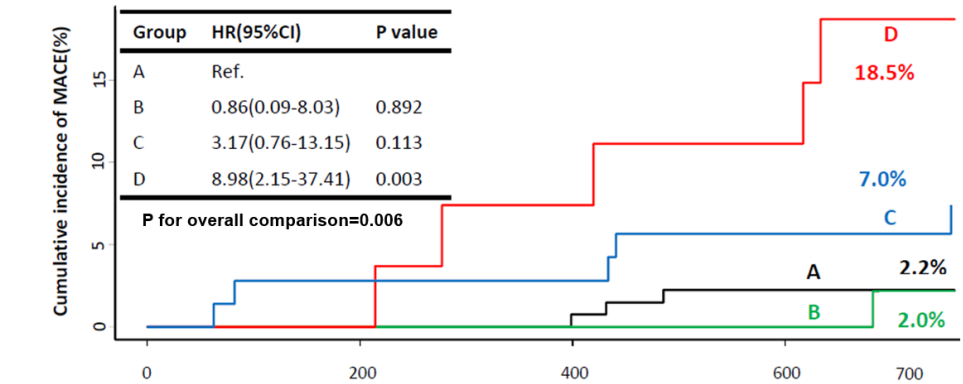


(B) Ischemia-driven revascularization



(A) Cumulative incidence of MACE in patients with or without DM. (B) Cumulative incidence of Ischemia-driven revascularization in patients with or without DM. Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; MACE, major adverse cardiac event (a composite of cardiac death, myocardial infarction and ischemia-driven revascularization).

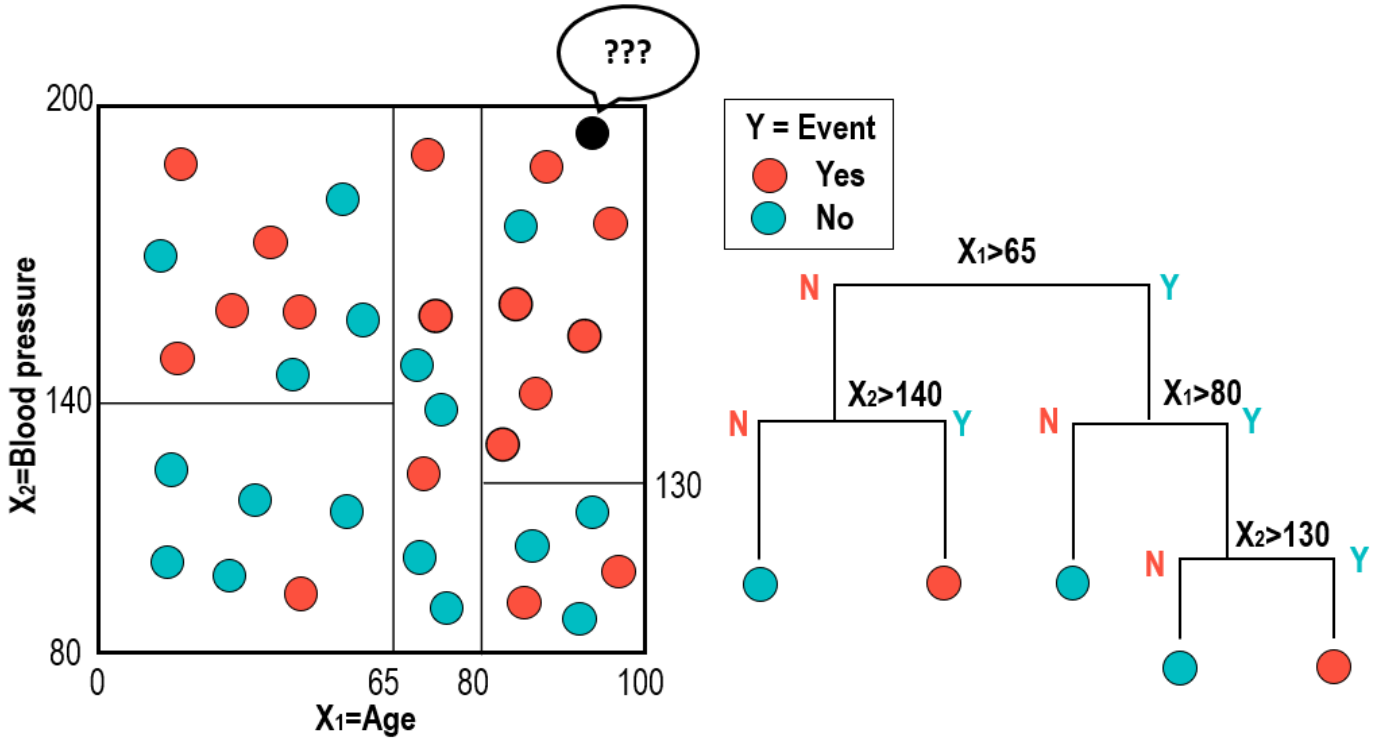
Figure 2. Cumulative incidence of MACE according the presence of DM and CMD



