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Original article

High-sensitivity cardiac troponin T level is associated with angiographic complexity of coronary artery disease : A Cross-Sectional Study

Troponin and SYNTAX score

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Abstract

Background: High levels of high-sensitivity cardiac troponin T (hs-cTnT) are associated with coronary artery disease (CAD). The SYNTAX score (SXscore) is an angiographic tool used to grade the complexity and extent of CAD. We investigated the relationship between hs-cTnT levels and SXscore.

Methods and Results: We conducted a cross-sectional analysis of 408 patients who underwent first diagnostic coronary angiography between December 2011 and December 2012. SXscore was recorded, and serum hs-cTnT levels were measured in all patients. The median hs-cTnT level was 0.009 μg/L. Elevated hs-cTnT levels (≥ 0.014 μg/L) were observed in 136 patients (33%). Twenty-seven patients (7%) had complex CAD as defined by intermediate or high SXscores. The levels of hs-cTnT were significantly higher in patients with high or intermediate SXscores than in those with low SXscores (0.044 ± 0.055 μg/L vs 0.018 ± 0.058 μg/L, $p = 0.03$). Multivariate analysis identified hs-cTnT level, and diabetes mellitus as independent predictors for complex CAD. The adjusted odds ratio of hs-cTnT level for predicting complex CAD was 2.86 (95% confidence interval 1.90–4.45, $p < 0.0001$). Predictive value of the adjusted area under the receiver operating characteristic curve for complex CAD significantly improved after inclusion of the hs-cTnT (C statistic, 0.882 vs. 0.784).

Conclusions: Measurement of serum hs-cTnT level has an important role in the risk stratification of patients who have a plan for diagnostic coronary angiography. In patients with clinically stable angina pectoris, slightly elevated hs-cTnT levels may indicate the presence of complex CAD.

Introduction

A number of biochemical markers are used to assess cardiovascular disease, and cardiac troponin assays are widely used to diagnose patients with acute myocardial infarction and coronary artery disease (CAD) [1,2]. An elevation of cardiac troponin always suggests myocyte necrosis [3]. However, the new fifth generation high-sensitivity cardiac troponin T (hs-cTnT) assay can identify slightly elevated hs-cTnT levels in patients with suspected ischemic heart disease, and can even detect circulating hs-cTnT levels in normal individuals [4]. A previous study found slightly elevated hs-cTnT levels were detectable in the majority of patients with stable angina pectoris and preserved left ventricular function and were significantly associated with an increased incidence of cardiovascular death and heart failure [5]. Another study showed that in patients with stable angina pectoris, there was a close relationship between hs-cTnT levels and the extent of CAD [6]. Therefore, hs-cTnT levels may be associated with the severity of CAD. The recently developed SYNTAX score (SXscore) is a comprehensive angiographic scoring system derived from the coronary anatomy and the characteristics of coronary lesions [7]. We conducted a cross-sectional analysis to investigate the relationship between hs-cTnT levels and the angiographic complexity of CAD as determined by SXscore.

Methods

Study patients

We retrospectively reviewed 1023 patients who had undergone diagnostic coronary angiography in our hospital between December 2011 and December 2012. Diagnostic coronary angiography has been performed to evaluate ischaemic heart disease or cardiomyopathy and as the preoperative investigation for ischaemic heart, aortic disease, or valvular diseases. Of these, patients who had serum hs-cTnT measured prior to first coronary angiography were enrolled in the present study. Exclusion criteria included ST elevation or non-ST elevation acute coronary syndromes diagnosed at baseline, cardiac

shock, hemodialysis and previous coronary artery bypass graft surgery (Figure 1). Our study complied with the Declaration of Helsinki, and written informed consent for angiographic examination and plasma collection was obtained from all patients.

Biochemical measurements

Blood samples were collected into tubes containing lithium–heparin as an anticoagulant. Blood was centrifuged at room temperature within 30 min of collection, and the plasma supernatant was immediately separated and stored frozen at −70°C until analysis. Serum hs-cTnT was measured using Cobas 6000 (Roche Diagnostics, Tokyo, Japan) with a lower detection limit of 0.003 μg/L, (99th percentile 0.014 μg/L and ≤10% coefficient of variation 0.013 μg/L). Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured using Cobas 6000 immunoanalyzer (Roche Diagnostics). Determination of high-sensitivity C-reactive protein was performed on a LABOSPECT 008 (Hitachi, Tokyo, Japan). Other laboratory data were measured as part of routine clinical care. The estimated glomerular filtration rate (e-GFR) was used as an indicator of renal function based on the abbreviated Modification of Diet in Renal Disease study formula [8].

