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Original Article

Serum Endothelin-1 Level >2.0 pg/mL associates with High-Risk Duke Treadmill Score among Chronic Coronary Syndrome Patients

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Abstract

Background: Chronic Coronary Syndrome (CCS) contributes to morbidity and increased risk of acute coronary syndrome within 5 years. Duke Treadmill Score (DTS) is the most robust risk stratification based on cardiac exercise stress test, which predicts 5-year survival. Those with high-risk DTS (DTS <- 11) had the poorest survival. Endothelin-1, a potent vasoconstrictor peptide, affects 5-year survival in CCS. This study sought to investigate whether serum endothelin-1 level and DTS risk stratification were associated among patients with CCS.

Methods: This was a cross-sectional study that recruited consecutive patients with CCS after Coronary Angiography (CAG). The DTS data were collected from the previous Treadmill Test (TMT) and were classified into high-risk DTS (DTS ≤-11) and low-moderate-risk DTS (DTS >-11). A serum sample for measuring endothelin-1 was withdrawn during CAG and used in the ELISA protocol. A high endothelin-1 level was defined as > 2.0 pg/mL. An association between variables was assessed using statistical analysis (significance at $p < 0.05$).

Results: Eighty subjects were enrolled. Median time interval of TMT and endothelin-1 measurement was 30 days. Mean age was 58.48±8.73 years old, with males predominant (82.5%). Hypertension (71.3%) and previous Acute Coronary Syndrome (ACS) (52.5%) were dominant. The proportion of subjects with high-risk DTS was 52.5%. Median endothelin-1 level was 1.8 pg/mL (range: 0.4 - 6.8 pg/mL). Serum endothelin-1 level > 2.0 pg/mL was observed in 34 subjects (42.5%), of whom 23 (67.6%) had high-risk DTS. There was a significantly increased risk of high-risk DTS in subjects with serum endothelin-1 >2.0 pg/mL (OR 2.97; 95% CI 1.18-7.51; p=0.020). Based on bivariate analysis, two variables, namely hypertension (p=0.052) and history of ACS (p=0.036), were also significantly associated with high-risk DTS. In multivariate analysis, endothelin-1 level >2.0 pg/mL had an adjusted OR of 1.75 (95% CI: 0.60-5.13, p=0.305), indicating no statistically significant independent association with high-risk DTS. Hypertension and a history of ACS had an independent and significant association with high-risk DTS.

Conclusions: Among CCS patients, serum endothelin-1 level > 2.0 pg/mL was associated with high-risk DTS from TMT examination. However, this association was not independent, as in hypertension and history of ACS.

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Keywords: Chronic Coronary Syndrome; Treadmill Test; Duke Treadmill Score; Endothelin-1; Cardiovascular Disease

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Introduction

Chronic Coronary Syndrome (CCS) is one of Cardiovascular Diseases (CVD), which becomes a substantial contributor to morbidity and reduced quality of life among its patients.[1] A substantial number of patients with CCS ultimately require hospitalization due to Acute Coronary Syndrome (ACS).[1] Major Adverse Cardiovascular Events (MACE) are also significant morbidity and mortality outcomes among patients with CCS, necessitating relevant interventions to prevent the complication.[2]

Non-invasive examination modalities are capable of demonstrating the presence of myocardial ischemia. Cardiac Exercise Stress Test (CEST) with Electrocardiogram (ECG) recording by Treadmill Test (TMT) remains an important and frequently used examination in establishing the diagnosis of CCS by assessing myocardial ischemic response to the application of graded exercise that increases myocardial oxygen demand.[3] In addition to diagnosis, TMT can be utilized to determine risk stratification and assess prognosis in CCS.[3-4] For this purpose, the Duke Treadmill Score (DTS) is one of the robust methods that has been validated by several studies. Risk stratification based on the DTS is divided into low (DTS ≥5), moderate (DTS between 4 and -10), and high risk (DTS ≤-11), which predict 5-year survival in patients with CCS.[4]

Endothelin-1, a potent vasoconstrictor peptide, is proposed as a new prognostic indicator for ACS. Among Indonesians, this vasoactive biomarker is positively associated with poor prognosis in ACS.[5-6] Its role in predicting MACE among CCS patients remains unclear. A previous study in the Asian population showed that endothelin-1 contributes to the development and severity of CCS.[7] This study aimed to examine whether serum endothelin-1 level and DTS risk stratification were associated among Indonesian patients suffering CCS.

