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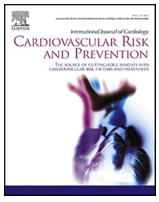

Association of testosterone with myocardial infarction and severity of coronary artery disease among male patients

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ABSTRACT

Background: Coronary heart disease (CHD) remains a leading cause of morbidity and mortality, particularly in aging populations. Men typically exhibit higher rates of CHD compared to women, with testosterone levels inversely associated with cardiovascular risk. This study investigates the relationship between testosterone levels and angiographically confirmed CHD, disease severity, and myocardial infarction (MI) among CHD cases.
Methods: A cohort of 1724 male patients undergoing diagnostic or interventional coronary angiography was examined. Demographic, clinical, and biochemical data were collected, including serum total testosterone levels. The severity of CHD was assessed using the Gensini score, and MI cases were diagnosed according to World Health Organization criteria.
Results: Results revealed significant differences in testosterone levels among CHD subtypes, particularly between MI and unstable angina/stable angina groups ($p < 0.001$). Testosterone levels were inversely correlated with CHD severity, as evidenced by the Gensini score (Pearson coefficient $= -0.062$, $P = 0.004$). Cross-validation random forest analysis demonstrated the significant contribution of testosterone to CHD severity discrimination ($p < 0.05$).
Conclusions: There is an association between testosterone and a predisposition to severe CAD indicated by Gensini score and myocardial infarction.

1. Introduction

Age-related morbidity and mortality rates from coronary heart disease (CHD) are higher in men than in women. Testosterone, the principal male sex hormone, is responsible for the maturation of male sexual organs and promotion of muscle mass, strength, bone density. Testosterone levels decrease with age, low serum testosterone levels are linked to premature coronary artery disease (CAD) and with increased risk of cardiovascular (CV) mortality. Reduced levels of testosterone are also a risk factor for type 2 diabetes (T2D), inflammation, dyslipidemia and metabolic syndrome (MS) [1–5]. A systematic meta-analysis enrolled 3467 male patients with T2DM (1079 patients with a low testosterone level versus 2388 patients with a normal testosterone level) and investigated the association between testosterone level and cardiovascular risk in male patients with type 2 diabetes mellitus (T2DM). Results showed that low testosterone level was associated with a higher CAD/cardiovascular risk of disease in male patients with type 2 diabetes mellitus (T2DM) [6].

Testosterone replacement therapy was initiated to restore normal levels of testosterone in order to reduce risk of CV risk, especially for these older men with hypogonadism. There is conflicting evidence in literature, ranging from increased to reduced risk. At least 10 retrospective analyses reported beneficial effects of testosterone replacement therapy on a broad variety of CV outcomes, ranging from stroke, MI, mortality, all-cause death, MACE, and atrial fibrillation. However, contrary to these results, the use of testosterone therapy was also reported to be associated with increased risk of adverse CV outcomes. Clinical trials using testosterone replacement treatment of older men with low testosterone was associated with greater progression of non-calcified plaque (NCP) [7]. While the Testosterone Trials (TTrials) included seven placebo controlled, double-blind trials in 788 men with a mean age of 72 years to determine the efficacy of increasing the

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testosterone levels of older men with STD, results showed that TT was not associated with more CV or prostate adverse events than placebo [8]. The TRAVERSE trial, enrolling 6000 men, was implemented in 2018, aimed at evaluating the effect of testosterone therapy on MACE and efficacy measures in hypogonadal men [9]. The results of the TRAVERSE trial was released recently, which indicated that in men with hypogonadism and preexisting or a high risk of cardiovascular disease, testosterone-replacement therapy was noninferior to placebo with respect to the incidence of major adverse cardiac events [10].

The inconsistency of these findings prompted us to further investigate the relationship between testosterone and coronary heart disease. In the present study, we examined a cohort of individuals undergoing diagnostic or interventional coronary angiography and ascertained whether there was an association of testosterone with angiographically confirmed CAD, with the extent of atherosclerosis in CAD patients, and/or with the occurrence of myocardial infarction (MI) among CAD cases.