NO at risk					
Group A	134	134	132	129	101
Group B	51	51	51	51	37
Group C	71	69	69	67	53
Group D	27	27	25	24	20

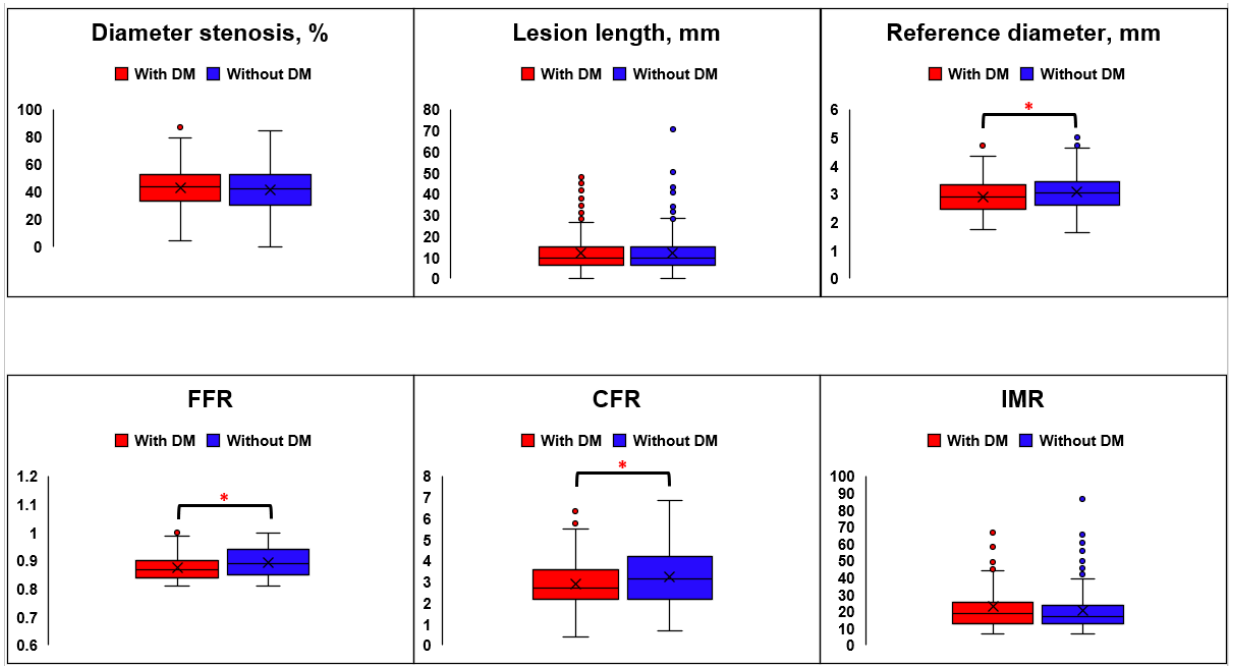
The cumulative incidence of MACE was compared among 4 groups divided according DM and CMD. Abbreviations: CI, confidence interval; CMD, coronary microvascular dysfunction; DM, diabetes mellitus; HR, hazard ratio; MACE, major adverse cardiac event (a composite of cardiac death, myocardial infarction and ischemia-driven revascularization).