Angiographic assessment and SXscore

It was defined as CAD if it was confirmed the presence of obstruction of ≥ 50% of the luminal diameter of at least one native vessel on coronary angiography. On baseline diagnostic angiograms, each coronary lesion producing ≥50% diameter stenosis in vessels ≥1.5 mm in diameter was scored separately. These scores were added together to produce the overall SXscore, which was calculated using the algorithm available on the SYNTAX website [9]. SXscores were independently assessed by two experienced interventional cardiologists (with experience in calculating SXscores of >100 patients each) blinded to the blood sample data. The κ values for interobserver and intraobserver variability for estimation of SXscores were 0.75 and 0.86, respectively. When there was disagreement regarding SXscores, the average of the values from the two assessors was used as the final value [10].

Statistical analysis

The Shapiro–Wilk test was used to check for normal distribution of continuous data. Non-normally distributed data are presented as the median [interquartile range (IQR)]. Normally distributed data are presented as mean ± standard deviation (SD) or as percentages (%). Multivariate logistic regression analyses were used to assess the independent correlates of the presence of CAD and intermediate or high SXscores. Covariates in univariate analysis were age, male gender, body mass index, hypertension, systolic and diastolic pressures, diabetes, HbA1c, dyslipidemia, low-density lipoprotein, high-density lipoprotein, triglyceride, smoking, high-sensitivity cardiac troponin-T, high-sensitivety C-reactive protein, N-terminal pro-brain natriuretic peptide, estimated glomerular filtration rate, previous stroke, previous peripheral artery disease, left ventricular ejection fraction, and statin therapy. Values for hs-cTnT and NT-proBNP were entered into the model after logarithmic transformation. The odds ratio and 95% confidence intervals (CI) for clinically relevant variables with $p < 0.05$ following univariate analysis were used for multivariate analysis. The area under the receiver operator characteristic (ROC) curve was used to determine the optimal serum hs-cTnT level to detect CAD or patients with intermediate or high SXscores. The optimal cut-off value was calculated by determining the value of hs-cTnT that provided the highest sum of sensitivity and specificity. Areas under the ROC curves for these two scoring systems were compared using DeLong's test. The net reclassification index (NRI) was also analyzed to evaluate the incremental prognostic utility of hs-cTnT for predicting the patients of CAD and of intermediate or high SXscores. All analyses were performed with IBM-SPSS statistics version 19 (IBM Corporation, Armonk, New York) and the R statistical package. A p-value < 0.05 was considered to indicate statistical significance.

Results

Patient characteristics

During the 1-year study period, 408 patients (median age 72 years, 268 men [66%]) met the study inclusion criteria. Patient characteristics, clinical features, laboratory data, and SXscores are presented in Table 1. Serum hs-cTnT levels increased as the complexity of CAD, based on SXscore, increased (0.018 ± 0.058 μg/L, 0.041 ± 0.062 μg/L, and 0.057 ± 0.028 μg/L for patients with low, intermediate, and high SXscores, respectively, p = 0.07).

Prediction of the presence of coronary artery disease

CAD was confirmed in 197 patients (48%). Serum hs-cTnT levels were significantly higher in patients with CAD than in patients without CAD (0.009 ± 0.006 μg/L vs 0.031 ± 0.082 μg/L, p < 0.0003). The area under the ROC curve for the hs-cTnT level to predict the presence of CAD was 0.664 (95% CI 0.612–0.716, p < 0.0001) with low discriminatory capacity, and the optimal cut-off value to predict the presence of CAD was 0.009 μg/L close to the normal distribution. As shown in Table 2, clinically relevant 9 variables were entered into the model 1, and diabetes and male sex were identified as an independent correlate of patients with CAD. Also the model 2 which was addition of the hs-cTnT to the model 1 demonstrated that the hs-cTnT was an independent predictor of patient with CAD. Predictivity of the hs-cTnT in regarding to CAD was assessed by calculating the adjust AUC in multivariable model 1 and 2 (Figure 3-A). The c-statistics on the basis of AUCs of model 1 and 2 were 0.706 (95%Cl: 0.656 to 0.756) and 0.719 (95%Cl 0.670 to 0.768), respectively. The difference was not statistically significant between model 1 and 2 (Delong test, z test= - 0.666, p value = 0.506). For identifying CAD, the NRI was also not significant for addition of hs-cTnT to traditional risk factors (p=0.577).

Prediction of the complexity of coronary artery disease

On the basis of intermediate or high SXscores, 27 patients (7%) were identified with complex CAD and as candidates for coronary artery bypass graft surgery. Serum hs-cTnT levels were significantly higher in patients with high or intermediate SXscores than in those with low SXscores (0.044 ± 0.055 μg/L vs 0.018 ± 0.058 μg/L, p = 0.03). As shown in Figure 2, The area under the ROC curve