2. Subjects and methods

2.1. Subjects

The male patients scheduled to undergo clinically indicated diagnostic or therapeutic coronary catheterization at the First Affiliated Hospital of Zhejiang University Medical School during the period from January 1, 2012 to December 31, 2015 were recruited in this study. Patients who had used drugs known to affect testosterone levels within the past 3 months, such as testosterone replacement therapy, were excluded from this study. Patients with no significant stenosis (stenosis less than 30 %) on coronary angiography and patients with missing testosterone measurements were ultimately not included in the study. A total of 1724 coronary angiography confirmed CAD male patients were finally enrolled in this study. All subjects were Chinese and older than 18 years. The research ethics committee of the First Affiliated Hospital of Zhejiang University School of Medicine approved the study.

Demographic and clinical data including age, BMI, blood pressure, coronary angiographic findings, and prevalent or incident MI were collected from hospital records. Venous blood samples were drawn from all subjects after an overnight fast of at least 8 h. Total cholesterol (TC) level, low-density-lipoprotein-cholesterol (LDLc) level, high-density-lipoprotein-cholesterol (HDLc) level, triglycerides level, fasting blood glucose (FBG) , uric acid and other biochemical test results as well as serum total testosterone levels of all patients were measured by the clinical chemistry department of the First Affiliated Hospital of Zhejiang University. Plasma total testosterone levels were measured with Siemens Immulite 2000 Total Testosterone Kits on Siemens Immulite 2000 Immunoassay Analyzer according to the manufacturer's protocols. This method has been validated by one of our previous study [11].

Coronary angiography was carried out by experienced interventional cardiologists. CAD was defined as $\geq$50 % diameter stenosis in any of the major epicardial coronary artery, as measured by quantitative coronary angiography [12]. Disease severity was determined by the Gensini score. Scoring criteria: diseased vessels are divided into left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA). The degree of coronary stenosis: $\leq$25 %, 1 point, 26%–50 %, 2 points, 51%–75 %, 4 points, 76%–90 %, 8 points, 91%–99 %, 16 points, 100 %, 32 points. The score of each coronary artery is multiplied by the corresponding coefficient: the score of the left main branch is multiplied by 5, the score of the proximal part of the anterior descending branch and the proximal part of the circumflex branch is multiplied by 2.5, the score of the middle part of the anterior descending branch is multiplied by 1.5, and the score of the second diagonal branch is multiplied by 0.5. The scores of the rest of the lesions were multiplied by 1.0, and the cumulative score of the above-mentioned vessels was the Gensini score [13]. MI was diagnosed according to the World Health Organization criteria.

2.2. Statistical analysis

Data were analyzed using SPSS software, version 21.0 (SPSS Inc., Chicago, IL). The T-test and analysis of variance (ANOVA) were used to determine any differences in age, systolic blood pressure, diastolic blood pressure, TC level, LDLc level, HDLc level, and triglycerides level, between study groups. Logistic regression analyses were performed to ascertain a relationship between testosterone levels and the severity of CAD cases with or without adjustment for age, TC and LDLc, and to test a relationship between testosterone and MI among CAD cases with or without adjustment for sex, systolic blood pressure, diastolic blood pressure and triglyceride. All p-values are two sided.

Cross-validation random forest analysis was conducted to understand the contribution of Testosterone in the cross-validation of the model and the ability to improve the model. Briefly, we constructed the 10-fold cross-validated model by the Caret package in R, and optimized the number of trees in constructing the model by GridSearch. The strategy of cross-validation aims to ensure the stability and generalizability of the results, and squared, mean decreased accuracy, and mean decreased Gini were applied to evaluate the contribution of each variable in discriminating the CAD subtypes, which were widely applied indicators.

The random forest model was developed to evaluated the performance of different clinical indicators in discriminating the outcome variables. Specifically, the random forest model was developed in 10 folds cross-validation by the Caret package to ensure the stability and generalizability of the explained variables. The hyperparameters of the cross-validated random forest model, that was mtry, was automatically optimized by GridSearch from 10 to 500. The indicators of cross-validated random forest, including R squared, mean decreased accuracy, and mean decreased Gini, were used to evaluated the importance of each clinical parameters.

