IJC Heart & Vasculature 40 (2022) 101033

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Association between erectile dysfunction, cardiovascular risk factors, and coronary artery disease: Role of exercise stress testing and International Index of Erectile Function (IIEF-5) questionnaire

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ARTICLE INFO

Keywords:
Erectile dysfunction
Coronary artery disease
Cardiovascular risk factors
Exercise stress testing
International Index of Erectile Function (IIEF-5) questionnaire
Risk factors

ABSTRACT

Background: The exercise stress test (EST) is a non-invasive investigation to diagnose coronary artery disease. This research aimed to determine the relationship between erectile dysfunction (ED), cardiovascular risk factors, and coronary artery disease (CAD) in men referred for EST.

Methods: A prospective cohort study enrolling 303 patients from August 2020 through September 2021. All patients filled out the international Index of Erectile Function (IIEF-5) questionnaire. . They underwent an exercise stress test (EST). A two-tailed independent sample *t*-test, chi-square tests, and binary logistic regression were used for statistical analysis.

Results: EST was positive in 110 (36.3%) patients, negative in 154 (50.8%), and inconclusive in 39 (12.8%) patients. ED was present in 225 (74.3%) patients and absent in 78 (25.8%) patients. 278 (91.7%) had one or more cardiovascular risk factors. This study reported a significant relationship between diabetes mellitus (DM), hypertension (HTN), and the results of EST and ED. Compared to patients without ED, patients with ED had a positive EST result. Definite CAD was diagnosed in 21% of patients with ED compared to 1.3% in patients without ED. For a one-unit increase in age, the odds of ED increased by about 5%. Similarly, a negative EST is compared to a positive EST. Negative EST reduced the likelihood of ED by 82%.

Conclusions: This research found a statistically significant connection between CAD, certain cardiovascular risk factors, and ED using the EST and IIEF-5 questionnaires. This research is significant because it may alter the way cardiovascular risk stratification is done.

1. Introduction

Coronary artery disease (CAD) and erectile dysfunction (ED) are prevalent diseases that often coexist [1–3]. Globally, about half of males aged 45 to 75 years have erectile dysfunction. This affects around 155 million people and is estimated to reach 322 million by 2025 [4]. Several underlying risk factors contribute to erectile dysfunction and CAD [5]. They are age, dyslipidemia, hypertension, diabetes, smoking, obesity, and a sedentary lifestyle [6–8]. As per the literature, ED is a precursor to CAD [9–11]. As a result, the presence of an ED should prompt examinations and assessment for cardiovascular risk factors and CVD [12,13]. For this reason, it has been incorporated as a risk factor into the atherosclerotic cardiovascular disease (ASCVD) 10-year risk calculator QRISK-3 by the United Kingdom (UK) [14]. Several studies have shown that ED is common in men with CAD, diabetes, and hypertension (2). Initially, it was thought to be a late result of widespread artery damage. Later, accumulating evidence suggests that ED is a precursor to systemic arterial disease and a predictor of CAD [15–18].

To find a relationship between CAD and ED, we used screening tools such as exercise stress testing (EST) and the International Index of Erectile Function (IIEF-5) questionnaire for ED. We wanted to see whether there was a connection among the results of EST, ED, and

Abbreviations: ED, Erectile dysfunction; EST, Exercise Stress Test; IIEF, International Index of Erectile Function; CAD, Coronary Artery Disease.

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https://doi.org/10.1016/j.ijcha.2022.101033
Received 8 December 2021; Received in revised form 17 March 2022; Accepted 11 April 2022

cardiovascular risk factors. To our knowledge, no prior attempts have been made to determine the relationship between EST, cardiovascular risk factors, and ED. Both EST and IIEF-5 questionnaires are well-established, reliable, inexpensive, and widely used screening tools for diagnosing CAD and ED. The study's rationale was to utilize the connection between CAD and ED by using EST and IIEF-5 questionnaires to establish an association between them. This might change the way cardiovascular risk stratification is done. Both of these screening tools may enable us to identify early those patients who are at high risk of having cardiovascular events in the future; therefore, an appropriate aggressive treatment strategy might be implicated for prevention [19].