for the hs-cTnT level to predict the complexity of CAD, based on SXscore, was 0.879 (95% CI 0.827–0.932, p < 0.0001), and ROC curve analysis revealed an optimal cut-off value of 0.016 μg/L to predict the presence of complex CAD, with 81.5% sensitivity, 80.3% specificity, a positive predictive value of 1.6%, and a negative predictive value of 77.3%. Table 3 showed multivariate analyses for predicting patients with complex CAD. The model 2 which was additional of the hs-cTnT to the model 1 with clinically relevant variables demonstrated that the hs-cTnT was an independent predictor of patients with complex CAD. Predictivity of the hs-cTnT in regarding to complex CAD was assessed by calculating the adjust AUC in multivariable model 1 and 2 (Figure 3-B). The c statistics on the basis of AUCs of model 1 and 2 were 0.784 (95%Cl: 0.686 to 0.883) and 0.882 (95%Cl 0.817 to 0.947), respectively. The model 2 that added the hs-cTnT significantly improved the C statistics for predicting of complex CAD compared to the model 1 (Delong test, z test= - 2.54, p value = 0.011). The model 2 also improved the NRI compared with the model 1 (p < 0.0001).

Discussion

In the present study, we evaluated the relationship between hs-cTnT levels and the presence of CAD and angiographic complexity in patients who had undergone diagnostic coronary angiography. Our findings indicated that hs-cTnT could predict and the complexity of CAD as defined by SXscores, after adjustment for many traditional risk factors for CAD.

Patients with multiple coronary artery lesions have a poor clinical outcome, and require invasive coronary revascularization such as coronary artery bypass graft surgery or percutaneous coronary intervention [11, 12]. The guidelines recommend performing risk assessment and non-invasive tests before proceeding to cardiac catheterization. However, one study found that, even when non-invasive tests were performed before coronary angiography, the diagnostic yield for elective cardiac catheterization was < 40% [13]. Therefore, stratification of CAD severity according to hs-cTnT levels could be useful to identify the subset of patients at high risk. Previous research has

demonstrated a close relationship between hs-cTnT levels and the severity of CAD confirmed by the number of narrowed coronary arteries in patients with clinically stable and angiographically proved CAD [6]. However, in regards to assessing the need for revascularization therapy for multiple coronary artery lesions, the number of diseased coronary arteries was not the only important factor in determining the complexity of CAD. Indeed, the SYNTAX trial demonstrated that in patients with multiple coronary artery lesions, the clinical outcomes after coronary intervention and coronary artery bypass surgery were related to the complexity of the culprit lesions, including location, the presence of chronic totally occluded lesions, and calcification of the vessels [7]. In brief, patients with multiple coronary artery lesions can have SXscores ranging from low to high, and clinical outcomes after revascularization can differ based on SXscore. The present study showed that hs-cTnT levels increased significantly as SXscore increased. Specifically, our findings indicated a strong positive relationship between the complexity of CAD and hs-cTnT levels.

Relationship between SXscore and hs-cTnT

The reason for the positive relationship between SXscores and hs-cTnT levels was not clearly determined in the present study. In general, elevated cardiac troponin levels result from cardiomyocyte damage or necrosis [3]. In previous generation cardiac troponin assays, cardiac troponin levels < 0.01 μg/L are undetectable and considered normal, and 0.01–0.035 μg/L are interpreted as likely abnormal, but are associated with high imprecision [14]. However, the newer high sensitivity assays can detect lower circulating cardiac troponin levels in many patients with previously undetectable levels. The hs-cTnT cut-off value of < 0.014 μg/L represents the 99th percentile for healthy subjects [3]. In the present study, hs-cTnT levels of ≥ 0.014 μg/L were observed in 33% of patients with suspected CAD. Similarly, there is increasing evidence that, even in patients with stable angina pectoris and preserved left ventricular function, very low levels of cardiac troponin are detectable and are associated with an increased risk of cardiovascular death and heart failure [5, 15]. The detection of low levels of hs-cTnT in patients with stable angina could be

explained by large plaque volumes in patients with higher SXscores. One study using cardiac computed tomographic angiography demonstrated that hs-cTnT level in patients with stable angina pectoris was positively correlated with the plaque burden score and the Agatston score [16]. The presence of hs-cTnT might also indicate silent coronary plaque rupture and spontaneous microembolization, both of which can occur even patients with clinically stable CAD. Even very small pieces of debris from atherosclerotic plaques may cause myocardial injury, and consequently low hs-cTnT levels may be detected [17].

The area under the ROC curve demonstrated that the measurement of hs-cTnT for identifying CAD patients was low discriminatory capacity. Conversely, the optimal cut-off value of hs-cTnT of 0.016 μg/L for identifying patients with intermediate or high SXscores was slightly elevated compared with those with low SXscore. The findings from this study have certain clinical implication, that is, a slightly elevated level of hs-cTnT could be used to identify complex CAD in patients who have a plan for diagnostic coronary angiography. Moreover, in patients with chest pain syndromes or with coronary risk factors including diabetes and so on, the measurement of hs-cTnT levels may provide necessity of diagnostic coronary angiography and an important information on lesional complexity of coronary arteries.