3. Results

3.1. Demographic and clinical characteristics of the study subjects

In the description of baseline characteristics (Table 1), we found that there were differences in the distribution of different blood test indicators among CAD subtypes, so we adjusted for these factors in the subsequent analysis. We have found significant differences in the distribution of various well-known risk factors among different CAD subgroups, including age, hypertension, blood glucose, uric acid, and LDL-c levels. Higher glucose level, CRP level and LDL-c level were found in myocardial infarction patients. While lower uric acid level, testosterone level and HDL-c level were found in those patients. Most interestingly, patients with myocardial infarction are younger than patients with stable/unstable angina. There is no variation observed in the distribution of TG and BMI across different CAD subgroups. We also found that the distribution of Gensini Score among CAD subtypes was significantly different, which suggested that the disease severity of different CAD subtypes may be different.

3.2. Testosterone levels across CAD subtypes

Testosterone levels were assessed among patients with different CAD subtypes, including myocardial infarction (MI), unstable angina (UA), and stable angina (SA). Interestingly, a notable difference in testosterone levels was observed, particularly between patients with MI and those with UA/SA. Specifically, patients diagnosed with myocardial infarction exhibited lower testosterone levels compared to the UA/SA groups (MI group: 344.2 $\pm$ 150.2; UA group: 391.2 $\pm$ 140.9; SA group: 378.3 $\pm$ 137.1) ($p < 0.001$). However, when comparing testosterone levels between UA and SA groups, no statistically significant difference was found (Fig. 1A). These findings suggest a potential association between testosterone levels and certain CAD subtypes, particularly

Table 1
Demographic table.

Characteristics	Subtypes of Coronary Artery Disease (n=1724)			
	AMI (n=287)	Unstable angina (n=468)	Stable angina (n=969)	p Value
Age, yrs	61 (40–88)	65 (37–88)	65 (40–90)	<0.001
BMI, kg/m2	24.5 (14.5–36.8)	24.4 (16.0–43.8)	24.3 (15.1 41.6)	0.9
Hypertension				
No	203 (70.7 %)	326 (69.7 %)	631 (65.1 %)	<0.001
Yes	84 (29.3 %)	142 (30.3 %)	338 (34.9 %)	
smoker				
No	95 (33.10 %)	172 (36.75 %)	427 (35.91 %)	<0.001
Yes	192 (66.90 %)	296 (63.25 %)	542 (64.09 %)	
diabetes				
No	258 (89.90 %)	425 (90.81 %)	955 (98.56 %)	<0.001
Yes	29 (10.10 %)	43 (9.19 %)	14 (1.44 %)	
Glu, mg/dl	97.9 (0–293.7)	82.5 (0–199.7)	85.6 (0–325.6)	<0.001
CRP, mg/dl	7.7 (0–213.0)	1.9 (0–161.1)	1.9 (0–168.0)	<0.001
Uric acid, mg/dl	329.0 (28.0–867.0)	353.0 (183.0–912.0)	358.0 (102.0–862.0)	<0.001
TG, mg/dl	110.8 (0–746.0)	111.2 (0–699.1)	109.9 (0–715.0)	0.6
TC, mmol/l	3.7 (2.0–8.6)	3.5 (1.7–12.8)	3.6 (0.4,10.0)	0.02
HDL-C, mmol/l	0.9 (0.3–2.9)	1.0 (0.5–2.2)	1.0 (0.4,2.4)	0.01
LDL-C, mmol/l	1.9 (0.7–5.9)	1.8 (0.7–9.7)	1.8 (0.4–6.9)	<0.001
Testosterone	313.5 (60.1–895.1)	384.5 (27.7–1079.0)	357.0 (89.8–1007.0)	<0.001
GENSINI score	61.0 (23.5–285.0)	46.5 (23.5–230.5)	47.0 (23.0–216.0)	<0.001

Values are n (%), or median (interquartile range).
BMI = Body mass index; TG = Triglyceride; TC = Total cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

myocardial infarction.