2. Methods

This prospective cohort study enrolled 303 patients from the EST department from August 31st, 2020, through September 30th, 2021. A validated questionnaire was used to screen these patients for ED. All patients underwent clinically appropriate EST as advised by their referring physician. Patients on beta-blockers or thiazide diuretics, who had not been sexually active in the previous six months or had a history of prostate and/or penile surgery, were not eligible for the study. All participants' cardiovascular risk factors, comorbidities, pharmacological history, and EST results were reported on the physician sheet. The institutional review board (IRB) is the hospital's ethics committee that approved this study under vide # 665. Informed consent was taken from all patients. The participants completed the EST using treadmill equipment provided by the exercise stress test unit. The treadmills used were Marquette Model Case Premium, Marquette Model Case 15, and Mortara Model X-Scribe. EST was done following the Bruce protocol [20]. The International Index of Erectile Function (IIEF) was utilised to assess sexual function [21,22]. Participants were given a questionnaire in their native language and additional assistance as needed. The IIEF-5 questions were graded on a 5-point scale. Patients were classified as per their sexual function [21]. The maximum potential score was 25, with a higher score indicating better sexual function. Patients with an IIEF-5 score greater than 22 were labelled as having "no ED", patients with a score between 22 and 16 were labelled as having "mild ED", patients with a score between 8 and 16 were labelled as having "moderate ED", and patients with a score<8 were labelled as having "severe ED".

For further convenience, the ED severity ratings were categorised into negative ED (no ED) and positive ED (mild, moderate, or severe ED).

2.1. Statistical analysis

A Kolmogorov-Smirnov test was conducted to determine the normal distribution of data. Based on the normality of data, we applied a two-tailed independent samples *t*-test to compare continuous variables between the categories of ED, and chi-square tests were used for comparing categorical variables. Binary logistic regression was carried out to adjust for confounding factors and establish the predictors of CAD.

3. Results

In this research, a total of 303 patients were enrolled. The age distribution was normally distributed, with a mean age of 54.5 ± 10.5 (Mdn = 55) years. A mean IIEF-5 score of 15.8 ± 9.9 (Mdn = 16) was obtained. Out of 303 enrolled patients, 278 (91.7%) had one or more risk factors, while 25 patients did not have any risk factors. Among the 278 patients with risk factors, 109 (35.97%) were diabetic, 169 (55.78%) had hypertension, 180 (59.41%) were

yperlipidemic, 61 (20.13%) were smokers, and 117 (38.61%) had a family history of coronary artery disease (CAD). These results are depicted in Fig. 1. A total of 53 (17.41%) patients had only one risk factor, 91 (30.03%) had two risk factors, 58 (19.14%) had three risk factors, 52 (17.16%) had four risk factors, 21 (6.93%) had five risk factors, and only 3 (0.9%) patients suffered from all the risk factors i.e., diabetes, hypertension, hyperlipidemia, smoking, and a family history of CAD. These baseline characteristics are given in Table 1.

All enrolled patients underwent EST, a non-invasive test for the evaluation of CAD. The results of EST came out positive in 110 (36.3%) patients, negative in 154 (50.8%), and inconclusive in 39 (12.8%) patients. Screening for ED was carried out through the IIEF-5 questionnaire.

Upon filling out the (IIEF-5) questionnaires, ED was present in 225 (74.3%) patients and absent in 78 (25.8%) patients. A total of 59 (19.5%) patients had mild ED, 116 (38.28%) suffered from moderate ED, and 50 (16.5%) suffered from severe ED. Similarly, coronary angiography was carried out in 58(19.14%) patients, whereas 245 (80.86%) did not undergo further invasive testing. These results are shown in Table 2.

