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Risk factors associated with the false positive of cardiopulmonary exercise test in the diagnosis of coronary heart disease

Xinwei Wang[1], Haibo Zhu[2], Sheng Jing[2], Wenhao Li[3] and Jing Huang[1*]

Abstract

Purpose Cardiopulmonary exercise test (CPET) is a common method for preliminary evaluating coronary heart disease (CHD), but it may experience false positive. The present study aimed to reveal the potential factors relating to the false positive of CPET, including blood glucose and lipids.

Methods This observational cohort study included 103 subjects with false positive of CPET and 65 subjects with true positive of CPET. The baseline characteristics, blood glucose, and blood lipids between the true and false positive groups were compared. After adjusting for the age and sex, logistic regression analysis was performed to reveal the potential risk factors of false positive. Receiver operating characteristic curve analysis was performed to evaluate the potential of related factors in distinguishing between true and false positive results.

Results Males, smokers, and patients with diabetes were less likely to suffer from false positive of CPET. Compared with the true positive group, the false positive group exhibited significantly higher levels of high-density lipoprotein (HDL) and apolipoprotein A1 (Apo-A1), and lower levels of fasting blood glucose (FBG) and glycosylated hemoglobin (GHb). After adjustment, FBG and GHb were protective factors of the true positive of CPET, and they both had moderate ability to distinguish false positive from true positive in females. However, their combination did not improve the discriminative effect more obviously than FBG alone.

Conclusions Sex, smoking, diabetes, and blood glucose were associated with the false positive of CPET. FBG was valuable in predicting the risk of false positive of CPET in females with suspected CHD.

Trial Registration The present study is registered in Chinese Clinical Trial Register (ChiCTR2400089239).

Keywords Treadmill exercise test, False positive, Coronary heart disease, Blood glucose

Introduction

Coronary heart disease (CHD) is a common cardiovascular disease that seriously threatens human health [1]. The formation of plaques that comprised by lipids, calcium, and inflammatory cells is a typical pathological characteristic of CHD, which can result in ischemic injury through inducing the stenosis or obstruction of the vascular cavity [2, 3]. Worldwide, CHD is accompanied by high morbidity and mortality, and a variety of risk factors contribute to its progression, such as lipid disorders, smoking, obesity, diabetes, hypertension, and physical

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inactivity [4, 5]. For the diagnosis of CHD, coronary angiography is still the gold approach in clinical practice [6]. However, coronary angiography is invasive, which may lead to physical damage and adverse complications [7]. Research on non-invasive diagnostic methods with high efficiency is of great clinical significance.

In the human body, stress exercise can enhance cardiac load by elevating myocardial oxygen demand, and the diseased coronary artery can be reflected by abnormal electrocardiogram (ECG) when the blood flow is unable to meet the requirements of the myocardium [8]. Cardiopulmonary exercise test (CPET) is a common method for evaluating coronary events by collecting the signal changes of ECG during exercise [9]. Clinically, CPET has various forms, and treadmill exercise test and cycle ergometry are the most common ones [10]. Since CPET is safe, non-invasive, convenient, and affordable, it is widely applied for the initial diagnosis of CHD [11]. However, CPET may experience false positive in clinical practice. Evidence has determined that the false positive rate of CPET in the diagnosis of CHD is around 25% [12–15]. Until now, diverse factors have been reported to be related to the false positive of CPET. For example, Guerreiro et al. found that the false positive rate of CPET is significantly lower in males and in patients with diabetes [16]. Khan et al. revealed that the positive predictive value of CPET is higher in males, smokers, and patients with hypertension and diabetes [17]. Zeng et al. reported that male, hyperlipidemia, smoking, typical chest pain, and a family history of CHD are associated with a lower risk of false positive of CPET [18]. Towashiraporn et al. found that female and the use of statin are associated with the false positive of CPET [12]. These studies indicate that the false positive of CPET is related with the above factors. However, the potential influencing factors for the false positive of CPET have not been fully revealed. We speculate that some routine biochemical parameters may also be related to the false positive of CPET.

In the present study, subjects with false and true positive of CPET were included for analysis. In addition to the baseline characteristics, the blood glucose and lipids in the true and false positive groups were mainly analyzed. The present study is designed to reveal more potential factors relating to the false positive of CPET, especially blood glucose and lipids. Our results may provide guidance for reducing the risk of false positive of CPET in clinical practice.