Figure 3. Example of Single Decision Tree - Unit of Random Survival Forest



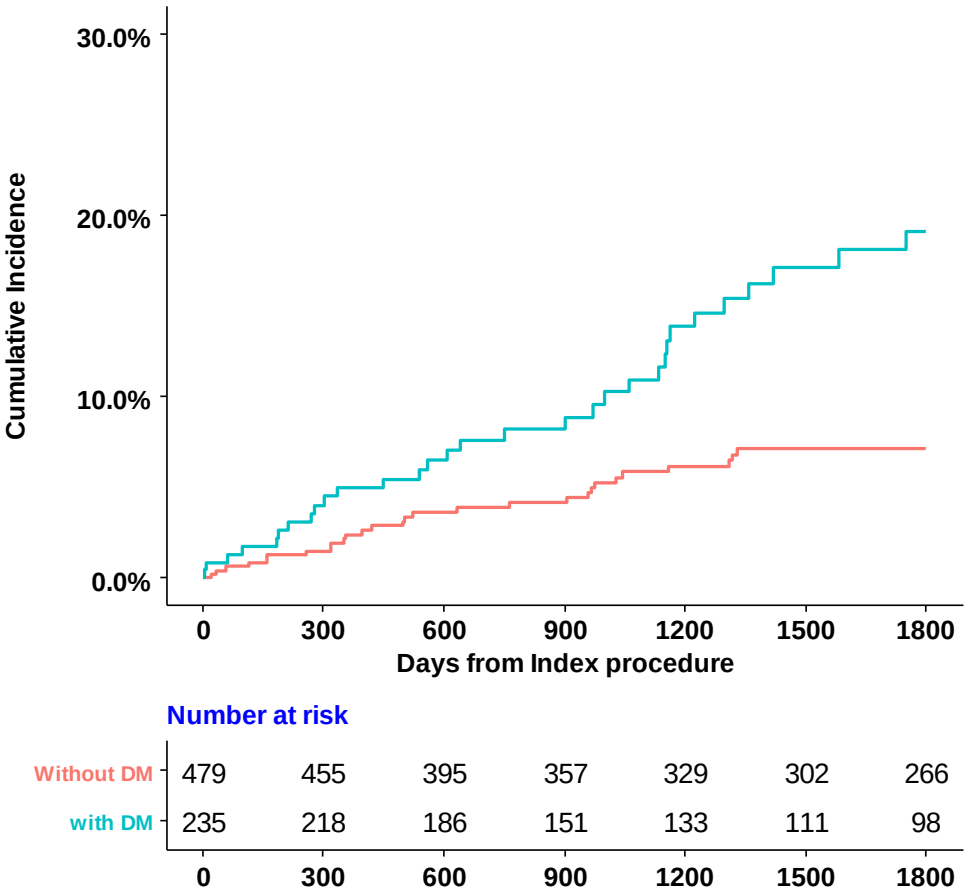
Decision Tree is a binary tree which is a decision tool that uses a binary tree-like graph or model of decisions and their possible consequences. It is a flowchart like structure where each node represents a decision (based on a selected variable) and the two branches of the node represent the outcome of the test.

Figure 4. Angiographic and physiologic characteristics according to the presence of DM



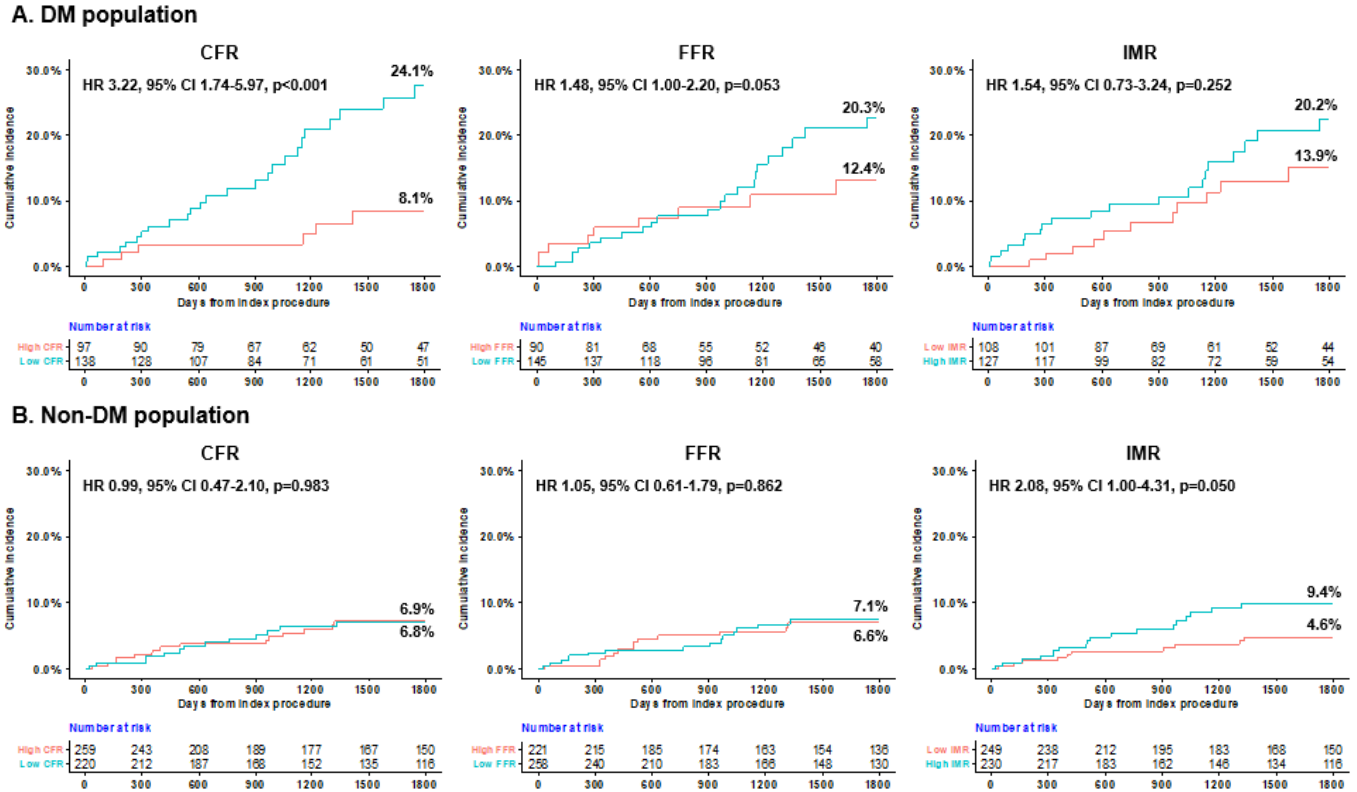
Angiographic lesion severity, described by % diameter stenosis and lesion length, was not significantly different among patients with or without DM. For coronary physiologic indices, CFR and FFR values were lower in patients with DM than those without DM. Each box ranges from upper quartile to lower quartile of the parameters and line and x inside the box indicate the location of the median and mean values. The whiskers expand from the box to upper (upper quartile + 1.5xIQR) and lower (lower quartile - 1.5 x IQR) extreme and outliers are plotted as individual dots. Red star represents a statistically significant difference using the Student's t-test. Abbreviations: CFR, coronary flow reserve; DM, diabetes mellitus; FFR, fractional flow reserve; IMR, index of microcirculatory index; IQR, interquartile ran.