Methods

This study used a cross-sectional methodology. The site of this research was Dr. Sardjito Hospital, Yogyakarta, Indonesia. The Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta, Indonesia, granted ethical clearance for this study (Reff. number: KE/FK/1910/EC/2024).

The subjects were patients with CCS who had an elective Coronary Angiography (CAG) examination at the site hospital. The recruitment of subjects was conducted using consecutive sampling. Inclusion criteria were the following: 1) male or female patients with an age of ≥ 30 years old, 2) patients diagnosed with CCS, and 3) patients had biomarker examination. The following were exclusion criteria: (1) patients who had malignancy, (2) patients with chronic kidney disease, (3) patients with proven peripheral artery disease, and (4) patients without adequate TMT interpretation data. Informed consent was signed by all participating subjects. Subjects' enrollment, data collection, and biomarker examination were conducted from 2018 to 2019. For this current study, the analysis was finalized in 2024.

Among all eligible subjects, those who met the inclusion and exclusion criteria were analyzed. Data on demographics, cardiovascular disease risk factors, medications, and TMT results were collected. The TMT results were collected within 1.5 years before biomarker measurement. A CCS is chest pain/discomfort due to a disproportion between myocardial oxygen supply and demand, due to the presence of coronary stenosis, determined by CAG. A TMT is a CEST examination with a conveyor belt whose stress load is regulated by an electric machine and controlled by a programmable protocol by the Treadmill machine. The TMT procedures were Bruce or modified Bruce protocols. The termination criteria for the TMT procedure were in accordance with the national guideline and were determined by the clinicians who supervised the TMT.[4] The exercise time was the duration from the start of exercise until the end of exercise (start recovery). Chest pain was a subjective complaint of chest tightness during TMT and was assessed by clinicians who supervised the TMT as either no angina or angina. Limiting angina was chest pain that prompted subjects to stop the TMT, and non-limiting angina was chest pain present on the TMT but did not prompt subjects to stop the TMT. ST deviation was determined based on the national guideline for CEST.[4]

From the TMT, the DTS is calculated based on the presence of chest pain, time of exercise, and the depth of ST changes from baseline. The formula is: [DTS = exercise time (minutes) – 5 x ST segment deviation (mm) – 4 x index of anginal pain (value 0 = no angina, 1 = non-limiting angina, 2 = limiting angina)].[4] It is a scoring system for risk stratification and is useful for assessing the CVD prognosis in 5 years.[4] In this study, the DTS was classified into high-risk DTS (DTS ≤-11) and low-moderate-risk DTS (DTS >-11).

Endothelin-1 is a peptide measured in serum by ELISA and has normal levels between 0.7 and 2.0 pg/mL.[8] A level of >2.0 pg/mL was defined as a high endothelin-1 level. A blood sample was withdrawn to measure endothelin-1 levels when subjects were admitted to the hospital for a CAG examination. Fasting blood samples from peripheral veins were withdrawn before the CAG procedure, collected in BD Vacutainer tubes (Becton Dickinson, USA), and stored at room temperature for 20–30 min. Subsequently, the Vacutainer tubes were centrifuged at 200 g for 20 min, and the supernatants were stored frozen at −80 °C in the Biobank Unit of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada. The process of measuring endothelin-1 was based on the manufacturer's instructions for the Endothelin-1 immunoassay Quantikine® ELISA kit (R&D Systems, Minneapolis, MN, U.S.A.), as previously described.[9]

For statistical analysis, the S.P.S.S. software v.25 (I.B.M., U.S.A.) was used. The categorical data were exhibited as a number (%). The numerical data were presented as the mean and Standard Deviation (SD) when normally distributed, or as the median (range: minimum-maximum values) when skewed. Following the bivariate analysis, a multivariate logistic regression was performed to assess the association between two main variables: serum endothelin-1 level and high-risk DTS. Covariates were included in logistic regression if the p-value was <0.250 in the bivariate analysis. The p-value <0.05 was a statistically significant cut-off.