Methods

Subjects

This is an observational cohort study. Between September 2019 and September 2023, a total of 103 subjects (Chinese, Han nationality) with false positive of CPET in The First affiliated Hospital of Ningbo university (Ningbo, China; sea-levelish altitude, 984.9 m) were included in the analysis. False positive of CPET was defined as a positive result for CPET but a negative result for coronary angiography. CHD was accurately diagnosed by ≥ 50% stenosis or complete occlusion in any coronary arteries under coronary angiography (Allura FD20, PHILIPS, Best, the Netherlands). At the same period, 65 patients with positive results of both CPET and coronary angiography were included as the true positive group for the analysis (Fig. 1).

The exclusion criteria included: 1) ECG abnormality in resting-state; 2) history of open surgery or interventional surgery of cardiovascular internal medicine, such as coronary stent implantation, coronary artery bypass grafting, radiofrequency ablation, and valve repair or replacement surgery; 3) the use of antiarrhythmic drugs, such as digitalis within 8 days before CPET; 4) patients with diseases affecting the ST segments, such as acute myocardial infarction, complete left bundle branch block, heart valve disease, congenital heart disease, preexcitation syndrome, cardiomyopathy, and electrolyte disorders. The baseline characteristics of participants, including the sex, age, BMI, smoking, drinking, and the presence of hypertension or diabetes were recorded.

CPET

Before CPET, the examination process and possible discomfort were informed to all subjects in details. CPET was performed on treadmill in subjects with suspected CHD using a Wireless CPET system (X-SCRIBE II, Mortara, Milwaukee, WI, USA) according to the Bruce protocol [19, 20]. The heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate-pressure product (RPP) were recorded. The end-points of CPET included: 1) onset of typical angina pectoris; 2) presence of complications of arrhythmia; 3) heart rate meets expected standard; 4) a decrease of blood pressure > 10 mmHg; 5) unable to continue the exercise due to syncope, gait disturbance, and disability; 6) observation of positive results of dynamic electrocardiogram. Positive CPET was identified by: 1) observation of typical symptoms of angina; 2) horizontal or downward-sloping ST-segment depression of ≥ 1 mm for ≥ 2 min during or after CPET; 3) elevation of ST-segment by ≥ 1 mm in each lead; 4) a decrease of blood pressure by > 10 mmHg during CPET. An experienced physician performed the CPET, who was blind to group assignment.

Measurement of blood glucose and lipids

Before CPET, blood glucose and lipids were measured by an automatic biochemical analyzer (AU5821, Beckman Coulter, Brea, CA, USA). In details, fasting blood

