Association between Superoxide Dismutase, C-Reactive Protein, Fibrinogen and Heart Failure in Patients with Diabetes and Acute Coronary Syndrome

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Article

Keywords: Superoxide dismutase, Inflammation marker, C-reactive protein, Fibrinogen, Diabetes with acute coronary syndrome, Heart failure, Left ventricular ejection fraction

Posted Date: July 7th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1733313/v1

Abstract

Background: Superoxide dismutase (SOD) and inflammatory markers are reported to have association with cardiovascular disease. However, no previous study has assessed the value of SOD and inflammatory markers as predictive indicator of heart failure in patients with diabetes and acute coronary syndrome (ACS) in the same study.

Objective: The objective of this study is to compare the predictive implications of SOD activity, C-reactive protein (CRP) and fibrinogen for reduced left ventricular ejection fraction (LVEF) in patients with diabetes and ACS.

Method: The study included 2377 inpatients with type 2 diabetes who had an ACS admitted to the Shandong Provincial Hospital affiliated to Shandong First Medical University from January 2016 to January 2021.

Result: Despite taking the lowest quartile as reference (OR 0.368, 95% CI 0.493–0.825, P = 0.001) or examining 1 normalized unit increase (OR 0.651, 95% CI 0.482–0.880, P = 0.005), the SOD activity was exhibited to be the strongest predictive indicator of reduced LVEF, independent of confounding factors. The SOD activity showed the most powerful predictor value for reduced LVEF with the highest area under the receiver operating characteristic curve of 0.658.

Conclusions: SOD activity is a stronger predictor of reduced LVEF than CRP and fibrinogen in patients with diabetes and ACS.

Introduction

The patients with acute coronary syndrome (ACS) remain at high risk for recurrent cardiovascular events (CVEs) despite the use of guideline-recommended treatment. This risk is particularly high among patients with diabetes mellitus (1). Heart failure (HF) is the terminal stage of a wide range of CVEs that result in the decompensation of the heart's ability to contract or relax. The burden of HF events and HF death remains substantially high in patients with type 2 diabetes and established cardiovascular disease (2, 3), even in patients with optimally controlled background risk factors and glycemic control (4). Therefore, identify the low-cost, easily accessible and applicable biomarkers in patients with diabetes and ACS is crucial for better clinical management to reduce future CVEs.

The pathophysiology of HF is mediated by a variety of biological mechanisms and thus a great number of biomarkers can be measured that potentially give the clinician important predictive information. During the last decade, superoxide dismutase (SOD), C-reaction protein (CRP) and fibrinogen have been studied to identify subgroups of patients at high risk of HF (5, 6), although cardiac troponins and natriuretic peptides are the most widely used predictive biomarkers in the management of HF(7). SOD, CRP and fibrinogen reflect the different pathophysiological pathways in HF.

Oxidative stress is involved in the development and progression of experimental and clinical heart failure(8–11). Oxidative stress is defined as a dysregulation between the production of reactive oxygen species (ROS) and the endogenous antioxidant defense mechanisms. Superoxide dismutase (SOD) is responsible for the inactivation of ROS in cardiomyocytes. Previous studies have found that SOD plays an important role in the

development of HF in animal model (12–14) and clinical practice (5). To our knowledge, although a study has recently shown that SOD is a potential link between left ventricular structure remodeling and the development of subsequent HF in patients with cardiovascular disease(15), the relationship between SOD and LVEF has not been evaluated in the patients with diabetes and ACS.