Further cross-validation random forest results show that the contribution of Testosterone in the cross-validation of the model and the ability to improve the model are significant ($p < 0.05$) (Fig. 1B). In addition, in terms of explanatory power for a single CAD subtype, Testosterone has a higher and significantly higher explanatory power for MI and UA ($p < 0.05$) (Table 2).

3.3. Testosterone is associated with the severity of CAD

We further found that testosterone was linearly correlated with the degree of CAD disease ($p < 0.001$) (Fig. 2A). In order to exclude the influence of strong influence points, after dividing according to its quartiles (Fig. 2B), the p trend test still indicated the strong negative correlation ($p < 0.001$). Further, we fit the test model about Gensini Score based on the generalized linear model. In the step-wise adjusted model, we found the testosterone improved the discriminative model significantly even if it was adjusted for age (Model 1), which was demonstrated as an important confounder in discriminating the CAD subtypes. However, when the model was adjusted for glucose, uric acid, and CRP, its exertion on discrimination became moderate (Model2). In this regard, our results suggested that the testosterone may exert its discriminatory effects on CAD subtypes by interacting with glucose, uric acid, or CRP. Further experimental evidence is warranted. The results suggest that the diagnostic performance of the model is significantly improved after adding the Testosterone variable (Table 3), and Testosterone has a significant importance ($p < 0.05$) (Fig. 2C). These results suggest that Testosterone is a key predictor of CAD severity.

3.4. Testosterone is associated with NYHA class

Testosterone also showed significant differences among patients with different NYHA class, patients with lower testosterone levels associated with worse heart function class (testosterone level 399.0 ± 157.1; 397.4 ± 150.2; 363.2 ± 159.3 and 335.2 ± 202.0 for NYHA I, II, III and IV respectively) ($p < 0.001$). This difference suggests that Testosterone has the potential to aid in the treatment of heart failure which may need to be further evaluated (Fig. 3).

4. Discussion

Cardiovascular disease remains the leading cause of death in most of the developed world despite advances in both prevention and treatment. At the same time, the incidence rates of cardiovascular disease differ greatly between the genders, with men more likely than women to manifest ischemic heart disease. In previous studies, serum testosterone level was reported to be negatively associated with the severity of coronary atherosclerosis and low endogenous testosterone level predicted overall and CV mortality, as well as CV morbidity [14–16].

Also in our study, we found that serum testosterone level was inversely linearly correlated with the Gensini score of coronary angiography confirmed CAD patients, and testosterone has a significant importance on the severity of coronary heart disease. Furthermore, patients diagnosed with myocardial infarction exhibited lower testosterone levels compared to the UA/SA groups, suggesting a potential association between testosterone levels and certain CAD subtypes, particularly myocardial infarction. However, it's essential to interpret these results cautiously, considering the broader context. Testosterone

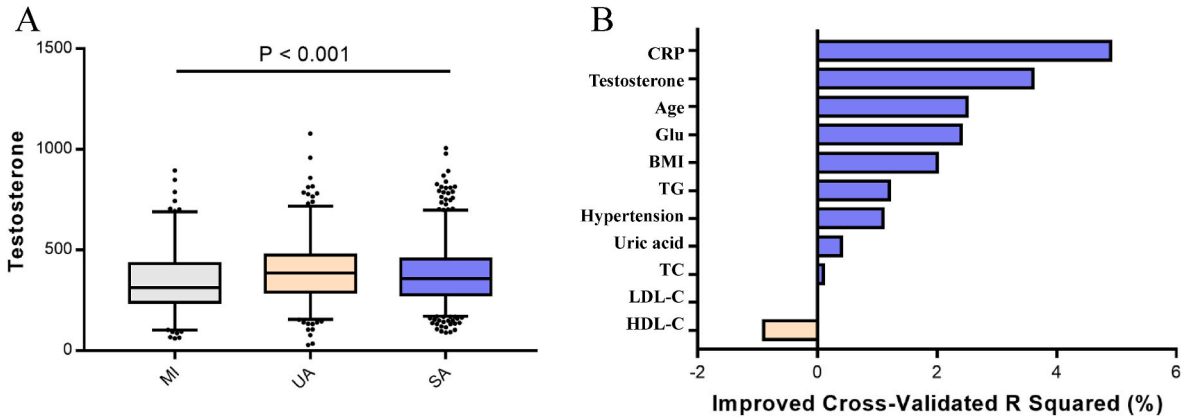

Fig. 1. Testosterone showed significant differences among patients with MI, UA, and SA. (A): Patients with myocardial infarction showed lower testosterone levels compared to UA/SA groups ($p < 0.001$). (B): The contribution of Testosterone in the cross-validation of the model and the ability to improve the model are significant ($p < 0.05$).