Figure 5. Cumulative incidence of patient-oriented composite outcome according to the presence of DM



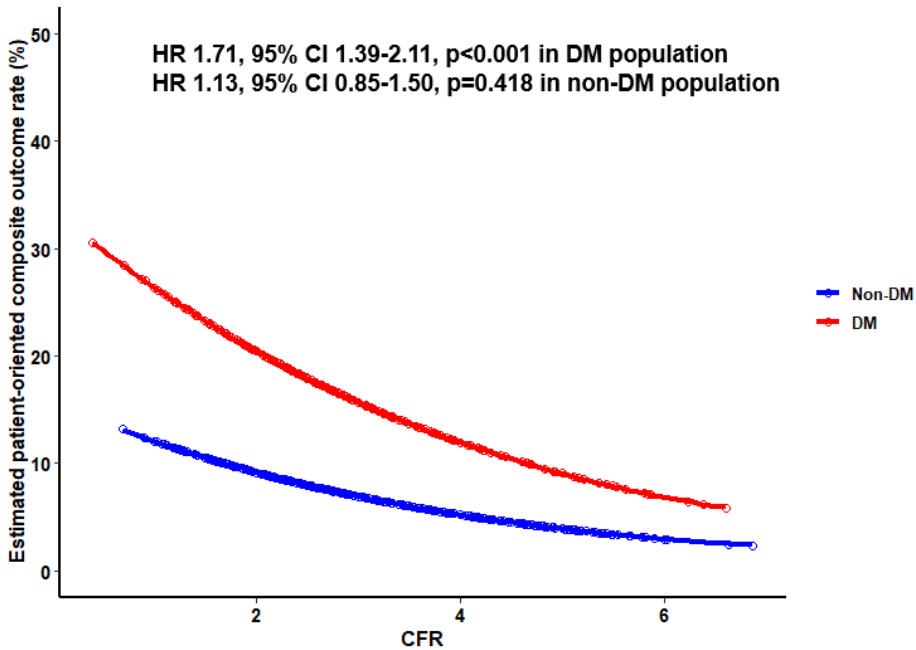
The higher risk of patient-oriented composite outcome in the DM population than the non-DM population is shown. Abbreviation: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio.

Figure 6. Cumulative incidence of POCO according to physiologic indices and the presence of DM



