

ORIGINAL ARTICLE

Systemic Immune-Inflammation Index and Coronary Microvascular Dysfunction in Patients with Non-Obstructive Coronary Arteries

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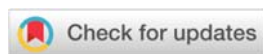
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**ABSTRACT**

Background: Coronary microvascular dysfunction contributes to ischaemic symptoms in individuals with non-obstructive coronary arteries. Systemic inflammation might lead to endothelial dysfunction and irregular coronary microvascular resistance. The systemic immune-inflammation index is an indicator obtained from the numbers of neutrophils, lymphocytes, and platelets.

Aim: To assess the correlation between the systemic immune-inflammation index and coronary microvascular dysfunction in individuals with non-obstructive coronary arteries.

Methods: This cross-sectional investigation included 150 individuals receiving coronary angiography at Mayo Hospital Lahore between June 2024 and June 2025. Individuals suffering from obstructive coronary artery disease, acute coronary syndrome, ongoing infections, inflammatory conditions, cancer, or diminished left ventricular ejection fraction were omitted. Coronary microvascular dysfunction was characterised by a coronary flow reserve of less than 2.0, a microvascular resistance score of 25 or higher, or both criteria. The systemic immune-inflammation index was determined by multiplying the platelet count by the neutrophil count and then dividing by the lymphocyte count.

Results: Coronary microvascular impairment was detected in 62 individuals (41.3%). The median systemic immune-inflammation score was elevated in individuals exhibiting dysfunction compared to those with intact microvascular function (821 vs 487; $p < 0.001$). The index exhibited a negative correlation with coronary flow reserve ($r = -0.49$) and a positive correlation with microvascular resistance ($r = 0.53$), both $p < 0.001$. Following multivariable correction, every 100-unit increment continued to be independently linked to dysfunction (adjusted odds ratio 1.18; 95% confidence range 1.09–1.28). A threshold of 620 demonstrated 80.6% sensitivity and 73.9% specificity.

Conclusion: The systemic immune-inflammation score was independently linked to coronary microvascular dysfunction and might aid in risk classification for individuals with non-obstructive coronary arteries.

Keywords: coronary microvascular dysfunction; systemic immune-inflammation index; non-obstructive coronary arteries; coronary flow reserve; microvascular resistance; inflammation

INTRODUCTION

Individuals experiencing recurring thoracic discomfort or demonstrable signs of myocardial ischaemia often have

coronary angiography, while not exhibiting substantial constriction of the main epicardial coronary vessels¹. This condition is known as Ischaemia with Non-Obstructive

Coronary Arteries, representing a significant clinical concern rather than a trivial angiographic observation. Chronic angina, reduced exercise capacity, recurrent hospital admissions, and lowered quality of life are the primary factors associated with coronary microvascular dysfunction in these individuals².

Coronary microvascular dysfunction refers to the failure of the tiny intramyocardial arteries and arterioles to adequately dilate in response to heightened oxygen requirements³. This anomaly may result from endothelial injury, impaired relaxation of vascular smooth muscle, alterations in resistance vessel structure, capillary rarefaction, perivascular fibrosis, and/or an elevation in baseline coronary blood flow. Traditional coronary angiography fails to provide direct observation of these minor vessels, and patients may have normal or slightly compromised coronary arteries while experiencing clinically relevant myocardial perfusion deficits⁴.

To evaluate coronary microvascular performance, coronary flow reserve and the index of microvascular resistance are used⁵. Nonetheless, whereas the coronary flow reserve quantifies the ability of the coronary circulation to enhance flow at maximum vasodilation, the microvascular resistance index more accurately assesses resistance inside the coronary microcirculation. Coronary microvascular dysfunction may be indicated by diminished coronary flow reserve, heightened microvascular resistance, or a combination of both. These assessments need specialised apparatus and skilled personnel, and they consume more time, rendering them seldom accessible in several healthcare environments⁶.

A disruption in the systemic inflammatory response has emerged as a crucial element linked to coronary microvascular dysfunction⁷. Persistent inflammatory processes may lead to diminished nitric oxide levels, heightened oxidative stress, endothelial impairment, alterations in vascular tone, and structural reconfiguration of the coronary microcirculation. Neutrophils may exacerbate injury to the endothelium layer by the generation of reactive oxygen species, proteolytic enzymes, and inflammatory mediators. Platelets has the ability to enhance inflammation via their interactions with leukocytes and vascular endothelial cells. A diminished lymphocyte count may signify heightened physiological stress, a compromised capacity to manage the immune system, and an intensified inflammatory response⁸.

The systemic immune-inflammation index is a composite haematological measure calculated by multiplying the platelet count by the neutrophil count and then dividing by the lymphocyte count⁹. This index may provide a more thorough assessment of inflammatory activity in the body compared to any individual blood-cell index, since it encompasses the activity of three circulating

cell populations involved in inflammation, thrombosis, and immunological modulation. It is easily accessible and affordable, may be conducted several times, and is included in a conventional complete blood count, making it beneficial in both resource-constrained and sophisticated medical settings¹⁰.