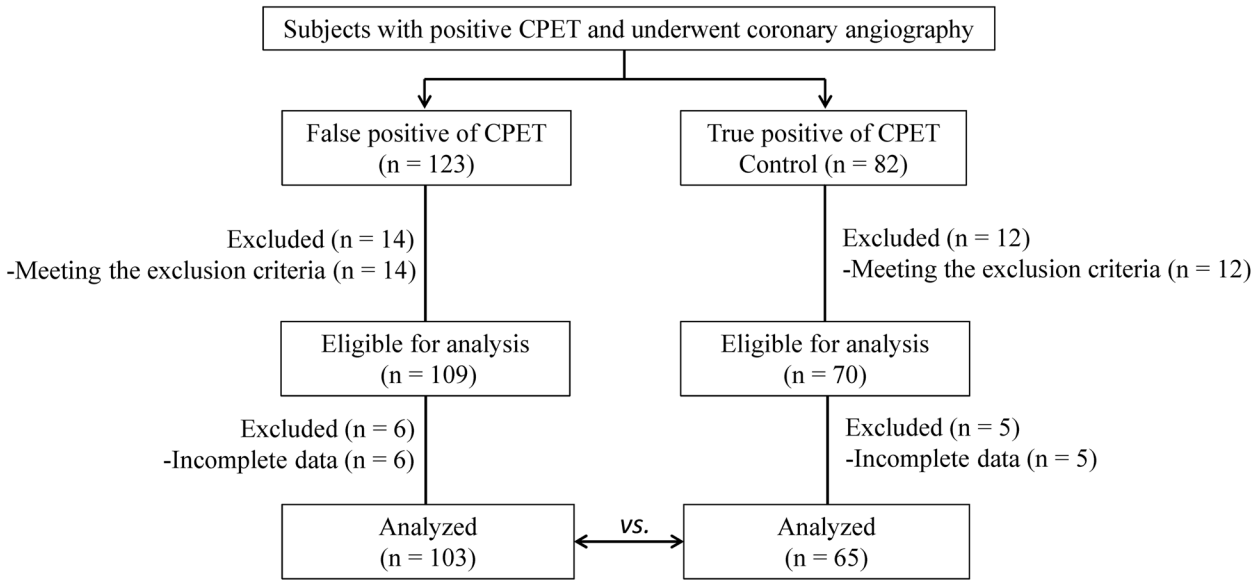

Fig. 1 A recruitment diagram of the subjects in the present study

glucose (FBG) and glycosylated hemoglobin (GHb) were measured to reflect the blood glucose, and triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A1 (Apo-A1), and apolipoprotein B (Apo-B) were measured to reflect the blood lipids. All samples were analysed in the same laboratory, and the examiner was blind to group assignment.

Statistical analysis

Sample size was calculated using the formula of $N=2(SD^2/D^2)\times(Z\alpha+Z\beta)^2$. FBG with a difference (D) of 0.69 and a standard deviation (SD) of 1.11 was used as the primary parameter. To achieve 95% confidence interval ($\alpha=0.05$) and 90% power ($\beta=0.1$), the sample size was calculated to be 54. Based on a 10% dropout rate, at least 60 participants were needed in each group.

Statistical analyses were performed using SPSS software (version 21.0; IBM, Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation, and the differences between true and false positive groups were compared by independent-samples t-test. Effect size was calculated using the following formula: Cohen'd = (m1-m2)/sd_pooled. Categorical data were expressed as N (%), and the differences were compared by chi-square test (X^2). In addition, the potential risk/protective factors of false positive were determined by logistic regression analyses after adjusting for age and sex (potential confounders). Receiver operating characteristic curve (ROC) analysis was further performed to evaluate the potential of FBG/GHb on distinguishing false positive from true positive. A P-value less than 0.05 represented statistically significant.

Results

The baseline characteristics of participants with true and false positive of CPET

Total 103 subjects with false positive of CPET and 65 subjects with true positive of CPET were included in the present study. The results of CPET showed that the HRmax, SBPmax, and RPP were significantly higher in the false positive group than those in the true positive group ($P<0.01$). Although the total time and DBPmax were relatively higher in the false positive group, the differences were not significant (Table 1).

The baseline characteristics of these participants were then compared. As shown in Table 2, females were more likely to suffer from false positive than males ($P<0.001$). Compared with the true positive rate, the false positive rate was significantly lower in participants with smoking ($P=0.003$) and diabetes ($P=0.018$). However, the age, BMI, drinking, and hypertension were not significantly different between participants with true and false positive results.

The blood glucose and lipids of participants with true and false positive of CPET

FBG and GHb were measured to reveal the difference in blood glucose between participants with true and false positive of CPET. As shown in Table 3, the levels of FBG and GHb were both significantly lower in the false positive group than those in the true positive

Table 1 Comparisons of cardiopulmonary exercise test (CPET) results between participants with true and false positive results

Parameters	True positive (*N* = 65)	False positive (*N* = 103)	t	*P*-value	Cohen's d
Total time	7.89 ± 2.19	8.26 ± 2.15	-1.079	0.282	-0.170
HRmax	148.98 ± 18.59	158.20 ± 19.94	-2.995	0.003*	-0.478
SBPmax	179.67 ± 25.62	191.80 ± 27.05	-2.889	0.004*	-0.460
DBPmax	76.90 ± 14.17	79.96 ± 12.24	-1.484	0.140	-0.231
RPP	26,864.02 ± 5633.35	30,483.04 ± 5971.74	-3.910	< 0.001*	-0.623

HR heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *RPP* rate-pressure product

* statistically significant at $P < 0.05$

Table 2 Comparisons of the baseline characteristics between participants with true and false positive results of cardiopulmonary exercise test (CPET)