Before drawing conclusions, the findings of the present study should be carefully interpreted. Chronic kidney disease was present in 57% of the patients in our study population. This number seems to be considerably high. The stages of chronic kidney disease were as follows; grade 1 (e-GFR > 90ml/min, n=13 [3.2%]), grade 2 (e-GFR 60-89 ml/min, n=164 [40.2%]), grade 3a (e-GFR 45-59 ml/min, n=133 [32.6%]), grade 3b (e-GFR 30-44 ml/min, n=84 [20.6%]), and grade 4 (e-GFR < 30ml/min, n=14 [3.4%]). It should also be noted that elevated cardiac troponin levels have been reported with patients with chronic kidney disease [18]. Therefore, patient's selection bias of this study may be the source of limitation. However, adjustment using multivariate analyses did not identify the confounder of e-GFR, thus minimizing the potential for bias. Moreover, diagnosis of CAD was a relatively low rate (48%) in the present study. The reasons why first diagnostic coronary

angiography was performed in the present study were investigation of suspected ischemic heart disease (n=281, 69%), cardiomyopathy (n=18, 4%), and the preoperative investigation (n=109, 27%). The incidences of CAD in patients with cardiomyopathy and preoperative investigation were 11.1% and 20.4% with low rate, respectively. The bias referred for diagnostic coronary angiography might be another limitation.

In conclusion, measurement of serum hs-cTnT levels, a valuable tool for the prompt diagnosis of acute myocardial infarction, has a potentially important role in the risk stratification of patients who have a plan for diagnostic coronary angiography. In patients with clinically stable angina pectoris, slightly elevated hs-cTnT levels may indicate the presence of complex CAD and the presence of multiple coronary artery lesions.

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We confirm that this manuscript has not been published and is not being considered for publication All the authors have significantly contributed to this work, have read the manuscript, and approved its submission.

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Disclosures

All authors have no financial conflicts of interest to disclose concerning the manuscript.

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Figure legends

Figure 1

Study flow chart

Figure 2.

The area under the receiver operating characteristic curve for the hs-cTnT level to identify patients with intermediate or high SYNTAX scores.

Figure 3-A

Adjusted receiver-operating characteristic curves to identify patients the presence of coronary artery disease by the model 1 and 2. 95%Cl, 95% confidence interval.

Model 1: Clinically relevant variables

Model 2: Model 1 plus high-sensitivity cardiac troponin T

Figure 3-B

Adjusted receiver-operating characteristic curves to identify patients with intermediate or high SYNTAX scores by the model 1 and 2. 95%Cl, 95% confidence interval.

Model 1: Clinically relevant variables

Model 2: Model 1 plus high-sensitivity cardiac troponin T

Table 1 Baseline patient characteristics

Total number	n = 408
Age, years	72 (64, 79)
Men	268 (66%)
Body mass index, kg/m^2	23.2 (21.2, 25.3)
Hypertension	277 (68%)
Systolic blood pressure, mmHg	122 (110, 132)
Diastolic blood pressure, mmHg	66 (60, 72)
Diabetes mellitus	123 (30%)
Insulin user	19 (5%)
HbA1c, %	5.5 (5.2, 6.1)
Dyslipidemia	233 (57%)
Low-density lipoprotein, mg/dL	103 (85, 124)
High-density lipoprotein, mg/dL	55 (45, 67)
Triglyceride, mg/dL	112 (78, 164)
Smoker	154 (38%)
High-sensitivity cardiac troponin T, μg/L	0.009 (0.004, 0.016)
High-sensitivity cardiac troponin T, ≥0.014 μg/L	136 (33%)
High-sensitivity C-reactive protein, mg/dL	0.056 (0.023, 0.125)
N-terminal pro-brain natriuretic peptide, ng/L	187 (70, 612)

Estimated glomerular filtration rate, mL/min	57.9 (47.9, 68.8)
Chronic kidney disease	231 (57%)
Previous stroke events	28 (7%)
Previous peripheral artery disease	23 (6%)
Left ventricular ejection fraction, %	65 (60, 70)
Statin therapy on admission	197 (48%)
Presence of coronary artery disease	197 (48%)
SYNTAX score	
Low (0–22)	381 (93%)
Intermediate (23–32)	21 (5%)
High (≥ 33)	6 (2%)

Data are presented as median (25th, 75th percentiles) or number of patients (percentage).