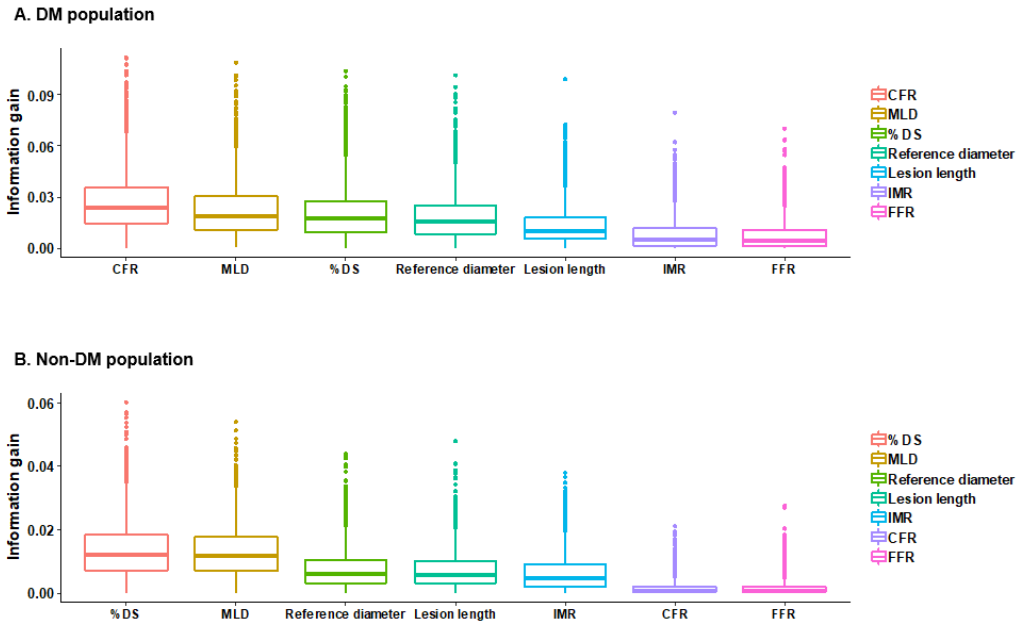
The differences in the impact of coronary physiologic indices on patient-oriented composite outcome according to the presence of DM are presented. Abbreviation: CFR, coronary flow reserve; CI, confidence interval; DM, diabetes mellitus; FFR, fractional flow reserve; HR, hazard ratio; IMR, index of microcirculatory index.

Figure 7. Association between CFR and patient-oriented composite outcome



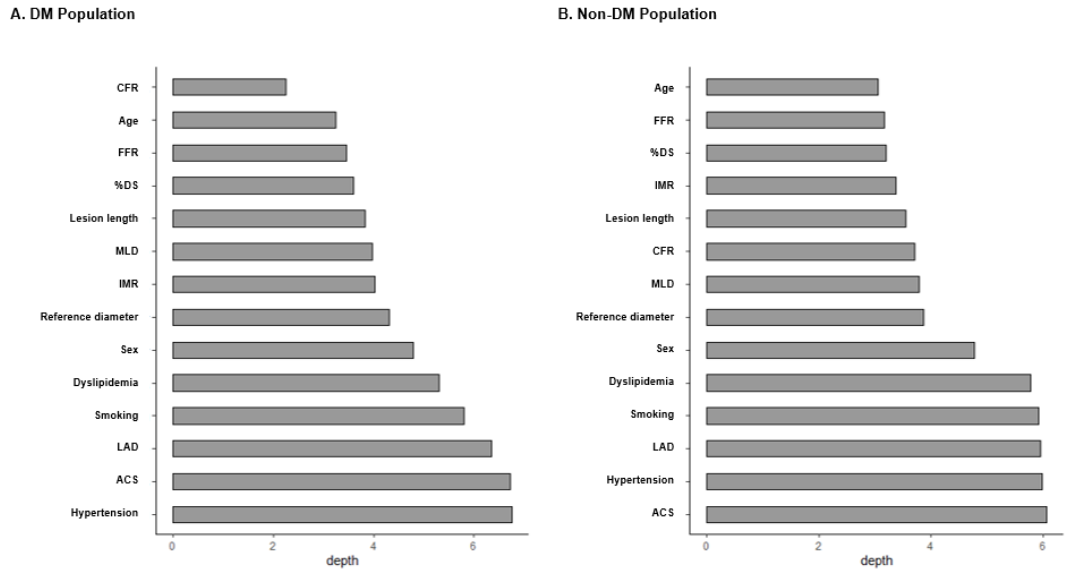
The estimated risk of patient-oriented composite outcome and its relationship with coronary flow reserve is shown. Abbreviations: CFR, coronary flow reserve; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio.