Among those who underwent coronary angiography, 8(13.8%) patients had a normal coronary angiogram, 15(25.9%) patients were labeled as a single-vessel disease (SVD), 17(29.3%) had doubl vessel disease and 18(31%) were diagnosed as triple vessel disease (TVD). Definite coronary CAD was present in 50 (16.5%) patients. The results

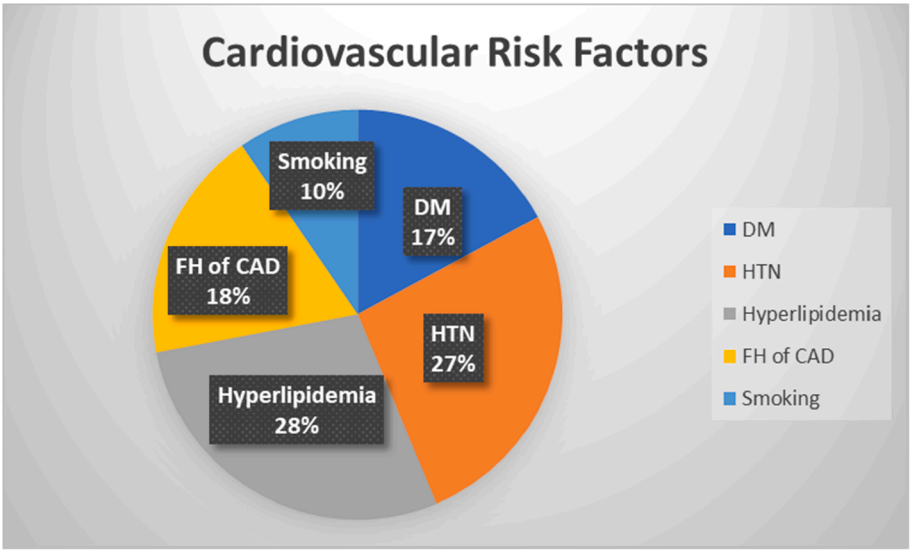

Fig. 1. Pie chart showing percentages of cardiovascular risk factors.

Table 1
Baseline characteristics.

Variable	M[a]	SD[b]	Mdn [c]	N[d]	%
Age	54.52	10.47	55.00		
Waist	91.22	13.16	92.00		
Height	170.23	87.02	166.00		
Weight	74.60	15.38	72.80		
Cardiovascular Risk Factors				278	91.7%
DM [e]				109	35.97
HTN [f]				169	55.78
Hyperlipidemia				180	59.41
FH [g] of CAD [h]				117	38.61
Smoking				61	20.13
Number of risk factors					
No risk factor				25	8.25
One				53	17.49
Two				91	30.03
Three				58	19.14
Four				52	17.16
Five				21	6.93
All				3	0.99

[a.] M, Mean; [b.]SD, Standard Deviation, [c.]Mdn, Median, [d.]N, Frequency [e.]Diabetes Mellitus (DM), [f.]Hypertension (HTN), [g.]Family History (FH); [h.]Coronary artery disease (CAD).

Table 2
Results of exercise stress testing, erectile dysfunction and coronary angiography.

Result of Exercise Stress Testing (EST)	n	%
Positive	110	36.30
Negative	154	50.83
Inconclusive	39	12.87
Erectile Dysfunction (ED)		
Present	225	74.26
Absent	78	25.74
Severity of ED		
Mild ED	59	19.47
Moderate ED	116	38.28
Severe ED	50	16.50
Coronary angiography		
Yes	58	19.14
No	245	80.86

are depicted in Table 3.

Because the Kolmogorov-Smirnov test revealed that our data were normally distributed, we used a two-tailed independent sample *t*-test and chi-square tests to compare continuous and categorical variables between the two ED categories. The results of these tests are shown in Tables 4,5 and Fig. 2.

The results indicated that age, DM, HTN, and results of EST were significantly correlated to ED.