Systemic inflammation has been recognized as a common pathobiologic feature of heart failure (HF) (16, 17). CRP has been established a classical marker for systemic inflammation, and fibrinogen reflects both inflammation and thrombosis. Elevated CRP and fibrinogen have been reported to predict increased risk of incident HF in a population with a high prevalence of diabetes (6). However, conclusions from some studies are inconsistent. For example, Biasucci et al.(18) reported that CRP was a significant predictor of cardiovascular disease only among individuals without diabetes, whereas Kaptoge et al.(19) and Kengne et al. (20) reported that the association between CRP and cardiovascular mortality was similar in individuals with and without diabetes (19, 20). Analysis from The AtheroGene Study reported that the fibrinogen could not provide additional information to that provided by traditional cardiovascular risk factors in predicting cardiovascular events in adults without known cardiovascular disease (21). However, results from The Strong Heart Study showed that fibrinogen was strongly associated with incident HF and the association persisted after adjusting for conventional risk factors (6). Therefore, it is worthwhile to further evaluate the association between CRP, fibrinogen and the risk of HF. In addition, although SOD, CRP and fibrinogen are reported to associate with heart failure, few studies have compared their predictive implications in heart failure in the patients with diabetes and ACS, particularly in the context of many other known risk factors for clinical outcomes within one population.

It has reported that left ventricular ejection fraction (LVEF) was an important predictor of fatal and nonfatal cardiovascular outcomes in those with moderate to severe reductions in left ventricular systolic function, but a poorer predictor of cardiovascular outcomes in those with an LVEF above 45% (22). Therefore, in this study, we aimed to compare the predictive implications of SOD, CRP and fibrinogen for incident of LVEF $\leq$ 45% in patients with diabetes and ACS after adjustment for other relevant clinical covariates.

Methods

Study subjects. The study included 4302 inpatients with type 2 diabetes who had an ACS admitted to the Shandong Provincial Hospital affiliated to Shandong First Medical University from January 2016 to January 2021. Patients could have T2DM diagnosed by World Health Organization criteria before the qualifying ACS, and ACS was defined as an ST-segment elevation MI (STEMI), non-STEMI, or unstable angina (23). Major exclusion criteria were 1) type 1 diabetes; 2)an age is less than 30 years; 3) a previous history of percutaneous coronary intervention, coronary-artery bypass graft surgery, coronary revascularization procedure, uncontrolled arrhythmias, significant valve disease, renal dysfunction, liver problems, all types of cancer; 4) missing or incomplete echocardiography parameters, laboratory measurements, clinical characteristics, or demographic characteristics. Therefore, a total of 2377 subjects (1442 men and 935women), in whom LVEF was available after acute coronary syndrome, were included.

Written informed consents were obtained from all subjects. The study was approved by the institutional review board of Shandong Provincial Hospital affiliated to Shandong First Medical University. All methods were

performed in accordance with the relevant guidelines and regulations.

Clinical and laboratory assessment. The blood samples were collected on initial presentation to hospital and were sent to the laboratory for testing as soon as possible. Baseline population characteristics were collected from medical records, prior medication and self-reports. Routine blood test, myocardial injury assessment, liver and nephric function tests as well as echocardiography were performed on admission or the next morning after hospital admission, then reviewed when needed. SOD activity was measured by using pyorgallol auto xidation method (Superoxide Dismutase Assay Kit, Fuyuan Biotechnology Co. Ltd., Fujian, China) and level of serum CRP was detected by immunoturbidimetric method (Full Range C-Reactive Protein reagent Kit, Dongou Biotechnology Co. Ltd., Zhejiang, China), following the manufacturer's instructions using an automatic analyzer (Beckman Coulter chemistry analyzer AU5800, Beckman Coulter Co., Ltd, Tokyo, Japan). Level of serum fibrinogen was measured by HemoslL Fibrinogen-C XL using coagulation instrument (Werfen ACL TOP700, Instrumentation Laboratory Co., NY, USA). LVEF was measured using a General Electric GE Vivid E9 Ultrasound System, and by the biplane method (Simpson) when the endocardial border of the left ventricle was well defined and whenever regional wall-motion abnormalities were present, or alternatively by the Teichholz method (24). The management of all data and quality control were performed with an electronic data capture system (Yiducloud Technologies Co., Ltd).