Figure 8. Information gain of angiographic and physiologic indices



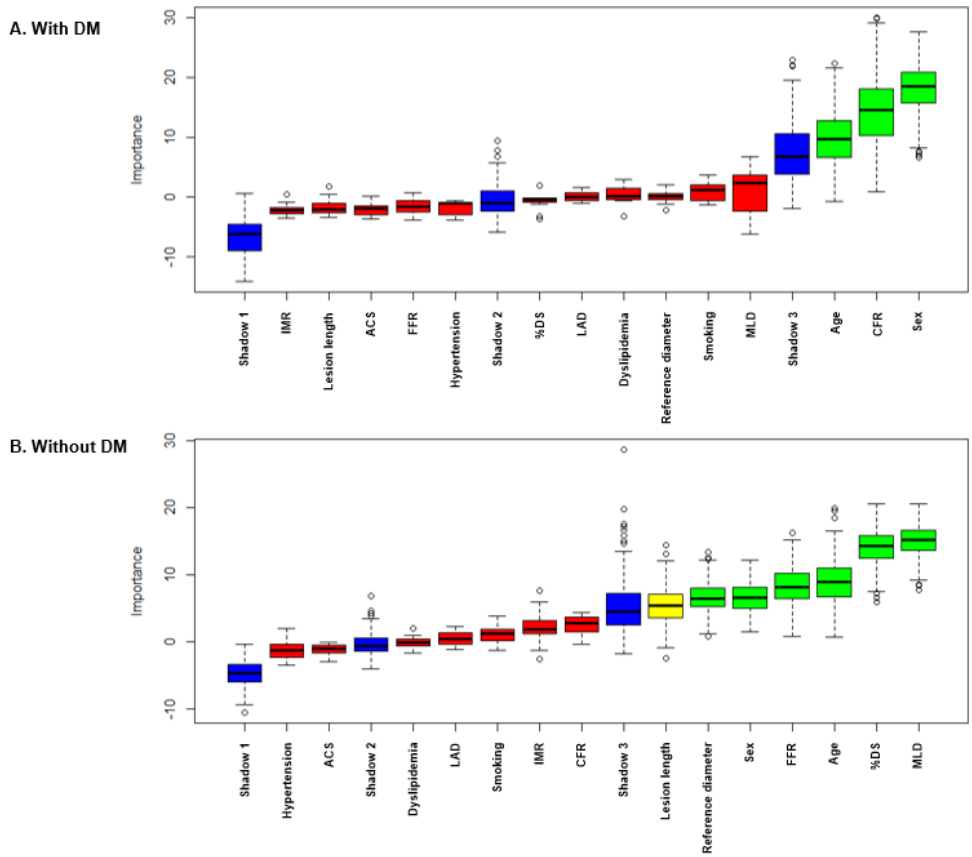
Among angiographic and physiologic indices, CFR showed the highest information gain for patient-oriented composite outcome at 5 years in the DM population and diameter stenosis in the non-DM population. Each box ranges from upper quartile to lower quartile, and line inside the box indicates the location of the median. The whiskers expand from the box to upper (upper quartile + 1.5 x IQR) and lower (lower quartile - 1.5 x IQR) extreme and outliers are plotted as individual dots. Abbreviations: CFR, coronary flow reserve; DM, diabetes mellitus; DS, diameter stenosis; FFR, fractional flow reserve; IMR, index of microcirculatory index; MLD, minimal lumen diameter; IQR, interquartile range.

Figure 9. Comparison of variable importance using "Minimal Depth" according to presence of DM



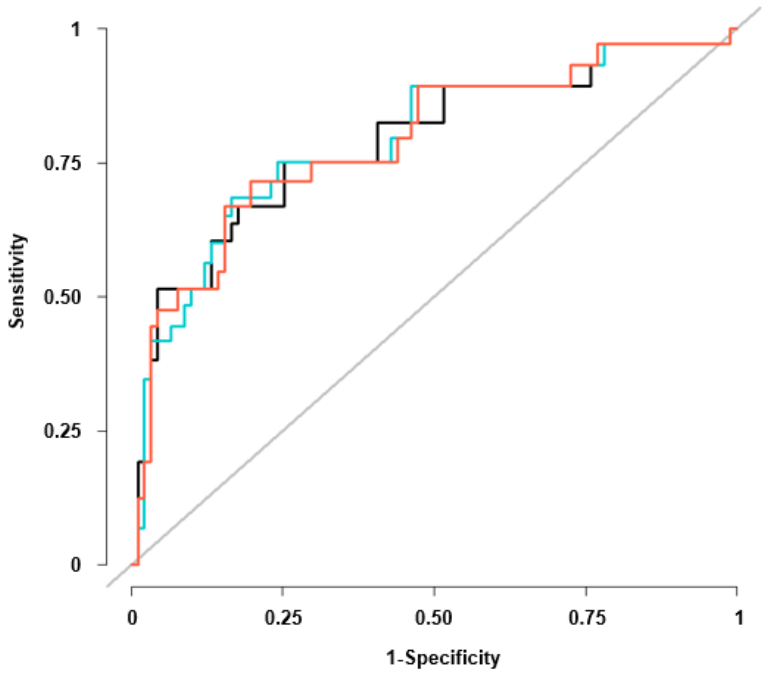
The shortest distance from the root node to the root of the closest maximal subtree of the variable was shown. The smaller value of minimal depth means the more predictive value. Abbreviations: ACS, acute coronary artery; CFR, coronary flow reserve; DM, diabetes mellitus; DS, diameter stenosis; FFR, fractional flow reserve; LAD, left anterior descending; IMR, index of microcirculatory index; MLD, minimal lumen diameter.

Figure 10. Comparison of variable importance using "Boruta" according to presence of DM



Important or unimportant features based on the comparison with random variables were shown. Abbreviations: ACS, acute coronary artery; CFR, coronary flow reserve; DM, diabetes mellitus; DS, diameter stenosis; FFR, fractional flow reserve; LAD, left anterior descending; IMR, index of microcirculatory index; MLD, minimal lumen diameter.