Table 2. Two models of predictors of patients with coronary artery disease

Variables	Unadjusted odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Model 1: Clinically relevant variables				
Diabetes mellitus	2.67 (1.73–4.17)	<0.0001	2.14 (1.29–3.58)	0.003
Male sex	1.82 (1.20–2.77)	0.005	2.29 (1.32–4.03)	0.004
Hypertension	2.32 (1.52–3.60)	0.0001	1.68 (0.99–2.88)	0.06
Age	1.04 (1.02–1.06)	<0.0001	1.03 (1.01–1.05)	0.016
Dyslipidemia	1.59 (1.07–2.37)	0.02	1.37 (0.83–2.26)	0.21
High-density lipoprotein	0.98 (0.97–0.99)	0.03	1.00 (0.98–1.01)	0.93
Estimated glomerular filtration rate	0.98 (0.96–0.99)	0.002	0.99 (0.98–1.01)	0.28
Smoker	1.70 (1.14–2.55)	0.01	1.22 (0.73–2.03)	0.44
High-sensitivity C-reactive protein	1.24 (1.06–1.45)	0.006	4.28 (1.31–17.14)	0.03
Model 2: Model 1 plus high-sensitivity cardiac troponin T				
High-sensitivity cardiac troponin T*	2.16 (1.70–2.81)	<0.0001	1.75 (1.29–2.44)	0.0006
Diabetes mellitus	2.67 (1.73–4.17)	<0.0001	2.05 (1.23–3.46)	0.006

Male sex	1.82 (1.20–2.77)	0.005	1.93 (1.10–3.44)	0.02
Hypertension	2.32 (1.52–3.60)	0.0001	1.62 (0.94–2.81)	0.08
Age	1.04 (1.02–1.06)	<0.0001	1.02 (0.99–1.04)	0.13
Dyslipidemia	1.59 (1.07–2.37)	0.02	1.44 (0.86–2.40)	0.16
High-density lipoprotein	0.98 (0.97–0.99)	0.03	1.00 (0.98–1.01)	0.92
Estimated glomerular filtration rate	0.98 (0.96–0.99)	0.002	1.00 (0.98–1.01)	0.78
Smoker	1.70 (1.14–2.55)	0.01	1.30 (0.77–2.19)	0.32
High-sensitivity C-reactive protein	1.24 (1.06–1.45)	0.006	1.98 (0.57–8.52)	0.32

*for each unit increase in natural logarithm

CI: confidence interval

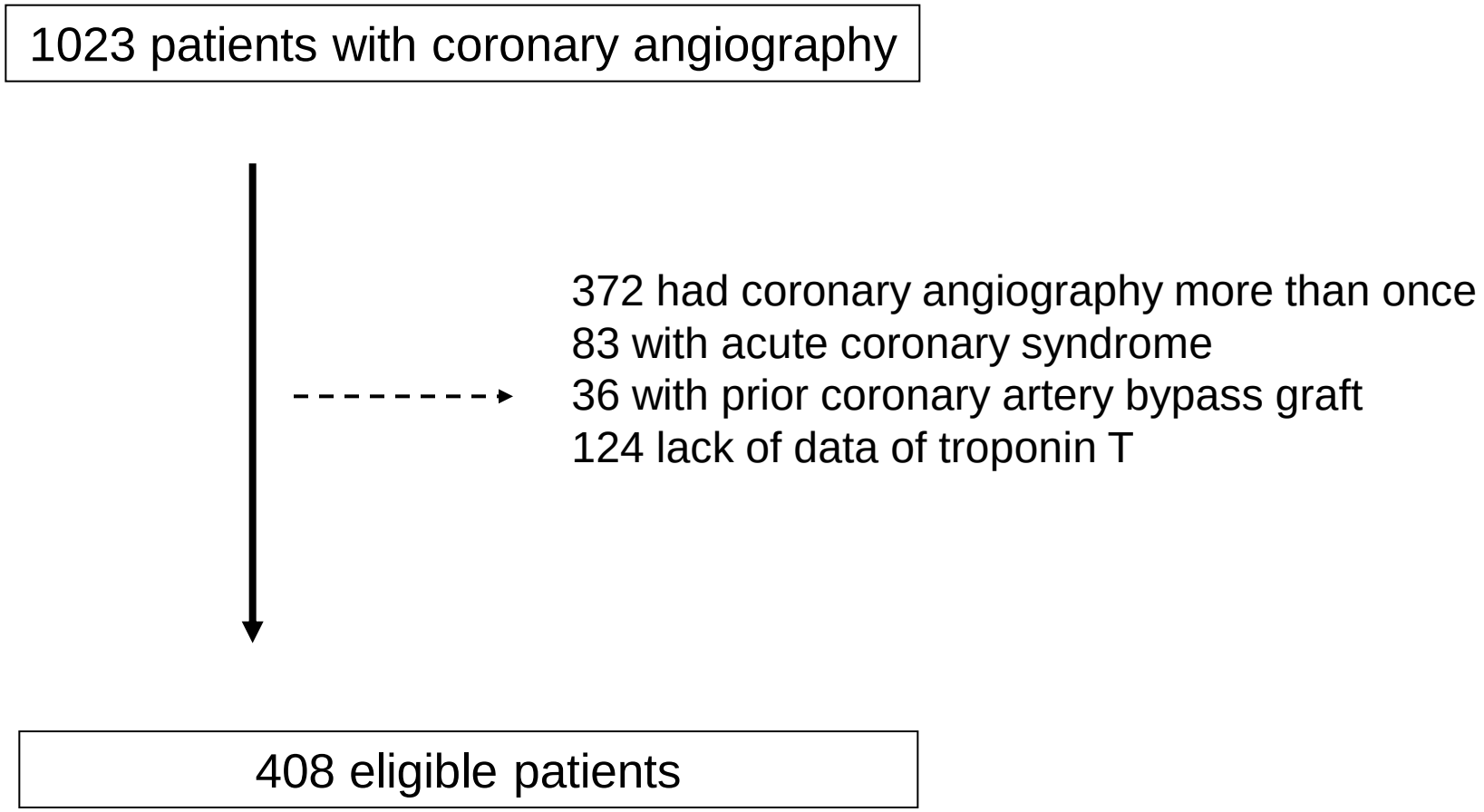
Table 3. Two models of predictors of patients with intermediate or high SYNTAX score