Elevated systemic immune-inflammation index values have been associated with an increased burden of cardiovascular disease, inadequate myocardial perfusion, and negative clinical outcomes¹¹. It has been proposed that it is linked to coronary microvascular dysfunction, which is significant since inflammation may relate not only to alterations in vasomotor control but also to structural modifications in the coronary microcirculation. Nonetheless, there is ambiguous information regarding its association with objectively assessed coronary microvascular dysfunction in individuals with non-obstructive coronary artery disease. A straightforward blood-based biomarker capable of identifying people at elevated risk for coronary MF might be advantageous for directing coronary functional assessments. May also assist in identifying individuals with coronary-related symptoms without obstructive angiography. The objective of the current investigation was to examine the correlation between the systemic immune-inflammation index and coronary microvascular dysfunction in individuals with non-obstructive coronary arteries. The conjecture posited that individuals with coronary microvascular dysfunction would have elevated systemic I-II levels, and that this relationship would be unaffected by conventional cardiovascular risk factors¹².

MATERIALS AND METHODS

This research is a one-year prospective cross-sectional investigation conducted from June 2024 to June 2025 inside the Cardiology Department of a Mayo Hospital Lahore. This study examined the relationship between coronary microvascular dysfunction and the systemic immune-inflammation index in people without obstructive coronary artery disease (CAD) who had symptoms and/or objective markers of myocardial ischaemia.

A cohort of 150 consecutive patients scheduled for elective coronary angiography due to recurrent chest discomfort, exertional angina, abnormal exercise tolerance tests, or myocardial ischaemia identified with non-invasive cardiac imaging was assembled. Only patients exhibiting normal coronary arteries or non-obstructive coronary disease (CAC) as determined by coronary angiography were included into the final study.

Individuals between the ages of 18 and 75 exhibiting signs indicative of myocardial ischaemia, with angiographic findings showing less than 50% stenosis in the major

epicardial coronary arteries, were included. All participants were required to possess extensive clinical, haematological, biochemical, angiographic, and coronary physiological information.

Individuals with a prior occurrence of acute coronary syndrome, obstructive coronary artery disease, previous myocardial infarction, prior percutaneous coronary intervention, coronary artery bypass grafting, heart failure with diminished ejection fraction, severe valvular heart disease, cardiomyopathy, uncontrolled cardiac arrhythmia, or notable congenital heart disease were excluded. Individuals with an active infection, chronic inflammatory or autoimmune disorders, malignancies, haematologic conditions, severe renal impairment, or chronic liver ailments, as well as those who underwent corticosteroid or immunosuppressive treatment within the last six months, were excluded due to the potential impact of these conditions on inflammatory cell counts and the systemic immune-inflammation index.

Demographic and clinical information was acquired via patient interviews and their medical documentation. The age, gender, body mass index, tobacco use, familial history of cardiovascular ailments, hypertension, diabetes, dyslipidaemia, and present cardiovascular treatments were documented. Following a minimum of 5 minutes of repose, blood pressure was assessed using a calibrated sphygmomanometer. The body weight (kg) divided by the square of height (m) is the body mass index. Prior to the coronary angiography operation, venous blood samples were taken after an overnight fast. Complete blood counts were performed using automated haemoglobin analysers. Each person's absolute neutrophil, absolute lymphocyte, and platelet counts were noted. Blood fasting glucose, glycated haemoglobin, creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and high sensitivity C-reactive protein were all measured using standard laboratory methods. By multiplying the platelet count by the absolute neutrophil count and dividing the result by the absolute lymphocyte count, the systemic immune-inflammation index was computed.

To reduce measurement variability, all blood specimens were examined in the same institutional laboratory. Prior to the coronary angiography, a conventional cardiac ultrasonography apparatus was used for the transthoracic echocardiography. The adjusted Simpson biplane technique was used to ascertain left ventricular ejection fraction. Evaluation of the heart chamber enlargement, regional wall motion irregularities, and existence of notable valvular abnormalities was conducted. Individuals having a left ventricular ejection fraction (LVEF) below 50% were omitted.

Diagnostic coronary angiography was performed using either the radial or femoral artery route by traditional techniques. To mitigate the influence of vasomotor activity on the size of the coronary lumen, intracoronary nitrate was administered before the evaluation of coronary anatomy. Two proficient interventional cardiologists independently evaluated the coronary angiograms without awareness of the inflammatory-index data.

Non-obstructive coronary arteries were defined by the absence of stenosis equal to or above 50% in the left main, left anterior descending, left circumflex, or right coronary artery. If the physiological relevance of an intermediate lesion was ambiguous, a fractional flow reserve assessment was conducted, and only individuals with fractional flow reserve measurements over 0.80 were included into the research.

Upon verification of the unobstructed coronary epicardial arteries, the evaluation of coronary microvascular function was conducted using the intracoronary pressure-temperature sensor guidewire. Upon aligning the guiding-catheter tip, the guidewire was advanced into the distal LAD.