Table 2
Testosterone has a higher and significantly higher explanatory power for MI and UA.

	P value			MeanDecreaseAccuracy	MeanDecreaseGini
	MI	UA	SA		
testosterone	0.02	0.02	0.64	0.07	0.5
Age	0.01	0.02	0.07	0.01	0.1
BMI	0.73	0.38	0.5	0.52	1
TC	0.12	0.3	0.03	0.01	1
HDL-C	0.47	0.23	0.16	0.14	0.99
LDL-C	0.05	0.72	0.01	0.01	0.97
Uric acid	0.01	0.08	0.03	0.01	0.14
TG	0.03	0.2	0.27	0.06	1
Glu	0.35	0.01	0.02	0.01	0.3
CRP	0.01	0.07	0.01	0.01	0.01
hypertension	0.97	0.06	0.01	0.04	0.82

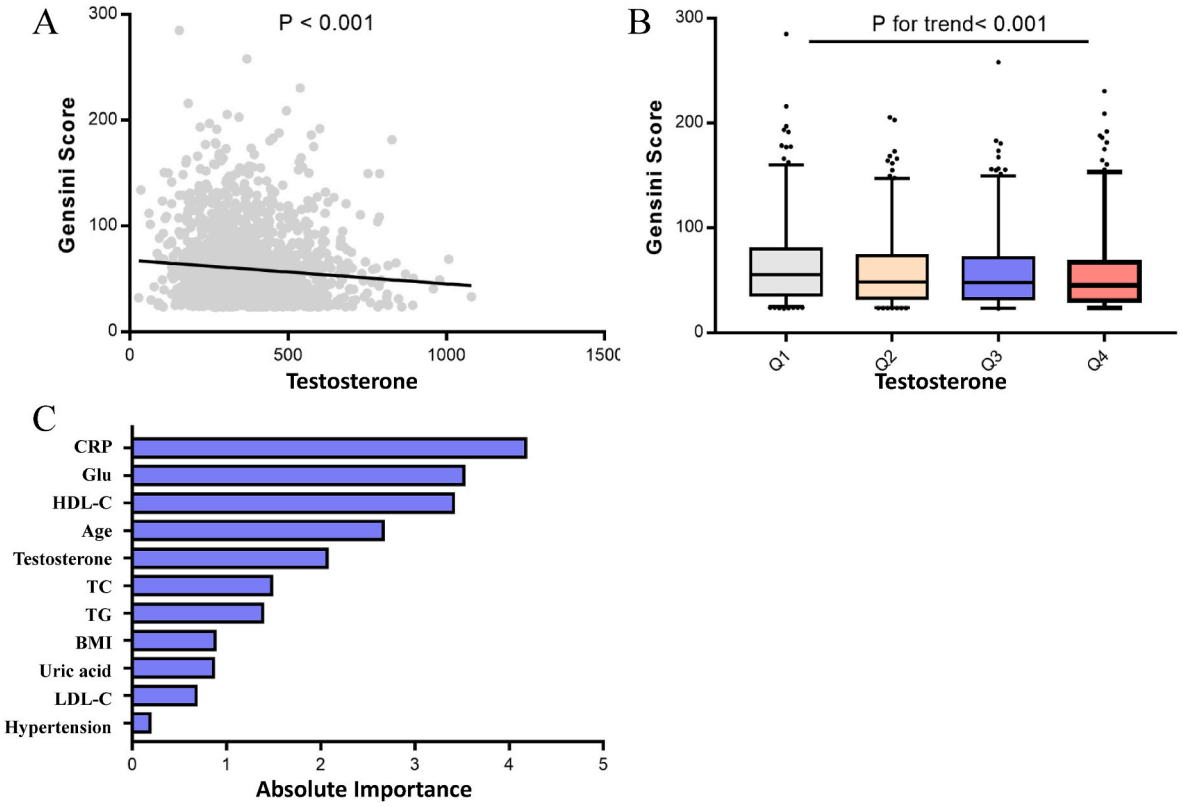

Fig. 2. Testosterone is associated with the severity of CAD. (A): The testosterone level was linearly correlated with the degree of CAD disease ($p < 0.001$). (B): The strong negative correlation between the testosterone level and Gensini score after dividing according to its quartiles ($p < 0.001$). (C): The testosterone improved the discriminative model of CAD subtypes significantly and the testosterone has a significant importance ($p < 0.05$).

Table 3
Testosterone significantly improved the diagnostic performance of the model.

	Model 1		**Model 2**		**Model 3**	
	Explained variance	**P value**	**Explained variance**	**P value**	**Explained variance**	**P value**
Without testosterone	0.07 %	$p < 0.001$	2.99 %	$p = 0.069$	5.62 %	$p < 0.001$
With testosterone	0.70 %		3.12 %		5.80 %	

Model 1: Adjusted for age, BMI, hypertension.
Model 2: Plus Glu, Uric acid, CRP.
Model 2: Plus TG, TC, HDL-C, LDL-C.

levels might be influenced by acute diseases such as myocardial infarction, and similar variations could be observed in other acute conditions, such as sepsis. Therefore, caution is warranted in attributing the observed differences solely to CAD subtype. In terms of explanatory power for individual CAD