Variables	Unadjusted odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Model 1: Clinically relevant variables				
Diabetes mellitus	3.72 (1.69–8.50)	0.001	3.36 (1.45–7.99)	0.005
Estimated glomerular filtration rate	0.97 (0.94–0.99)	0.009	0.99 (0.96–1.02)	0.48
High-sensitivity C-reactive protein	9.58 (3.41–31.50)	<0.0001	8.08 (2.31–32.41)	0.002
Model 2: Model 1 plus high-sensitivity cardiac troponin T				
High-sensitivity cardiac troponin T*	2.88 (2.07–4.20)	<0.0001	2.86 (1.90–4.45)	<0.0001
Diabetes mellitus	3.72 (1.69–8.50)	0.001	4.20 (1.70–11.09)	0.002
Estimated glomerular filtration rate	0.97 (0.94–0.99)	0.009	1.0 (0.97–1.03)	0.99
High-sensitivity C-reactive protein	9.58 (3.41–31.50)	<0.0001	1.74 (0.44–6.88)	0.42

*for each unit increase in natural logarithm

SYNTAX: The SYNergy between percutaneous intervention with TAXus drug-eluting stents and cardiac surgery, CI: confidence interval

Figure 1 Study Flow Chart



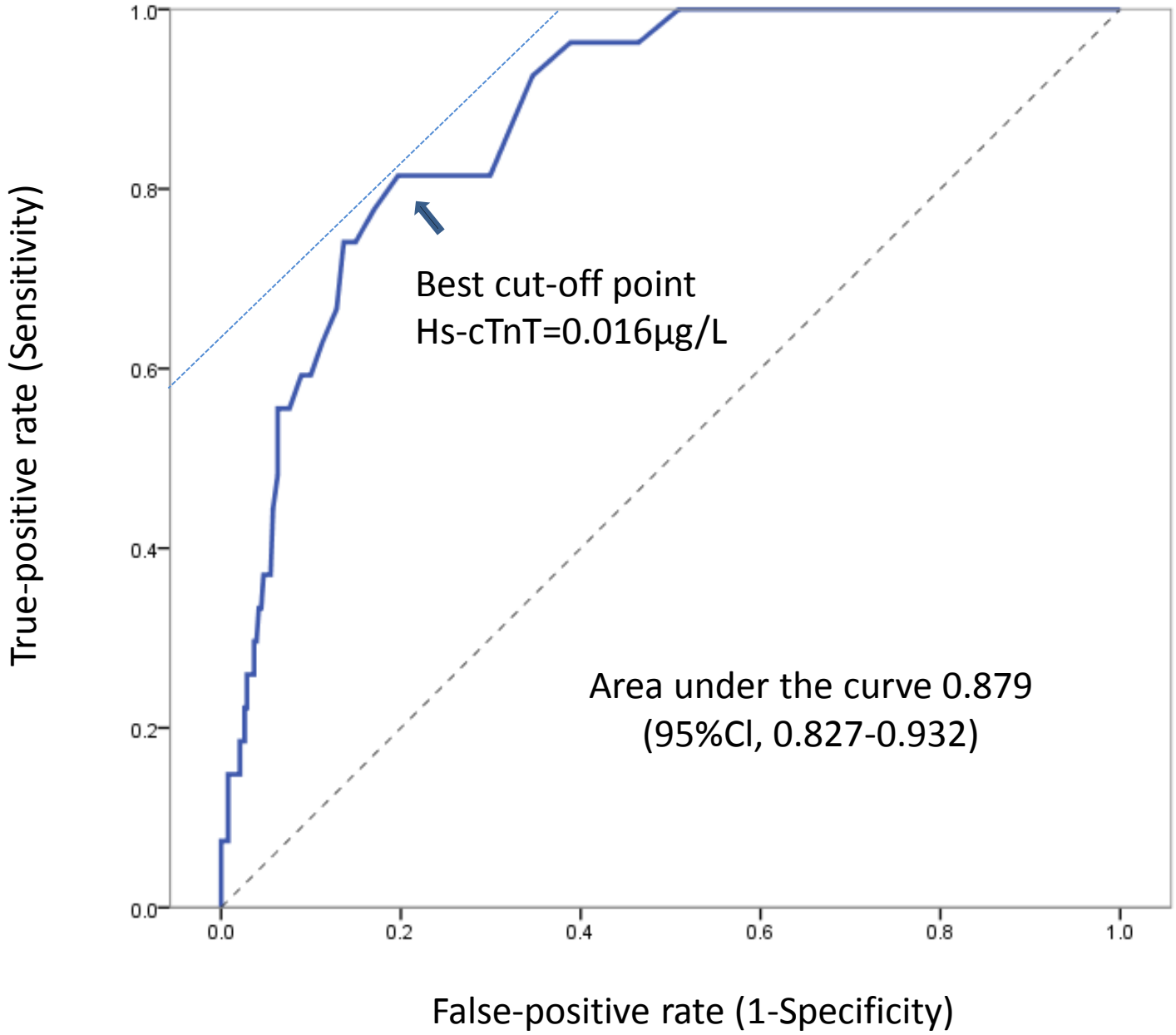
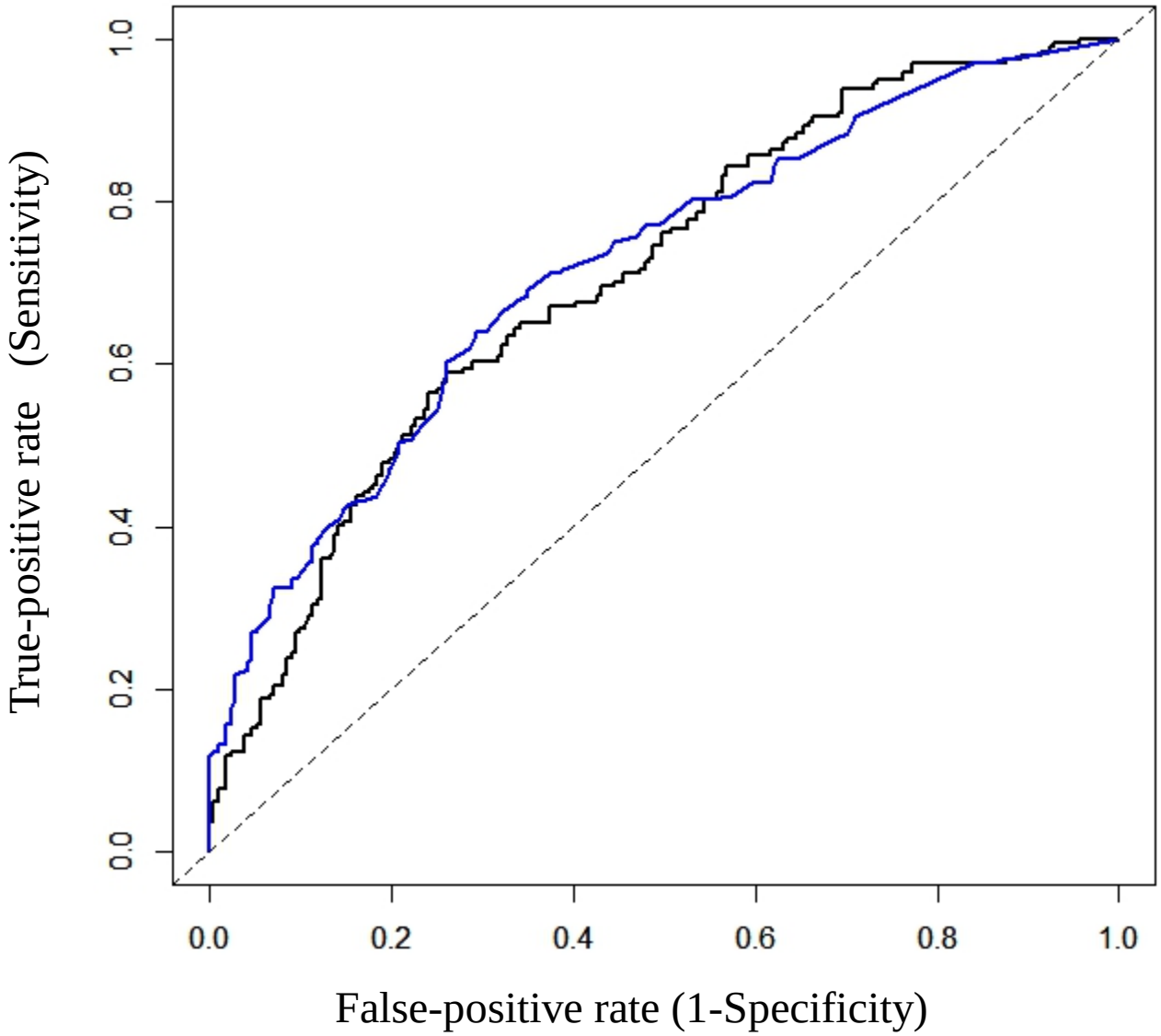