Statistical analysis. The distribution of the different variables was examined for normality by the Kolmogotov-Smirnov test. Continuous variables in mean (SD) or geometric mean (95% confidence interval) and categorical variables were expressed in percentages. Between-group differences with respect to continuous variables of normal distribution were assessed using Student T-test or one-way ANOVA, and continuous variables of non-normal distribution were assessed using Mann–Whitney U test or Kruskal–Wallis test. Between-group differences with respect to categorical variables were assessed using a Chi-square test.

Unadjusted and adjusted logistic regression analyses were performed to evaluate the intensity of the association between each biomarker and reduced LVEF. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. The variates were selected based on univariate analysis ($P < 0.05$). The model used in fully adjusted logistic regression analysis included gender, smoking history, systolic blood pressure (SBP), alanine aminotransferase (ALT), high density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), HbA1c, serum creatinine (Cr), serum uric acid (UA), NT-proBNP and hs-cTnT. As determinants of the biomarkers, age, diastolic blood pressure (DBP), aspartate aminotransferase (AST), low density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglyceride (TG) were not included. The odds ratio (OR) and 95% confidence interval (CI) for reduced LVEF were examined by taking each biomarker as a nominal and continuous variate, respectively. When being taken as a nominal variate, the OR was examined by regarding the lowest quartile of each biomarker as the reference. When being taken as a continuous variate, each biomarker was normalized by the Z-score method to compare the predictive value of them, then the OR was examined by evaluating 1 normalized unit increase.

The predictive value of each biomarker for reduced LVEF was assessed by receiver operating characteristic (ROC) analysis. The area under the ROC curves (AUCs) were determined and then compared by the nonparametric Z-test. Youden's index (sensitivity + specificity − 1) was used to determine the optimal cutoff

point of each indicator. Data analyses were performed with SPSS Statistics (version 19.0). P-value (two tailed) < 0.05 suggested statistical significance.

Results

The baseline demographic and clinical characteristics of the 2377 recruited patients with diabetes and ACS in this study are summarized in Table 1. The average age for all the participants was 63.0 (62.9, 63.6) years, and 1442 (60.7%) of them were male. Among all of the participants, 2185 (91.9%) patients with LVEF > 45%, 192 (8.1%) patients with LVEF ≤ 45%. A significant decrease in SOD activity was observed in the patients with LVEF ≤ 45% compared to patients with LVEF > 45% (149.1 (146.4, 151.9) vs 160.0 (159.0 161.1); $P < 0.001$). Compared with patients with LVEF > 45%, those with LVEF ≤ 45% were tended to have higher levels of CRP and fibrinogen. In addition, a higher SBP, AST, FBG, HbA1C, Cr, UA, NT-proBNP, Hs-cTnT, and the proportion of male patient smokers, along with a lower level of HDL-C and TG were observed in patients with LVEF ≤ 45% ($P < 0.01$ for all). No significant differences were observed on age ($P = 0.332$), DBP ($P = 0.112$), ALT ($P = 0.106$), LDL-C ($P = 0.972$) and TC ($P = 0.257$) between LVEF > 45% and LVEF ≤ 45% groups.

Table 1
Demographic characteristics and laboratory parameters of study participants.