Parameters	True positive (*N* = 65)	False positive (*N* = 103)	X^2/t	*P*-value	Cohen's d
Sex			12.92	< 0.001*	-
Male	45 (69.23%)	42 (40.78%)			
Female	20 (30.77%)	61 (59.22%)			
Age	59.11 ± 9.41	58.51 ± 7.85	0.441	0.660	0.069
BMI	24.98 ± 2.65	24.06 ± 3.20	1.915	0.057	0.313
Smoking	24 (36.92%)	17 (16.50%)	9.01	0.003*	-
Drinking	15 (23.08%)	17(16.50%)	1.12	0.291	-
Hypertension	38 (58.46%)	53 (51.46%)	0.79	0.375	-
Diabetes	15 (23.08%)	10 (9.71%)	5.62	0.018*	-

BMI body mass index

* statistically significant at $P < 0.05$

Table 3 Comparisons of blood glucose and lipids between participants with true and false positive results of cardiopulmonary exercise test (CPET)

Parameters	True positive (*N* = 65)	False positive (*N* = 103)	t	*P*-value	Cohen's d
FBG	5.99 ± 2.13	5.33 ± 1.03	2.603	0.010*	0.395
GHb	6.16 ± 1.10	5.80 ± 0.62	2.641	0.009*	0.403
TG	1.69 ± 1.30	1.49 ± 0.89	1.162	0.247	0.180
TC	4.23 ± 1.03	4.39 ± 0.98	-1.021	0.309	-0.159
HDL	1.09 ± 0.30	1.19 ± 0.24	-2.296	0.023*	-0.368
LDL	2.67 ± 0.77	2.79 ± 0.74	-0.913	0.362	-0.159
Apo-A1	1.15 ± 0.29	1.25 ± 0.25	-2.359	0.020*	-0.369
Apo-B	0.77 ± 0.26	0.76 ± 0.22	0.329	0.742	0.042

FBG fasting blood glucose, *GHb* glycosylated hemoglobin, *TG* triglyceride, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *Apo-A1* apolipoprotein A1, *Apo-B* apolipoprotein B

* statistically significant at $P < 0.05$

group ($P < 0.05$). Subsequently, blood lipids were evaluated by the levels of TG, TC, HDL, LDL, Apo-A1, and Apo-B. Compared with those in the true positive group, the levels of HDL and Apo-A1 were significantly higher in the false positive group ($P < 0.05$). However, no significant differences in TG, TC, LDL, and Apo-B were revealed between the true and false positive groups.

Identification of risk factors associated with the false positive of CPET

Whether blood glucose and lipids were risk/protective factors associated with the false positive were subsequently determined by logistic regression analysis. After adjusting for the age and sex, FBG and GHb were revealed as protective factors associated with the

true positive of CPET ($P<0.05$). The additional unit decrease in FBG/GHb was associated with an increase of 0.535/0.712 in the odds of subjects getting false positive of CPET. However, all parameters involving blood lipids were not significantly associated with the false positive of CPET (Table 4).

The potential of FBG and GHb in identifying false positive of CPET

Since FBG and GHb were associated with the false positive of CPET, their roles in distinguishing between true and false positive results were further analyzed by ROC analysis. In individuals regardless of sex, both FBG and GHb had moderate ability to distinguish false positive from true positive ($0.6 \leq AUC < 0.75$, $P<0.05$). The combination of FBG with GHb did not improve the discriminative effect more obviously (Fig. 2A). In males, FBG, GHb, and their combination all exhibited no significant effects on distinguishing false and true positive results (Fig. 2B). In females with more frequent false positive, FBG and GHb both exhibited moderate ability in identifying false positive ($0.6 \leq AUC < 0.75$, $P<0.05$), and the discriminative effects were slightly stronger than individuals regardless of gender. The discriminative effect of FBG + GHb did not exceed that of FBG alone (Fig. 2C) (Table 5). At its best, FBG was valuable in distinguishing false positive from true positive of CPET in females with suspected CHD.