subtypes, only testosterone and age had significant explanatory power for acute coronary syndrome (myocardial infarction and unstable angina). This observation has prompted new research initiatives to explain the discrepancy in heart disease prevalence and incidence between the sexes.

It is still unclear how testosterone regulated the progress of CAD.

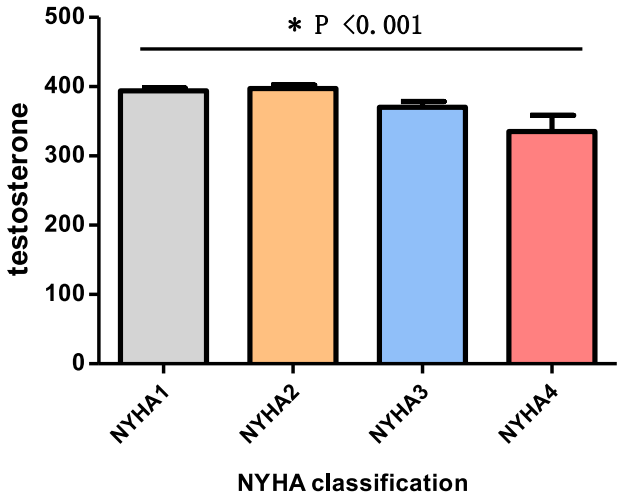

Fig. 3. Testosterone showed significant differences among patients with different NYHA class, patients with lower testosterone levels associated with worse heart function class ($p < 0.001$).

Previous studies shed lights on various risk factors of CAD. Testosterone was reported to influence renin–angiotensin–aldosterone system (RAAS) and thus regulate blood pressure, which is a well-known risk factor for CAD [17]. Animal studies showed that testosterone deficiency significantly damaged the mechanical adaptation of the vessel wall additively by causing inward eutrophic remodeling and impaired relaxation of coronary vascular bed, decreased triglyceride and VLDL levels, and testosterone therapy restored all of these parameters [18]. Animal study revealed that endogenous testosterone limits coronary neointima formation in male swine and provides support for a protective role for testosterone in coronary vasculo-proliferative diseases, such as restenosis and atherosclerosis [19]. Observational studies showed that low testosterone was an independent predictor of severity of CAD inverse association with coronary artery calcification [20,21]. These results indicated that testosterone may play a beneficial role in the cardiovascular system by regulating various risk factors, such as blood pressure, lipids profile, plaque stability et al.