Characteristic	*Total population (n = 2377)*	*With EF > 45% (n = 2185)*	*Patients with EF ≤ 45% (n = 192)*	*P value*
Age (years)	*63.0 (62.9, 63.6)*	*63.3(62.9 63.6)*	*62.9 (62.0, 63.8)*	*0.332*
Gender (male-n-%)	*1442 (60.7%)*	*1305 (59.7%)*	*137 (70.8%)*	*< 0.001*
Smoking (n-%)	*995 (41.9%)*	*895 (41.0%)*	*100 (52.1%)*	*< 0.001*
Systolic blood pressure (mmHg)	*137.1 (136.3, 137.9)*	*138.4 (137.6, 139.3)*	*128.9 (126.8, 131.0)*	*< 0.001*
Diastolic blood pressure (mmHg)	*79.3 (78.8, 79.7)*	*79.3 (76.8, 79.8)*	*79.1 (77.6, 80.6)*	*0.112*
ALT	*24.42 (23.84, 24.99)*	*24.04 (23.43, 24.64)*	*26.65 (24.88, 28.42)*	*0.106*
AST	*24.61 (24.10, 25.12)*	*24.48 (23.93, 25.04)*	*25.38 (24.05, 26.70)*	*0.04*
FBG (mmol/L)	*8.36 (8.23, 8.49)*	*8.22 (8.12, 8.33)*	*8.72 (8.37, 9.07)*	*0.033*
HbA1C(%)	*7.92 (7.85, 7.99)*	*7.89 (7.81, 7.96)*	*8.16 (7.95, 8.38)*	*0.007*
High-density lipoprotein (mmol/L)	*1.08 (1.08, 1.10)*	*1.09 (1.07, 1.10)*	*1.04 (1.01, 1.06)*	*0.001*
Low-density lipoprotein (mmol/L)	*2.64 (2.61, 2.69)*	*2.64 (2.61, 2.68)*	*2.66 (2.57 2.75)*	*0.972*
Total cholesterol (mmol/L)	*4.31(4.26, 4.36)*	*4.32 (4.27, 4.37)*	*4.26 (4.14, 4.39)*	*0.257*
Triglyceride (mmol/L)	*1.83(1.77, 1.88)*	*1.85 (1.79, 1.79)*	*1.70 (1.53, 1.86)*	*< 0.001*
Serum creatinine (μmol/L)	*66.83 (66.24, 67.42)*	*65.68 (65.06, 66.30)*	*73.63 (72.05, 75.21)*	*< 0.001*
Serum uric acid (μmol/L)	*321.9 (328.3, 335.5)*	*323.3 (319.7, 326.9)*	*382.6 (371.4, 393.7)*	*< 0.001*
SOD (u/ml)	*160.0 (159.0, 161.1)*	*161.9 (160.8, 163.0)*	*149.1 (146.4, 151.9)*	*< 0.001*
CRP (mg/L)	*7.28 (6.55, 8.02)*	*6.44 (5.74, 7.15)*	*12.26 (9.38, 15.14)*	*< 0.001*
Fibrinogen (g/L)	*3.37 (3.34, 3.41)*	*3.33 (3.29, 3.36)*	*3.64 (3.54, 3.75)*	*< 0.001*
NT-proBNP(pg/ml)	*924.4 (843.3, 1005.6)*	*559.9 (510.2, 609.6)*	*3095.4(2679.8, 3511.0)*	*< 0.001*

Characteristic	*Total population (n = 2377)*	*With EF > 45% (n = 2185)*	*Patients with EF ≤ 45% (n = 192)*	*P value*
Hs-cTnT (pg/ml)	*157.4 (138.7, 176.1)*	*143.9 (124.4, 163.4)*	*237.8 (179.1, 396.5)*	*< 0.001*

To determine independent variables for the incidence of LVEF < 45%, multivariate logistic regression analysis was performed and results showed in Table 2. Subjects with the lower SOD activity, higher levels of CRP and fibrinogen significantly increased in the patients with LVEF < 45% (P < 0.01 for all). After adjusting for gender, smoking habits, and systolic blood pressure, the associations between SOD activity, CRP, fibrinogen, and incident of LVEF < 45% had no change (model 1). After further adjustments were made for ALT, HDL-C, FBG, HbA1c, Cr, UA, NT-proBNP and hs-cTnT, the associations between SOD activity and incident of LVEF < 45% continued to maintain (model 2), despite taking the lowest quartile as reference (OR 0.368, 95% CI 0.493–0.825, P = 0.001) or examining 1 normalized unit increase (OR 0.651, 95% CI 0.482–0.880, P = 0.005). However, CRP (OR 1.076, 95% CI 0.846–1.368, P = 0.551 for taking the lowest quartile as reference, OR1.060, 95% CI 0.836–1.346, P = 0.63 for examining 1 normalized unit increase) and fibrinogen (OR 1.076, 95% CI 0.858–1.349, P = 0.528 for taking the lowest quartile as reference, OR 1.082, 95% CI 0.855–1.368, P = 0.512 for examining 1 normalized unit increase) had no longer predictive implications for incident of LVEF < 45%.