Compared to patients without ED, most patients with ED had a positive EST result (9% vs 91%, p.001). Surprisingly, when compared with a negative EST, ED was more common in patients with an inconclusive EST (60% vs 85%). To substantiate our findings, we carried out coronary angiographies in patients with and without ED. The results revealed that compared to patients without ED, the likelihood of the presence of a definite CAD diagnosed by performing coronary angiography in patients with ED was very high (1.29% vs 21.8%, p <.001).

Table 3
Result of Coronary angiography.

Result of Coronary Angiography	n	%
Normal Coronary Angiography	8	13.8
Single Vessel Disease (SVD)	15	25.9
Double Vessel Disease (DVD)	17	29.3
Triple Vessel Disease	18	31
Definite CAD		
Yes	50	16.50
No	253	83.50

Table 4
Results for testing the relationships for cardiovascular risk factors and exercise stress testing against the categories of Erectile dysfunction using chi-square test.

Variable	Present	Absent	Total	P-Value
Age range(years)				< 0.001
(20–45)	37 (59%)	26 (41%)	63 (100%)	
(45–70)	173 (77%)	52 (23%)	225 (100%)	
(more than 70)	15 (100%)	0 (0%)	15 (100%)	
Diabetes Mellitus II (DM)	92 (84%)	17 (16%)	109 (100%)	0.002
Hypertension (HTN)	134 (79%)	35 (21%)	169 (100%)	0.024
Hyperlipidemia	138 (77%)	42 (23%)	180 (100%)	0.246
FH of CAD	84 (72%)	33 (28%)	117 (100%)	0.437
Smoking	49 (80%)	12 (20%)	61 (100%)	0.225
Result of Exercise Stress test (EST)				< 0.001
Positive	100 (91%)	10 (9%)	110 (100%)	
Negative	92 (60%)	62 (40%)	154 (100%)	
Inconclusive	33 (85%)	6 (15%)	39 (100%)	

Note: Due to rounding error, %s may not sum to 100%.
ED, Erectile Dysfunction; Diabetes Mellitus (DM), Hypertension (HTN), Family History (FH); Coronary artery disease (CAD).

Table 5
Results for testing the relationships between ED and presence of a definite CAD using Chi-square Test.

	Definite CAD			P-Value
Variable	Yes	No	Total	
Result 0F ED				<0.001
Positive	49 (21.78%)	176 (78.22%)	225 (100.00%)	
Negative	1 (1.28%)	77 (98.72%)	78 (100.00%)	

Note: Due to rounding error, percentages may not sum to 100%.

We used a binary logistic regression to determine if age, cardiovascular risk factors, and EST's result had a statistically significant influence on the likelihood of having an ED or not. According to the binary logistic regression results, variables such as age and a negative EST had a statistically significant impact on ED. A one-unit increase in age increased the odds of ED by about 5% [B = 0.05, OR = 1.05, p.001]. Furthermore, a negative EST decreased the likelihood of having an ED by approximately 82% compared to a positive EST [B = -1.74, OR = 0.18, p <.001] (see Table 6).

4. Discussion

Distinguishing cardiac from non-cardiac chest discomfort is a difficult process that affects patients and clinicians. This study used the EST modality to assess chest pain, with a positive result indicating coronary artery disease. Given the undeniable link between ED and CAD, this study sought to demonstrate the link between cardiovascular risk factors, EST, and ED. The results revealed that increasing age, diabetes, and hypertension had a statistically significant relationship with ED. This research successfully established a link between EST and ED.

In our study, the proportion of patients with a positive EST was substantially higher in those with ED than in those without ED [100 (91%) vs 10 (9%), p <.001]. A study by Kloner et al. carried out on 76 patients with stable ischemic heart disease (SIHD) reported a prevalence of ED of 75% [23]. Though our study was not carried out on patients