Although the bidirectional link between hypogonadism and cardiovascular disease has been clarified, the association between testosterone and chronic heart failure (HF) is more controversial. Previous studies had shown that the prevalence of testosterone deficiency (30%–50 %) and symptomatic hypogonadism (15 %) in men with HF is significant [22–24]. Low testosterone correlates with HF severity, New York Heart Association class, exercise functional capacity, and a worse clinical prognosis and mortality [22,25–29]. Also, in our study, we found that testosterone level was significantly associated with heart failure severity (New York Heart Association class) in coronary artery disease patients, indicating the association between testosterone and ischemic heart failure. Unfortunately, not all of the patients has BNP levels, the association of testosterone level with BNP has not been analyzed here.

To the best of our knowledge, our study is currently the largest article analyzing the correlation between testosterone and the severity of coronary artery disease. Our study shows that testosterone levels differ among different subtypes of coronary artery disease, suggesting that testosterone may has an impact on the incidence of coronary artery disease (or the stability of coronary artery disease), and we may need further theoretical research to confirm this. Another important finding of this study is that testosterone levels are related to cardiac function class (indicated by NYHA). Another published study from US cohort also reported a significant association between high serum testosterone levels and reduced heart failure risk in individuals over 50 years old. Of course this only suggests that they are relevant, as for whether testosterone therapy can benefit patients with heart failure, there are currently no large clinical studies to confirm it. We hope further clinical studies can give us more evidence.

Several limitations should be considered. Firstly, the cross-sectional nature of the study prevents us from confirming the causal effects angiographically confirmed CAD cases in the pathogenesis of testosterone insufficiency. Secondly, myocardial infarction often indicates a poor prognosis for patients. However, in this study, lacking of follow-up data limited its persuasion. Long time follow up of this cohort is ongoing , hopefully we can analyze the prognosis of the patients. Thirdly, the correlation analysis between testosterone and the severity of coronary artery disease in the article (whether with coronary artery disease subtypes or the Gensini score) only suggests that they are related and cannot directly prove the impact of testosterone on coronary artery disease. This requires Further mechanism studies to confirm. Lastly, although our data showed significant differences among patients with different NYHA class, patients with lower testosterone levels associated with worse heart function class. As for whether testosterone therapy can benefit patients with heart failure. There are currently no large clinical studies to confirm it. More studies are needed to verify this hypothesis.

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Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. No animal studies are presented in this manuscript. The studies involving human participants were reviewed and approved by research ethics committee of the First Affiliated Hospital of Zhejiang University Medical College. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Inclusion of identifiable human data

Generated Statement: Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Data availability statement

Generated Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Consent to participate

Not applicable.

Consent to publish

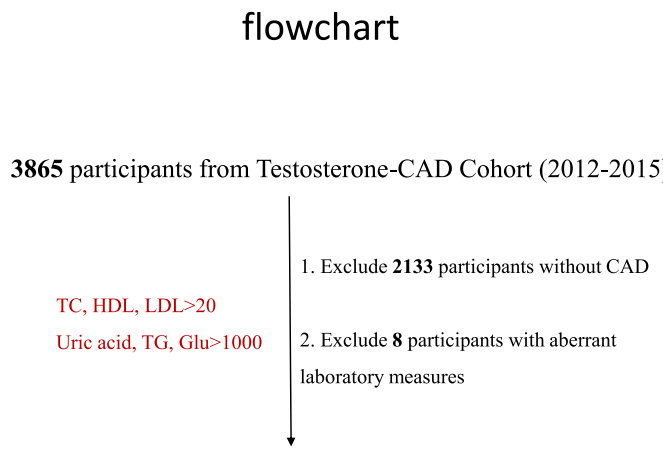
All authors have seen the manuscript and agree with publication.

CRediT authorship contribution statement

Lujing Tang: Writing – original draft, Validation, Methodology, Investigation, Data curation. **Mengsha Chen:** Validation, Methodology, Formal analysis, Data curation. **Jiahao Li:** Validation, Methodology, Investigation, Data curation. **Xiaodong Xu:** Writing – original draft,

Investigation, Formal analysis, Data curation. **Xiangyuan Pu:** Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Appendix A



Flowchart.

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