Discussion

CPET is a preliminary and noninvasive method that frequently used to evaluate the pathological status of coronary arteries for years [21]. However, some patients with a positive result of CPET may not present a positive result of coronary angiography, referring as false positive. The false positive greatly limited the effectiveness of CPET in the diagnosis of CHD. Although previous studies have revealed many factors relating to the false positive of CPET, the potential influencing factors have not been fully revealed. The present study showed that the false positive of CPET was associated with the sex, smoking, and diabetes. Subsequently, the potential associations of blood glucose and lipids with the false positive of CPET were studied, which are the main innovation of the present study. Encouragingly, the results showed that low levels of FBG and GHb were at risk for the false positive of CPET, which might also be valuable in prediction.

The false positive of CPET is associated with various factors, with sex being the most fundamental one. Previous studies around the world have demonstrated that females are more likely to suffer from the false positive of CPET. For example, a retrospective study in Thailand showed that female is an independent predictor for the false positive of CPET (60% vs. 40%) [12]. A cross-sectional study in Pakistan found that the rate of false positive of CPET is higher in females than males (64% vs. 36%) [17]. A single-center study in China found more females in the false positive group (65.52% vs. 34.48%) [18]. In the present study, the false positive of CPET was also found to be more frequent in females than males (59.22% vs. 40.78%). Our result is consistent with previous studies and illustrates that the false positive of CPET is more frequent in females. The potential reasons may include: 1) estrogens are associated with ST depression in females; 2) females have a lower exercise capacity than males; 3) the heart rate recovery and blood pressure response are different between males and females; 4) the dysfunction of autonomic nervous system may be more common in females [15]. For females with suspected CHD, special attention should be paid to the occurrence of false positive of CPET. In addition, the present study also found that the false positive rate was lower in individuals with smoking or diabetes than those without smoking or diabetes. These findings indicate that patients with smoking and diabetes are less likely to suffer from false positive of CPET, which are supported by some previous studies [16–18]. This phenomenon may be partially explained by that the diabetes and smoking can affect hemodynamics and they are both risk factors of CHD [22–24]. The disturbance of lipid metabolism is one of the most important factors in the pathogenesis of CHD [25]. The deposition and retention of LDL, an Apo-B-containing lipoprotein in the arterial intima directly contribute to the onset of atherosclerosis and subsequent CHD [26]. Evidence has determined that TG, LDL, and Apo-B are all risk factors of CHD [5]. However, whether

Table 4 Logistic regression analyses of risk/protective factors associated with the false positive result of cardiopulmonary exercise test (CPET)

Parameters	*B*	SE (*B*)	Exp (*B*)
FBG	-0.626	0.236	0.712*
GHb	-0.339	0.146	0.535*
TG	-0.165	0.170	0.848
TC	0.113	0.174	1.120
HDL	0.940	0.690	2.560
LDL	0.186	0.232	1.205
Apo-A1	1.116	0.728	3.052
Apo-B	-0.023	0.738	0.977

The data was analyzed after adjusting for the age and sex. *B*, regression coefficient; *SE* standard error, *Exp* exponential function, *FBG* fasting blood glucose, *GHb* glycosylated hemoglobin, *TG* triglyceride, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *Apo-A1* apolipoprotein A1, *Apo-B* apolipoprotein B