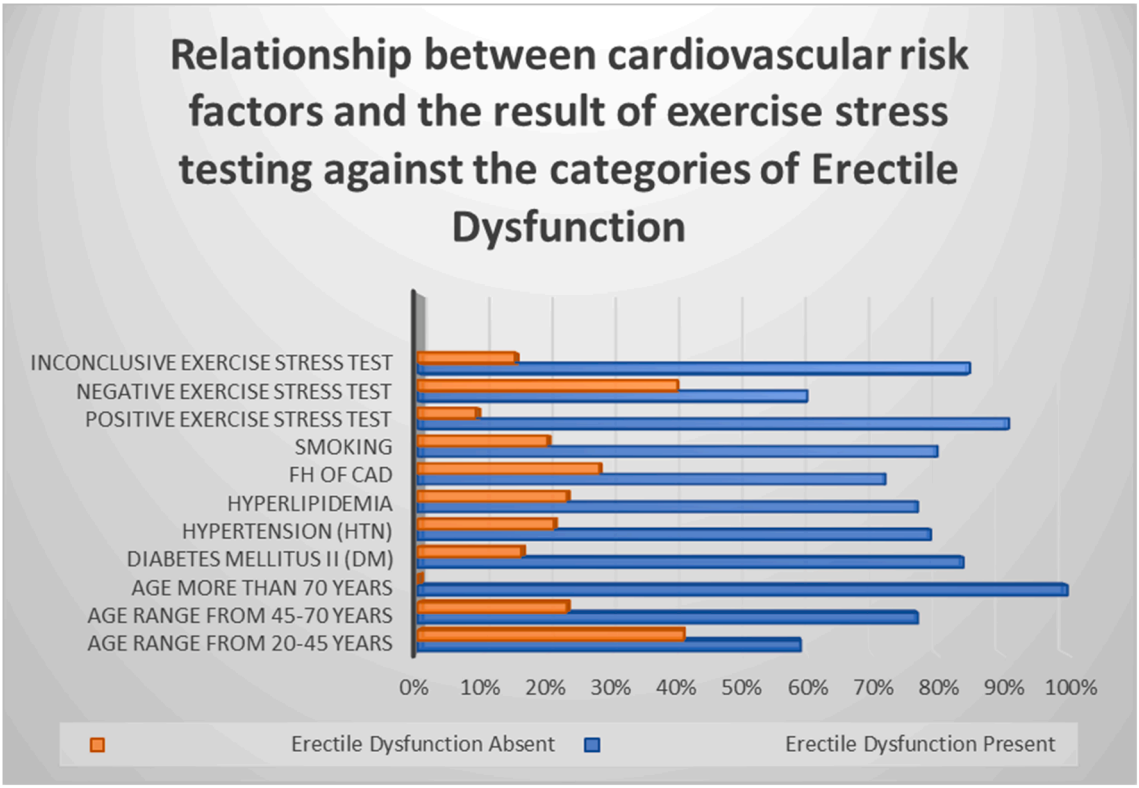

Fig. 2. Bar chart showing the relationship between cardiovascular risk factors and the result of exercise stress testing against the categories of erectile dysfunction.

Table 6
Binary logistic regression results with age, DM, HTN, hyperlipidemia, FH of CAD, smoking, and result of EST predicting ED.

Variable	B	SE	χ^2	p	OR	95% CI
(Intercept)	−0.05	0.90	0.00	0.952	-	-
Age	0.05	0.02	12.47	< 0.001	1.05	[1.02, 1.09]
Diabetes Mellitus (No)	−0.29	0.35	0.67	0.412	0.75	[0.38, 1.49]
Hypertension (No)	0.04	0.31	0.01	0.909	1.04	[0.56, 1.91]
Hyperlipidemia (No)	0.12	0.30	0.17	0.681	1.13	[0.63, 2.04]
FH of CAD	0.31	0.30	1.06	0.302	1.36	[0.76, 2.44]
Smoking (NO)	−0.78	0.40	3.76	0.053	0.46	[0.21, 1.01]
Result of EST (Negative)	−1.74	0.40	18.64	< 0.001	0.18	[0.08, 0.39]
Result of EST (Inconclusive)	−0.68	0.58	1.38	0.240	0.51	[0.16, 1.58]

CI, confidence interval; HR, Hazard ratio; B, Unstandardized beta; SE, Standard Error; z, ratio of regression coefficient to its standard error.

with known CAD, the prevalence of ED in our study was almost similar to that of Kloner et al.'s, i.e., 74%.