True-positive rate (Sensitivity)
1.0
0.8
0.6
0.4
0.2
0.0
Best cut-off point
Hs-cTnT=0.016μg/L
Area under the curve 0.879
(95%CI, 0.827-0.932)
0.0
0.2
0.4
0.6
0.8
1.0
False-positive rate (1-Specificity)

Figure 2

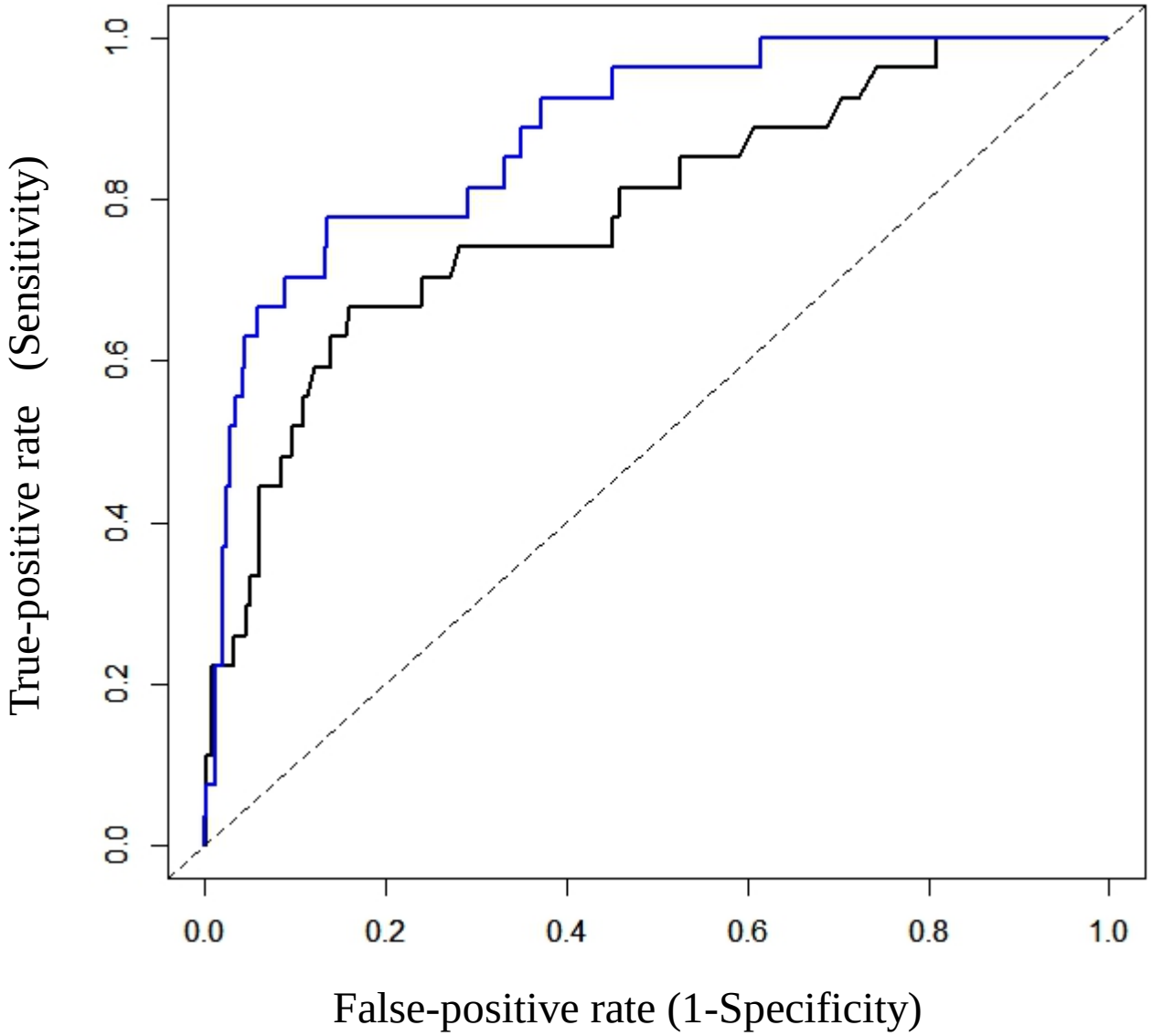
Figure 3-A



Model 1 : C statistic, 0.706 , 95%CI 0.656−0.756 (DeLong)

Model 2 : C statistic, 0.719 , 95%CI 0.670−0.768 (DeLong)

Figure 3-B



Model 1 : C statistic, 0.784 , 95%CI 0.686−0.883 (DeLong)

Model 2 : C statistic, 0.882 , 95%CI 0.817−0.947 (DeLong)