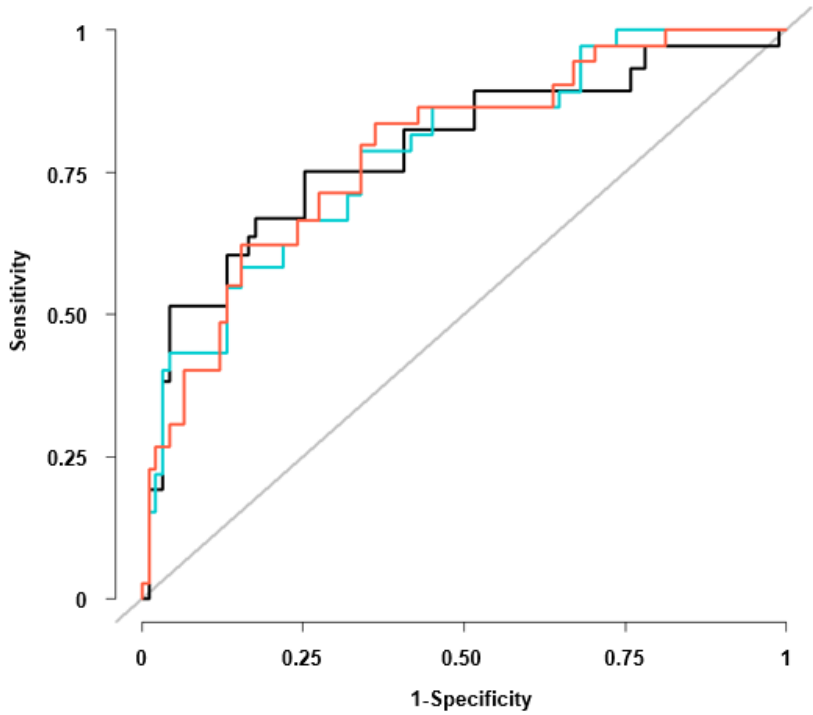
Figure 11. Comparison of Predictive Models Using Features Selected from Each Machine Learning Algorithm



	AUC	95% CI	p value
Model 1: Features from Boruta algorithm	0.73	0.63 – 0.83	Ref.
Model 2: Features from Minimal depth algorithm	0.74	0.63 – 0.85	0.606
Model 3:Features from Information gain algorithm	0.74	0.64 – 0.84	0.587

Model 1: age + sex + CFR; Model 2: CFR + age + FFR + diameter stenosis; Model 3: age + sex + CFR. Abbreviation: AUC, area under curve; CI, confidence interval.

Figure 12. Comparison of Predictive Models Using Features Selected from Each Machine Learning Algorithm



	AUC	95% CI	p value
Model 1: Features from Boruta algorithm	0.73	0.63 – 0.83	Ref.
Model 2: Model 1 + Clinical risk factors	0.75	0.65 – 0.85	0.500
Model 3: Model 2 + Invasive parameters	0.75	0.65 – 0.85	0.535

Model 1: age + sex + CFR; Clinical risk factors: acute coronary syndrome, hypertension, dyslipidemia and family history of coronary artery disease; Invasive parameters: %diameter stenosis, FFR and IMR. Abbreviation: AUC, area under curve; CI, confidence interval.

국문초록

당뇨 환자에서 기계학습을 이용한 생리학적 지표 및 위험요인이 심혈관계 예후에 미치는 영향에 대한 검증

장금룡

내과학 전공

서울대학교 의과대학 대학원

배경 및 목적:

유럽심장학회 (European Society of Cardiology) 및 유럽심장외과협회 (European Society of Cardio-Thoracific Academy) 지침에서 관상동맥 허혈 진단을 위한 침습적 표준 방법으로 분획혈류예비력 (FFR, Fractal Flow Reserve) 측정을 권고하고 있음. 그러나 표준지침으로 치료받은 일부 환자들은 여전히 심혈관 사건을 겪음. 이는 잠재적으로 허혈을 유발하거나 폐쇄성 질환의 진행을 촉진할 수 있는 미세혈관 기능장애 때문임. 이런 미세기능장애는 관상동맥 조영술로 평가할 수 없음. 관상동맥미세혈관기

능장애는 당뇨환자에서 더 자주 생기고 장기 예후의 주요 위험요인임. 종합적인 생리학적 평가로 미세혈관 기능의 평가가 가능하기 때문에 당뇨 및 관상동맥질환이 있는 환자에서 대한 침습적 생리지표로 정의한 미세혈관 장애가 예후에 미치는 영향을 조사하고자 본 연구의 Part 1을 시행하였음. 또 샘플 크기가 확장된 본 연구의 Part 2에서는 기계학습을 이용하여 당뇨 환자에서 생리학적 지표 및 위험요인이 심혈관계 예후에 미치는 영향을 검증하고자 시행하였음.