Results

During patients' eligibility screening, 183 patients underwent CAG and had serum endothelin-1 measurement. Of these patients, 95 lacked adequate TMT data (including DTS), and 8 lacked sufficient variables required for the study. Therefore, 103 patients were excluded from the study. Finally, 80 subjects were enrolled. The median time interval between TMT and endothelin-1 measurement was 30 days (range: 3 – 371 days). The characteristics of the subjects are exhibited in Table 1.

Table 1. Subject characteristics.

Variables	Total (n=80)
Male sex, n (%)	66 (82.5)
Age, years (mean±SD)	58.48±8.73
Diabetes mellitus, n(%)	20 (25.0)
Dyslipidemia, n(%)	41 (51.2)
Hypertension, n(%)	57 (71.3)
Smoking, n (%)	53 (66.3)
History of ACS, n(%)	42 (52.5)
Endothelin-1, pg/mL (median (min-max)	1.8 (0.4-6.8)
Time interval, days (median (min-max))	30 (3-371)
TMT result, n(%)	
High-risk DTS	42 (52.5)
Low-moderate-risk DTS	38 (47.5)
Beta blocker, n(%)	63 (78.8)
ACEi/ARB, n(%)	69 (86.3)
Statin, n(%)	72 (90.0)
Spironolactone, n(%)	3 (3.8)

SD: Standard deviation, ACS: Acute coronary syndrome, TMT: Treadmill test, DTS: Duke treadmill score, ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers.

Subjects' characteristics show that the mean age was 58.48±8.73 years old. Most of the subjects (82.5%) were males. Cardiovascular risk factors were hypertension (71.3%), diabetes mellitus (25%), active smoker (66.3%), and dyslipidemia (51.2%). Previous ACS occurred in 52.5% of subjects. From the TMT results, the number of subjects with high-risk DTS was 52.5%. Users of Angiotensin-converting Enzyme inhibitor (ACEi)/Angiotensin Receptor Blockers (ARB) drugs were 86.3%, beta blockers 78.8%, statins 90%, and spironolactone 3.8%. For the measurement of endothelin-1 levels,

a median of 1.8 pg/mL was obtained with a value range of 0.4-6.8 pg/mL.

An increased serum endothelin-1 level (>2.0 pg/mL) was observed in 34 subjects (42.5%). Among them, 23 subjects (67.6%) were classified as high-risk DTS, while 32.4% were classified as low-moderate-risk DTS. There was a significantly increased risk of high-risk DTS in subjects with serum endothelin-1 >2.0 pg/mL (OR 2.97; 95% CI 1.18-7.51; p=0.020), as shown in Table 2.

The variables associated with high-risk DTS are shown in Table 3. Based on bivariate analysis, a history of ACS (p=0.036) and endothelin-1 level >2.0 pg/mL (p=0.020) were significantly associated with high-risk DTS. Two covariates (p-value <0.250) were included in the multivariable analysis: hypertension (p=0.052) and a history of ACS. Table 4 shows the results of a logistic regression analysis that included hypertension, a history of ACS, and serum endothelin-1 >2.0 pg/mL. It was found that endothelin-1 level > 2.0 pg/mL had an adjusted OR of 1.75 (95% CI: 0.60-5.13, p=0.305), indicating no statistically significant independent association with high-risk DTR. Nevertheless, hypertension and a history of ACS had statistically independent, significant associations with high-risk DTS, with respective adjusted ORs of 0.31 (95% CI: 0.11-0.90, p=0.032) and 5.97 (95% CI: 1.16-30.65, p=0.032).