Table 2
The correlation between SOD, CRP, fibrinogen and the reduced LVEF in patients with diabetes and ACS.

Biomakers	*Variate type*	*No. EF < 45% Q1/Q2/Q3/Q4*	*No adjusted*		*Model 1*		*Model 2*	
			OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
SOD	*Nomical* [a]	*91/44/34/20*	*0.597 (0.517, 0.691)*	*< 0.001*	*0.586 (0.504, 0.681)*	*< 0.001*	*0.638 (0.493, 0.825)*	*0.001*
	Continuous [b]		*0.534 (0.449, 0.635)*	*< 0.001*	*0.519 (0.433, 0.621)*	*< 0.001*	*0.651(0.482, 0.880)*	*0.005*
CRP	*Nomical* [a]	*20/45/55/72*	*1.480 (1.287, 1.701)*	*< 0.001*	*1.462 (1.268, 1.685)*	*< 0.001*	*1.076 (0.846, 1.368)*	*0.551*
	Continuous [b]		*1.261 (1.134, 1.403)*	*< 0.001*	*1.218 (1.088, 1.363)*	*0.001*	*1.060 (0.836, 1.346)*	*0.63*
Fibrinogen	*Nomical* [a]	*32/40/54/66*	*1.319 (1.152, 1.510)*	*< 0.001*	*1.334 (1.162, 1.532)*	*< 0.001*	*1.076 (0.858, 1.349)*	*0.528*
	Continuous [b]		*1.379 (1.211, 1.569)*	*< 0.001*	*1.324 (1.160, 1.512)*	*< 0.001*	*1.082 (0.855, 1.368)*	*0.512*

Data are expressed as ORs (95% CI). No adjusted, simple logistic regression; Model 1, multiple logistic regression adjusted for gender, smoking habits, systolic blood pressure; Model 2, multiple logistic regression, using a forward stepwise procedure to select variables, further adjusted for alanine aminotransferase (ALT), high density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), HbA1c, serum creatinine (Cr), serum uric acid (UA), NT-proBNP and hs-cTnT.

a The OR was examined by regarding the lowest quartiles as reference; b The HR was examined by evaluating 1 normalized unit increase.

The accuracy of SOD, CRP and fibrinogen and their sensitivity and specificity in their correlation with incident of LVEF < 45% were compared and the results showed in Fig. 1 and Table 3. The AUC of SOD, CRP and fibrinogen were 0.658 (0.628, 0.688), 0.639 (0.613, 0.665) and 0.609 (0.528, 0.636) for incident of LVEF < 45%, respectively (P value for all < 0.001). Based on Youden's index, the optimal cutoff value of SOD activity, CRP and fibrinogen in assessing the correlation with incident of LVEF < 45% were 148.8U/ml, 2.56g/L, 3.05g/L, with a sensitivity and specificity of 51.6% and 73.3%, 62.9% and 60.0%, 74.6% and 42.8%, respectively. Further *Z* test was conducted to compare the area under ROC curve. The results showed that there was significant difference in AUC between SOD and fibrinogen (Z = 2.234, P < 0.05). However, there was no significant difference in AUC between SOD and CRP (Z = 0.896, P > 0.05), CRP and fibrinogen (Z = 1.368, P > 0.05).

Table 3
Areas under the ROC Curve (AUC), sensitivity and specificity by the optimized cutoff points for SOD, CRP and fibrinogen in assessing reduced LVEF.