방법:

본 연구의 첫번째 부분은 3V FFR-FRIENS study에서 사용 가능한 FFR 및 index of microcirculatory resistance (IMR)가 있는 환자 283명이 선택됨. CMD (coronary microvascular dysfunction)는 IMR≥25U로 정의함. 환자는 DM과 CMD에 따라 그룹 A(DM-, CMD-), 그룹 B(DM-, CMD+), 그룹 C(DM+, CMD-), 그룹 D(DM+, CMD+)로 분류됨. 이 선행 연구에서 1차 평가변수는 2년의 major adverse cardiac event (MACE, 심장사, 심근경색 및 허혈성 기반 혈관재개통술)로 정의함. 두번째 부분은 Korea-Japan-Spain registry에서 FFR (>0.80)에 따라 관상동맥 재개통술이 지연되고 관상동맥 혈류예비력(CFR, coronary flow reserve), IMR을 포함한 종합적인 생리학적 평가가 이루어진 환자 714명(DM을 가진 환자 235명)이 선택됨. CFR, IMR, FFR의 높은 그룹 또는 낮은 그룹을 분류하는데 중간값 CFR(2.88), FFR(0.88), IMR(17.85)이 사용됨. 이 부분의 1차 평가변수는 POCO (patient-oriented composite outcome) 5년 내의 모든 원인 사망, 심근경색, 모든 혈관

재개통술로 정의함.

결과:

첫 부분에서 당뇨 환자들은 비당뇨환자에 비해 MACE의 위험성이 높음(HR 4.88, 95% CI 1.54-15.48, p=0.003). 4개 그룹의 2년 MACE는 각각 2.2%, 2.0%, 7.0%, 18.5%. 그룹 D는 그룹 A에 비해 MACE의 위험도가 현저히 높음(HR 8.98, 95% CI 2.15-37.41, p=0.003). 다변량 회귀 분석에서 2년 MACE의 독립적인 예측인자는 CMD를 동반한 당뇨환자 (HR 11.24, 95% CI 2.53-49.88, p=0.002). CMD를 당뇨에 추가했을때 예측 능력이 향상됨(C-index 0.683 vs 0.710, p=0.010). 두번째 부분에서, 비당뇨군과 비교했을 때, 당뇨군은 5년 POCO의 위험성이 더 높음(HR 2.49, 95% CI 1.64-3.78, p<0.001). 당뇨군에서 낮은 CFR 그룹은 높은 CFR 그룹보다 POCO의 위험이 높음(HR 3.22, 95% CI 1.74-5.97, p<0.001). CFR 값은 비당뇨군에서 POCO의 위험을 구별할 수 없음. POCO의 위험성을 예측함에 있어서 CFR과 당뇨 사이에 유의한 상호작용이 있었다(interaction p=0.025). 5년 POCO에 대한 독립적인 예측 인자는 당뇨군에서 낮은 CFR과 관상동맥 가족력, 비당뇨군에서 관상동맥 질환의 percent diameter stenosis와 다혈관 질환임. 당뇨군에서 POCO를 예측함에 있어서 다른 요인에 비해 CFR은 가장 많은 정보를 가지고 있었음. "Minimum Depth" 알고리즘을 사용했을 때 CFR은 가장 중요한 예측요인이고 "Boruta" 알고리즘을 사용했을 때 의미 있는 요인으로 나타남. 당뇨군에서 임상적 위험 인자(c-index 0.75 0.65-0.85, p=0.500) 혹은 임상적 시술적 위험인자(c-index 0.75, 95%CI 0.65-

0.85, p=0.535)를 동시에 “Boruta” 알고리즘에서 선택되어진 위험인자로 구성된 모델(c-index 0.73, 95% CI 0.63-0.83)에 추가하였을 때 모델의 예측력은 유의하게 높아지지 않았음.

결론:

CMD를 동반한 당뇨는 심혈관 질환 위험의 증가와 관련이 있음. 당뇨환자에서 CMD의 추가는 MACE발생의 예측력을 높임. 관상동맥 생리학적 지표와 위험 인자들이 예후에 미치는 역할은 당뇨여부에 따라 다름. 어떤 방법을 사용하는지 불구하고 CFR은 예후를 예측하는 중요한 지표임. 기계학습은 가장 효과적이고 효율적인 변수조합을 찾아 예후를 더 잘 예측할 수 있음.

주요어: 관상동맥질환, 당뇨, 분획혈류예비력, 관상동맥 미세혈관 기능부전, 관상동맥혈류예비력, 관상동맥 미세혈관 저항지수, 기계학습.

학번: 2017-39235