Table 2. A bivariate analysis between serum endothelin-1 levels and DTS risk stratification.

Serum endothelin-1 level	DTS Stratification		OR (95% CI)	P value
	High Risk n (%)	Low-moderate Risk n (%)		
Level >2.0 pg/mL	23 (67.6)	11 (32.4)	2.97 (1.18-7.51)	0.020
Level ≤2.0 pg/mL	19 (41.3)	27 (58.7)		

DTS: Duke treadmill score; CI: Confidence interval; OR: Odds ratio.

Table 3. Comparison of variables based on DTS stratification.

Variables	DTS Stratification		P-value
	High Risk n (%)	Low-moderate Risk n (%)	
Age ≥60 years old	11 (57.9%)	8 (42.1%)	0.590
Male sex	34 (51.5%)	32 (48.5%)	0.702
Diabetes Mellitus	10 (50%)	10 (50%)	0.796
Dyslipidemia.	23 (56.1%)	18 (43.9%)	0.509
Hypertension	26 (45.6%)	31 (54.4%)	0.052
Smoke	27 (50.9%)	26 (49.1%)	0.696
History of ACS	18 (42.7%)	24 (57.3%)	0.036
Beta blocker	32 (50.8%)	31 (49.2%)	0.556
ACEi/ARB	35 (50.7%)	34 (49.3%)	0.426
Statin	37 (51%)	35 (49%)	0.292
Spironolactone	2 (66.7%)	1 (33.3%)	1.000
Endothelin-1 level >2.0 pg/mL	23 (67.6)	11 (32.4)	0.020

ACS: Acute coronary syndrome, TMT: Treadmill test, DTS: Duke treadmill score, ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers.

Table 4. Multivariate analysis for independent association between variables and high-risk DTS.

Variables	Phase I OR (95% CI; p value)	Phase II OR (95% CI; p value)
Serum endothelin-1 level >2.0 pg/mL	1.75 (0.60-5.13); 0.305	-
Hypertension	0.36 (0.12-1.06); 0.063	0.31 (0.11-0.90); 0.032
History of ACS	3.99 (0.66-24.24); 0.132	5.97 (1.16-30.65); 0.032

ACS: Acute coronary syndrome; CI: Confidence interval; OR: Odds ratio.

Discussion

This study showed that in CCS patients who had an increased serum endothelin-1 level > 2.0 pg/mL, there was an increased risk of 5-year mortality, determined by high-risk DTS preponderance. This increased risk was not independently associated due to an interaction with hypertension and a history of ACS. Therefore, a strategy to control hypertension and optimize ACS treatment is necessary to reduce 5-year mortality for patients who have higher serum endothelin-1 levels.

The majority of subjects had hypertension (71.3%), with 45.6% of them in the high-risk DTS. Hypertension was independently associated with high-risk DTS. Studies demonstrated the increased CCS risk among subjects with higher blood pressure, both systolic (>115 mmHg) and diastolic (>75 mmHg), which showed that those with a 20 mmHg increased of systolic blood pressure and a 10 mmHg of diastolic blood pressure had a 2-fold risk to develop CCS.[10]

Previous research determined that a normal serum endothelin-1 level is between 0.7 and 2.0 pg/mL.[8] The level of >2.0 pg/mL indicates high endothelin-1. In this study, 42.5% of subjects had high endothelin-1 levels, and 67.6% were classified as high-risk DTS. This is associated with nearly a threefold increased risk of high-risk DTS stratification. However, this association was not independent of covariates, such as hypertension and a history of ACS. This indicates that elevated endothelin-1 interacts with increased blood pressure and preceding acute CVD event in patients with CCS. Prior studies have shown that elevated endothelin-1 levels in coronary atherosclerosis actively contribute to regional myocardial ischemia.[11]