	AUC				*Cutoff*	*Sensitivity (%)*	*Specificity (%)*
	Est. (95% CI)	**P-value**	**P-value for comparison***	**P-value for comparison#**			
SOD (u/ml)	*0.658 (0.628, 0.688)*	*< 0.001*	*-*	*> 0.05*	*148.8*	*51.6*	*73.7*
CRP (mg/L)	*0.639 (0.613, 0.665)*	*< 0.001*	*> 0.05*	*-*	*2.56*	*62.9*	*60*
Fibrinogen (g/L)	*0.609 (0.582, 0.636)*	*< 0.001*	*< 0.05*	*> 0.05*	*3.05*	*74.6*	*42.8*

*, comparing to AUC of SOD; #, comparing to AUC of CRP.

Discussion

The current study examined the correlation between SOD activity, CRP, fibrinogen, and the reduced LVEF, moreover compared their correlation with reduced LVEF in patients with diabetes and ACS. Guidelines recommend that NT-proBNP is used in the predictive algorithm for HF (25) and hs-cTnT is an integral criterion in the diagnosis of AMI (26). Our results have demonstrated that SOD activity was the most relevant indicator of reduced LVEF after adjusting for hs-cTnT and NT-proBNP in addition to other potential confounding factors (including gender, smoking status, systolic blood pressure, ALT, HDL-C, FBG, HbA1c, Cr, UA) compared with CRP and fibrinogen. To our knowledge, this study is the first cross-sectional study to evaluate and compare the relationship between SOD, CRP, fibrinogen and educed LVEF within the patients with diabetes and ACS.

SOD, as a major endogenous components of the antioxidant defence, is responsible for the inactivation of ROS in cardiomyocytes. Accumulating evidence derived from animal studies has demonstrated that SOD plays an important role in the development of HF. For example, previous studies have observed a significant decrease in SOD activity in rat for heart failure(12, 13). Furthermore, gene deficiency mice lacking SOD exposed to cardiac injury have demonstrated worse outcomes when compared to wild-type mice (27), whereas mice overexpressing SOD when exposed to ischaemia/reperfusion injury were found to have severely decreased levels of superoxide production, improved contractile function, and a decrease in infarct size(14). Population studies have reported that the reduced SOD activity was closely associated with the increased vascular oxidative stress, which likely contributes to endothelial dysfunction in patients with HF(5). Results from the most current cross-sectional study showed that SOD activity is a potential link between left ventricular structure remodeling and the development of subsequent HF in patients with cardiovascular disease(15). In our present study, it is further confirmed that SOD activity is associated with the reduced LVEF in the patients with diabetes and ACS.

Molecular genetic studies have shown that a single-base substitution causing exchange of glycine for arginine213 (Arg213Gly) in the heparin binding domain of SOD is associated with markedly increased plasma concentrations of the enzyme (9–11). Previous studies has shown that SOD mutation was associated with excessive oxidative stress, endothelial dysfunction, increased risk of ischemic heart disease(28, 29). In the absence of mutations, higher SOD activity is the effective part to protect against oxidative stress in tissue (30). The SOD activity was normally distributed in our study with a mean level of 160.0 (159.0, 161.1) U/mL, which is consistent with previously published data from other authors (15), suggests that there were no carriers of *R213G* in our study population.