According to the Second Princeton Consensus Guidelines, a male with ED with no cardiac symptoms should be regarded as a cardiac (or vascular) patient unless proven differently [24]. The findings of our study corroborated this assertion, demonstrating that ED was more common in patients with an inconclusive EST than in patients with a negative EST [85% versus 60%, p.001]. As a result, patients in our research who had an inconclusive EST but a positive ED provided an invaluable opportunity to undergo further testing for occult CAD. This is because atherosclerosis is a chronic, systemic disorder that affects the whole blood circulation system, including the penile artery. Since penile arteries are smaller than coronary arteries, penile vascular disease (ED) may develop 2–3 years before coronary artery disease.

In our study, patients with ED had a higher prevalence of specific cardiovascular risk factors than those who did not have ED. Age, a non-modifiable CVD risk factor, was significantly linked to ED. It found that the incidence of ED increased with age, with a one-unit increase in age increasing the odds of ED by about 5% [B = 0.05, OR = 1.05, p.001], correlating with the findings of the Brazilian and KRIMPEN studies, which also revealed a rising yearly incidence rate [25,26].

The findings of this research also supported the Massachusetts Male Aging Study (MMAS) findings, which found that erectile dysfunction increased with age and that age is an independent risk factor for ED [27]. In the same study, the prevalence of ED increased three times with age [28].

Ponholzer A et al. used a validated IIEF-5 questionnaire to determine the prevalence and risk factors for erectile dysfunction in 2869 males. They discovered that 32% of men aged 20 to 80 years had some form of ED when tested using the IIEF-5 [29]. On the contrary, in this study, 173 (77%) of patients with ED were in the age range of 45 to 70 years, whereas 15 patients were over 70 years old, and they all had ED.

Diabetes is another cardiovascular risk factor considered equivalent to CVD [30]. The prevalence of ED in diabetic patients is higher than that of non-diabetics. Awole Seid et al. reported a prevalence of ED in 69.9% of diabetic patients in their study sample [31]. Similarly, Balasingam Nisahan et al. and Sreeharsha Nutalapati et al. reported a prevalence of 62.9% and 68.6%, respectively [32,33]. 84% had some form of ED when screened through the IIEF-5 questionnaire in our research. On the contrary, McCulloch et al. evaluated the incidence of ED in the diabetic community. As per their results, only 35% of diabetic males experienced ED [34].

Besides diabetes, hypertension in Pakistan is also on the rise. A recent study reported the prevalence of hypertension in Pakistan, ranging from 44% to 49% [35]. In our research, 169 (55.8%) were hypertensive patients. Hypertension has been demonstrated in epidemiological studies

as a major predictor of ED [36–38]. A recent *meta*-analysis confirmed that hypertensive men had a greater rate of severe ED than the general population [39]. In a case-control study in Pakistan, the prevalence of ED in hypertensive and normotensive individuals was reported as (61.79% vs 20.28%, p <.00001) [35]. Our results supported the findings of both the *meta*-analysis and the case-control study. In our study of 303 patients, 169 of them were hypertensive. We discovered a 60% prevalence of ED in hypertensive patients (p =.024).

Smoking is one of the most notorious cardiovascular risk factors and significantly contributes to vascular endothelial dysfunction [40]. This dysfunction is dosage-dependent [41]. As a result, epidemiological studies have linked persistent smoking to erectile dysfunction [40,42]. Smoking raises blood nicotine levels, causing sympathetic overactivity and erectile flaccidity [41,43]. Besides all the aforementioned causes, ED is characterised by atherosclerotic alterations in the erection-related arteries induced by smoking and other reasons [44]. Similar results were observed in the coronary vascular bed, indicating that cigarette smoking causes atherosclerosis, which has a gradual, cumulative impact on the development of atherosclerosis [43]. The accumulation of atherosclerosis in the pudendal artery due to smoking leading to arteriogenic ED is evident in the literature [45]. Hallanzy et al. reported an odds ratio of 1.2, meaning that smokers in their study had 1.2 times more chances of erectile dysfunction than non-smokers [46]. In our study, 61 (20.1%) patients were smokers, and out of those 61 patients, 49 (80%), p =.225) had ED. We reported an odds ratio of 0.46, but it did not achieve statistical significance.