Endothelin-1, emitted largely by endothelial cells, induces a strong and enduring vasoconstriction response by means of paracrine activity, primarily on its receptors in vascular smooth muscle cells.[12] Endothelin-1 vasoactive response plays a crucial role in CVD, where elevated circulating endothelin-1 or endothelin-1-related peptides frequently occur in CVD. Hypertension, pulmonary hypertension, and atherosclerosis were among the diseases affected by endothelin-1 activity.[12] Endothelin-1 production is triggered by various external stimuli or pathological conditions, such as inflammation, hypoxia, or mechanical stress on the blood vessel wall, which increase endothelin-1 mRNA expression and endothelin-1 release.[13] The inducible pathway is greater and can produce a more significant effect in increasing vasoconstriction or playing a role in pathological conditions such as hypertension or atherosclerosis.[13] In this study, elevated endothelin-1 levels were not independently associated with high-risk DTS stratification. There are possible interactions with variables, namely, history of ACS and hypertension, which showed a significant and independent association with high-risk DTS. These two clinical conditions are associated with elevated endothelin-1 levels.

Exercise stress testing by TMT is an established modality for diagnosis and prognosis of CAD, especially in patients with CCS.[4] For risk stratification of patients having TMT, the DTS is an established scoring system for risk stratification. Patients with high-risk DTS or DTS ≤-11 are considered candidates for CAG because the positivity rates of significant coronary stenosis require revascularisation and increased 5-year mortality.[14] Our study may provide insight into the risk of increased 5-year mortality in patients with CCS who had elevated endothelin-1 levels. These patients may need further strategies for secondary CVD prevention, especially in controlling hypertension and optimizing coronary medication.

Most subjects receive standard medication for CCS, namely beta-blockers (78.8%), ACEi/ARBs (86.3%), and statins (90%). These medications may affect endothelin-1 levels in patients with CCS.[15] In this study, more than half (57.5%) of subjects had an endothelin-1 level below 2.0 pg/mL. However, in this study, the impact of medications was neutral in terms of DTS risk stratification. Further study is needed to investigate the impact of medications on DTS risk stratification.

Several limitations were encountered in this study, namely: (1) small subjects enrolled in this study, which affected the result of multivariates analyis, (2) more than half of the study population was excluded due to incomplete data, (3) several conditions that may affect endothelin-1 levels, such as peripheral artery disease, could not be excluded due to the lack of relevant data, and (4) the study used secondary data, making it impossible to control the interval time of endothelin-1 blood sampling and the TMT examination.

Conclusion

In the conclusion, among patients with CCS, a serum endothelin-1 level > 2.0 pg/mL is associated with high-risk DTS on TMT examination. However, this increased risk was not independently associated due to interaction with hypertension and history of ACS. Hypertension and a history of ACS were

independent predictors for high-risk DTS, which was linked to reduced 5-year survival in CCS patients.

List of Abbreviations

ACEi	Angiotensin-converting Enzyme inhibitor
ACS	Acute Coronary Syndrome
ARB	Angiotensin Receptor Blockers
CAD	Coronary Artery Disease
CAG	Coronary Angiography
CCS	Chronic Coronary Syndrome
CEST	Cardiac Exercise Stress Test
CI	Confidence Interval
CVD	Cardiovascular Disease
DTS	Duke Treadmill Score
ECG	Electrocardiogram
ELISA	Enzyme Link Immunosorbent Assay
mRNA	:messenger Ribonucleid Acid
OR	Odds Ratio
SD	Standard Deviation
TMT	Treadmill Test

Ethical Clearance

Ethical approval was obtained from The Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta, Indonesia (Reff. number: KE/FK/1910/EC/2024).

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

MSP: conception and design, analysis and interpretation of data, drafting the article, and final approval of the version to be published. IAA: conception and design, revising the article critically for important intellectual content, and final approval of the version to be published. IP: conception and design, revising the article critically for important intellectual content, and final approval of the version to be published ABH: conception and design, revising the article critically for important intellectual content, and final approval of the version to be published All authors read and approved the final manuscript

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Conflict of Interest

None.

Availability of Data and Materials

Data and materials generated for this study are available on request to the corresponding author.

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

The author declares that no artificial intelligence (AI) tools were used in the writing, analysis, or preparation of this manuscript.

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