It has long been recognized that patients with HF may manifest some of the clinical features observed in chronic inflammatory conditions (31). CRP and fibrinogen are widely used inflammatory marker in routine clinical practice. Previous investigators have shown that CRP (32–35) and fibrinogen (36, 37) were correlated with cardiovascular events and HF independently from known cardiovascular factors. The results of recent study showed that patients with higher CRP have features of more severe HF, and plasma CRP is independently related to subsequent mortality and morbidity (38). However, the association between CRP and cardiovascular mortality in diabetes status is controversial. Some researchers found that CRP was a significant predictor of cardiovascular disease only among individuals without diabetes (18, 39, 40). The others, in contrast, have demonstrated that the association between CRP and cardiovascular mortality did not differ by diabetes status (19, 20, 41). The same is true for fibrinogen research. Although much positive evidence has been identified, the clinical significance of fibrinogen in the risk stratification for cardiovascular disease is still controversial. For example, analysis from AtheroGene Study reported that the fibrinogen could not provide additional information to that provided by traditional cardiovascular risk factors in predicting cardiovascular events in adults without known cardiovascular disease (21). However, the results from The Strong Heart Study showing that fibrinogen was strongly associated with incident HF in the cohort and this association persisted after adjusting for conventional risk factors (6). The results from the present study showed there is correlation between CRP, fibrinogen and reduced LVEF in diabetic patients with ACS. However, these correlations disappeared after a comprehensive logistic regression analysis of gender, smoking history, systolic blood pressure, ALT, HDL-C, FBG, HbA1c, Cr, UA, NT-proBNP and hs-cTnT. Recommendations regarding the use of CRP and fibrinogen in assessing the likelihood of reduced LVEF may need to be further reviewed.

Our results also showed that serum UA levels were significantly higher in patients with LVEF $\leq$ 45% than in patients with LVEF > 45%. The Endothelial dysfunction has been documented in coronary arteries in patients with HF (42). The previous study observed a positive correlation between UA levels, nitric oxide-mediated vasodilation and SOD activity in patients with HF(43). Together with our finding of the UA levels were within normal limits in majority of the study patients, it suggested that increased UA levels could be part of an adaptive response to the increased oxidative stress present in the present study. Further experimental trials should be conducted to clarify the real impact of serum UA in the physiology of patients with diabetes and ACS.

The present study provides beneficial data for comparing the value of SOD activity, levels of CRP and fibrinogen in assessing reduced LVEF in one report. In addition to showing that SOD activity could predict the reduced LVEF more than CRP or fibrinogen levels, the results also showed that there was no significant difference in the ability of CRP and fibrinogen to predict the reduced LVEF. This finding contrasts with reports

that fibrinogen is more strongly associated with HF events than CRP in American Indians with a high prevalence of obesity and diabetes (6). Given the variability according to ethnicity, further studies are needed to assess the biomarkers in other populations.

Our study has several limitations. First, the present findings were based on analyses using a historical cohort; however, the patients were consecutively added to the cohort. Second, we did not evaluate time-dependent changes in plasma SOD activity, CRP and fibrinogen levels during the treatment period. Third, the number of the study subjects was relatively small, therefore the statistical power may be limited due to the small number of incident cases. Fourth, this study was carried out in a single urban university hospital with limited representation, which may not be representative of the entire Chinese population with diabetes and ACS.

In conclusion, the present study has demonstrated that SOD activity, CRP and fibrinogen levels are correlated with the reduced LVEF, moreover SOD activity is the most relevant indicator of reduced LVEF in patients with diabetes and ACS after adjusting for hs-cTnT and NT-proBNP in addition to other potential confounding factors (including gender, smoking status, systolic blood pressure, ALT, HDL-C, FBG, HbA1c, Cr, UA). SOD activity conjunction with NT-proBNP and hs-cTnT may estimate cardiovascular disease severity in patients with diabetes and ACS.

Declarations

Author Contributions: X.-Y.J.—writing original draft and review, conceptualization; Q.C.—supervision and validation; X.-Y.C.—supervision and validation; Q.-Y.S.—investigation; F.J.—investigation; H.-Q.Z.—investigation; J.X.—investigation; X.-H.L.—conceptualization, formal analysis, methodology; Q.-B.G.—conceptualization, methodology. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Ethical approval: The study was approved by the institutional review board of Shandong Provincial Hospital affiliated to Shandong First Medical University.