Hyperlipidemia causes endothelial damage and inflammation, which increases the risk of erectile dysfunction [47,48]. Studies have shown that patients with ED after taking statin treatment demonstrate a rise in their IIEF score. In a *meta*-analysis, Kostis and Dobrzynski reported a 3.4-point rise in IIEF scores between the experimental and control groups [47]. Similarly, Cai et al. conducted a separate *meta*-analysis of seven trials employing two different statins. They found a 3.27-point rise in IIEF scores [49]. On the contrary, this study did not involve any intervention related to statin. In contrast, this study only compared patients with and without hyperlipidemia (a cardiovascular risk factor for the prevalence of ED). 180 (59.4%) of the 303 patients enrolled in this study were dyslipidemic. ED was diagnosed in 138 (77%, p =.246) of these 180 patients. Even though most hyperlipidemic patients had some degree of ED, we were unable to establish a statistically significant association between hyperlipidemia and ED.

Besides hyperlipidemia, we sought to establish an association between a positive family history of CAD and erectile dysfunction. Literature is limited regarding the direct relationship between a family history of CAD and ED. Studies have shown an indirect relationship between ED and Family history of CAD [50]. However, this study, specifically reported that 117 (38.6%) out of 303 patients enrolled had a family history of premature CAD. Among these 117 patients, 84 (72%, p =.437) suffered some degree of ED.

5. Limitations

Our study has a few limitations. Firstly, it was a single-center study. Secondly, the sample size was not large enough. Our study sets the stage for future studies to follow suit. This study did not follow the patients for major adverse cardiac events (MACE).

Further research to determine if MACE is tied to ED would be needed. Moreover, incorporating other advanced non-invasive investigations such as stress echocardiography, computed tomography calcium scoring, and myocardial perfusion scans would have added to the reliability of the association between CAD and ED. Large studies would be required to evaluate the deeper impact of ED on CAD.

6. Conclusion

This research revealed a link between cardiovascular risk factors, erectile dysfunction, and exercise stress testing. Patients with a positive EST with erectile dysfunction should be regarded as extremely high risk for cardiovascular events. This should lead us to conduct a thorough evaluation and management of such patients. Based on the significant link observed in our research between EST, ED, and a definite CAD we to recommend ED screening for all male patients referred for EST because it may serve as an easily accessible, non-invasive method of identifying and aggressively treating latent coronary artery disease. This is simple to incorporate into traditional risk assessments performed in outpatient departments.

Author contributions

Dr. Fahad Raja Khan had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Dr. Shakeel Ahmed Memon, Dr. Fahad Raja Khan, Dr. Samra Rehmat, and Dr. Muhammad Adil.

Data acquisition, analysis, or interpretation: Dr. Fahad Raja Khan, Dr. Nooh Zaad Gul, Dr. Safi Ullah Khattak, and Dr. Muhammad Adil.

Drafting of the manuscript: Dr. Shakeel Ahmed Memon, Dr. Muhammad Adil, and Dr.

Fahad Raja khan.

Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis**:** Dr. Fahad Raja khan, Dr. Nooh Zaad Gul and Dr. Muhammad Adil Data Collection: Dr. Safi Ullah, Dr. Samra Rehmat, Dr. Nooh Zaad Gul Administrative, technical, or material support: Dr. Safi Ullah Supervision: Dr. Shakeel.

Ahmed Memon, Dr. Nooh Zaad Gul.

Data availability

Data underlying this article can be shared at reasonable request to the corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Disclosure of funding

This research did not receive specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

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