* statistically significant at $P<0.05$

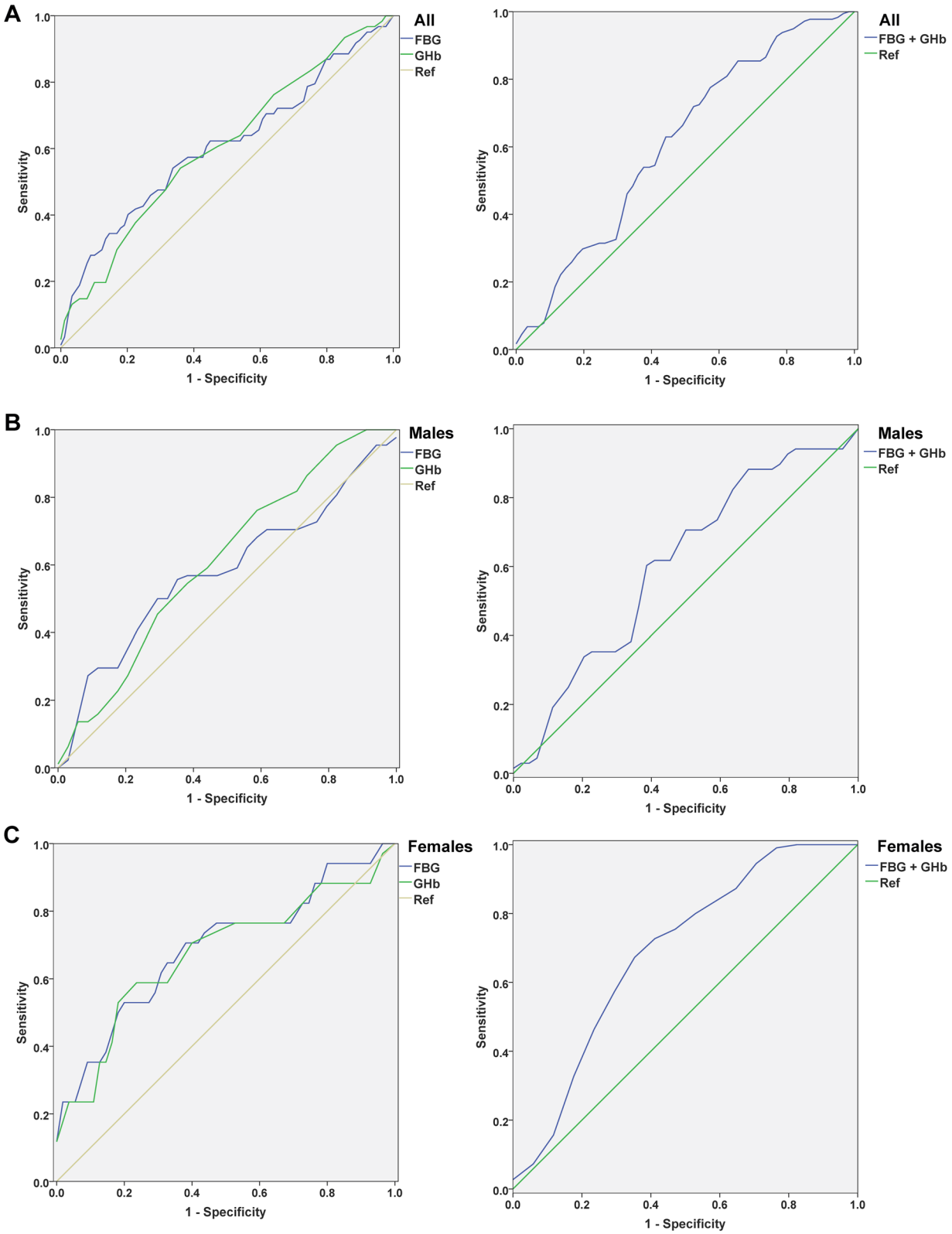

Fig. 2 ROC curves of FBG and GHb in distinguishing between true and false positive results of CPET. **A**, All participants regardless of sex, **B**, Males, **C**, Females

Table 5 The effects of FBG and GHb on distinguishing between true and false positive results of cardiopulmonary exercise test (CPET)

Parameters	Cutoff	Sensitivity (%)	Specificity (%)	AUC	95% CI	*P*-value
All participants						
FBG	5.31	54.10%	67.40%	0.607	0.512–0.702	0.027*
GHb	5.85	54.10%	64.00%	0.606	0.514–0.698	0.028*
FBG + GHb	0.57	85.40%	36.10%	0.614	0.520–0.707	0.018*
Males						
FBG	5.24	50.00%	73.50%	0.581	0.453–0.708	0.223
GHb	5.53	77.3%	41.20%	0.614	0.487–0.741	0.087
FBG + GHb	0.64	61.80%	61.4%	0.608	0.481–0.734	0.105
Females						
FBG	5.74	52.90%	81.80%	0.692	0.535–0.849	0.017*
GHb	6.05	58.80%	76.40%	0.676	0.513–0.840	0.029*
FBG + GHb	0.61	70.90%	64.70%	0.690	0.531–0.849	0.019*