Data Availability Statement: The management of all data and quality control were performed with an electronic data capture system (Yiducloud Technologies Co., Ltd). Data supporting reported results is available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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Figures

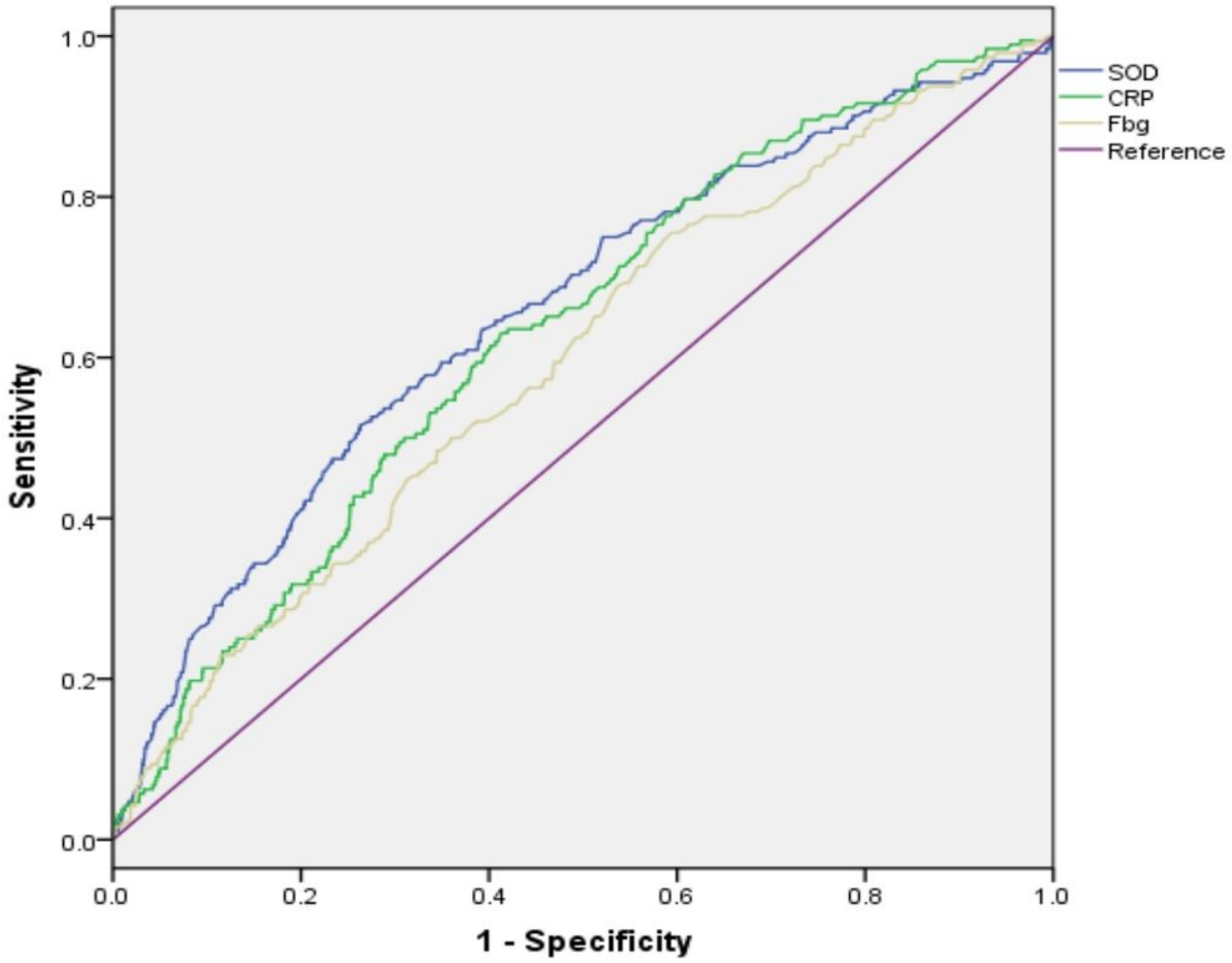

Figure 1

Receiver operating characteristic (ROC) curves of SOD, CRP and fibrinogen predicting incident of LVEF ≤ 45%.