AUC area under curve, *CI* confidence interval, *FBG* fasting blood glucose, *GHb* glycosylated hemoglobin. $0.5 < AUC < 0.6$, low discriminative effect; $0.6 \leq AUC < 0.75$, moderate discriminative effect; $0.75 \leq AUC < 1$, high discriminative effect. *statistically significant at $P < 0.05$

blood lipids can affect the accuracy of CPET remains unclear. In the present study, the levels of TG, TC, HDL, LDL, Apo-A1, and Apo-B were compared between the true and false positive groups. The results showed that HDL and Apo-A1 were significantly higher in the false positive group than those in the true positive group. This finding indicates that the elevation of HDL and Apo-A1 may be associated with the false positive of CPET. HDL is a kind of heterogeneous particle that functions in removing excess cholesterol through reverse transportation [27]. Correspondingly, Apo-A1 is the main structural protein of HDL, which can regulate the function of HDL [28]. Since HDL and Apo-A1 within an appropriate range are inversely associated with the risk of CHD, individuals with relatively high levels of HDL and Apo-A1 are less likely to suffer from CHD [5]. Nevertheless, this phenomenon does not mean that this group of people is more likely to suffer from false positive of CPET. Here, logistic regression analysis subsequently confirmed that HDL and Apo-A1 are not risk factors of the false positive of CPET. Thus, HDL and Apo-A1 may affect the accuracy of CPET, but cannot lead to the false positive of CPET.

Glucose is a simple sugar molecule that plays an important role in basic cell function by acting as a source of energy [29]. Evidence has determined that hyperglycaemia, a status of high blood glucose, is associated with the risk of cardiovascular diseases, including CHD [30, 31]. Glucose variability also exhibits detrimental effects on the coronary artery [32]. However, the effects of blood glucose on the accuracy of CPET remain unclear. The present study showed that individuals with true positive of CPET have higher levels of FBG and GHb than those with false positive result. This finding indicates that low levels of FBG and GHb may be associated with the false positive of CPET. The exercise capacity may partially explain this phenomenon. Adekunle et al. reported that FBG is associated with the exercise capacity of male and female patients with diabetes during CPET [33]. Lipinski et al. revealed that Hb is associated with exercise performance and ST-segment depression during CPET [34]. Additionally, abnormal glucose metabolism also contributes to exaggerated blood pressure response to CPET [35]. Therefore, individuals with relatively low FBG and GHb may be more likely to experience false positive of CPET. Our subsequent analyses just confirmed this point, evidenced by that FBG and GHb were protective factors of the true positive of CPET. Moreover, whether FBG and GHb are helpful in distinguishing between true and false positive of CPET were analyzed in the present study. ROC analysis showed that both FBG and GHb had moderate ability to distinguish false positive from true positive of CPET, especially in females, but their combination did not further improve the discriminative effect. Thus, in clinical practice, evaluation of FBG before CPET is recommended in individuals with suspected CHD, which may reduce the risk of false positive of CPET.

The present study has some limitations. For example, the clinical significance of the results is limited by a small sample size. The potential variability in subjects' characteristics, such as lifestyle, dietary habit, mental state, etc. may affect the results of CPET, and different ergometers may elicit different results. Based on a large population or a specific population (such as athletes, patients with specific diseases, etc.), further researches

on these issues are needed. Additionally, the associations of lung-related variables (such as OUES, OUEP, VE/VCO2, etc.) with the false positive of CPET should be investigated.

Conclusion

In conclusion, false positive of CPET was more frequent in females, non-smokers, and individuals without diabetes. For these subjects with suspected CHD, although the result of CPET is negative, CHD cannot be ruled out and other diagnostic strategies are still needed. Additionally, low levels of FBG and GHb were at risk for the false positive of CPET. Since FBG was valuable in predicting the false positive of CPET in females with suspected CHD, its detection before CPET is necessary.

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Authors' contributions
Xinwei Wang: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Visualization, Writing – original draft; Haibo Zhu: Data curation and Investigation; Sheng Jing: Data curation and Investigation; Wenhao Li, Data curation and Investigation; Jing Huang, Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Data availability
The dataset supporting the conclusions of this article is included within the article.

Declarations

Ethics approval and consent to participate
The studies involving humans were approved by The First affiliated Hospital of Ningbo University (2023-185RS-01). Written informed consent was obtained from all participates. The present study is registered in Chinese Clinical Trial Register (ChiCTR2400089239).

Competing interests
The authors declare no competing interests.

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