Three injections of room temperature normal saline were administered intracoronarily, and the resting mean transit time was measured. The peak coronary hyperaemia was then elicited with intravenous adenosine at a dosage of 140 µg/kg/min, accompanied by three additional saline infusions during stable hyperaemia; the mean hyperaemic transit time was recorded.

The average transit durations at rest and during hyperaemia were used to determine the coronary flow reserve. To calculate microvascular resistance, the maximum hyperaemic mean transit time (THMT) was multiplied by the microvascular pressure (distal coronary pressure during hyperaemia).

Coronary microvascular dysfunction was characterised by a CFR of less than 2.0, an IMR of 25 or above, or the presence of both criteria. Based on these criteria, the research subjects were divided into two categories—one exhibiting coronary microvascular dysfunction and the other demonstrating maintained microvascular function.

The primary result was the existence of coronary microvascular impairment. Secondary studies included the assessment of the correlation between the SII and CFR, as well as the examination of the relationship between the SII and microvascular resistance, in addition to the SII and the existence of coronary microvascular dysfunction.

The research received authorisation from the Institutional Review Board (IRB). All individuals provided informed permission before joining. All patient information remains private, and all research protocols are executed in accordance with the tenets of the Declaration of Helsinki.

Statistical software and its version were used to analyse the data. The normality of continuous data was evaluated using the Shapiro-Wilk test. An independent samples t-test was used to compare variables that had a normal distribution, which were represented by their mean and standard deviation. The Mann-Whitney U test was used for comparison, and the median and interquartile range were shown for variables that did not have a normal distribution. Frequencies and percentages were employed to represent categorical data, and these categories were compared using either Fisher's exact test or the chi-square test, as appropriate.

Depending on the data distribution, the connection between the systemic immune-inflammation index and coronary physiological parameters was assessed using Pearson or Spearman correlation analysis. The characteristics associated with coronary microvascular dysfunction were found using univariable logistic regression analysis. Additionally, a multivariable logistic regression model was constructed using clinically important covariates as well as those that showed a p value <0.10 in the univariable analysis. Receiver-operating-characteristic curve analysis was used to assess the systemic immune-inflammation index's effectiveness in identifying coronary microvascular dysfunction. Sensitivity, specificity, positive predictive value, and negative predictive value were assessed, and the optimal cut-off value was determined using the Youden index. A two-tailed p-value of less than 0.05 was used to determine statistically significant differences.

RESULTS

A cumulative total of 173 individuals underwent screening, with 23 being rejected due to obstructive coronary artery disease, prior coronary revascularization, active inflammatory conditions, diminished left ventricular ejection fraction, or insufficient physiological assessments. A comprehensive analysis was conducted on 150 individuals who had no coronary artery blockage. The average age was 53.5 years with a standard deviation of 9.4. A total of 84 males (56.0%) and 66 females (44.0%) were present. Coronary microvascular impairment was identified in 62 individuals (41.3%, including 31 males and 31 women), whereas 88 patients had intact microvascular function. Patients with microvascular dysfunction exhibited increased age, elevated BMI, and a greater prevalence of diabetes mellitus. Table 1 indicates that all other fundamental features were comparable across the groups.

Patients with coronary microvascular dysfunction had an elevated count of neutrophils and platelets with a decreased count of lymphocytes, in addition to an enhanced systemic immune-inflammation index. The amount of C-reactive protein was elevated in the dysfunction group. The coronary flow reserve was markedly diminished, whereas the index of microvascular resistance was considerably elevated, as seen in Table 2.

The systemic immune-inflammation index was significantly positively correlated with the microvascular resistance index ($r=0.53$; $P<0.001$) and significantly negatively correlated with coronary flow reserve ($r=-0.49$; $P<0.001$). Both genders showed the relationships.

Table 1: Baseline characteristics according to coronary microvascular function

Variable	Microvascular dysfunction present (n=62)	Microvascular dysfunction absent (n=88)	p-value
Age, years	55.7 ± 9.1	51.9 ± 9.3	0.014
Male sex, n (%)	31 (50.0)	53 (60.2)	0.218
Female sex, n (%)	31 (50.0)	35 (39.8)	0.218
Body mass index, kg/m ²	28.9 ± 3.7	27.3 ± 3.5	0.009
Hypertension, n (%)	36 (58.1)	41 (46.6)	0.167
Diabetes mellitus, n (%)	20 (32.3)	15 (17.0)	0.029
Dyslipidemia, n (%)	35 (56.5)	42 (47.7)	0.292
Current smoking, n (%)	10 (16.1)	17 (19.3)	0.619

Table 2: Laboratory and coronary physiological findings

Variable	Microvascular dysfunction present (n=62)	Microvascular dysfunction absent (n=88)	p-value
Neutrophil count, ×10 ⁹ /L	5.18 ± 1.39	4.29 ± 1.16	<0.001
Lymphocyte count, ×10 ⁹ /L	1.73 ± 0.46	2.10 ± 0.53	<0.001
Platelet count, ×10 ⁹ /L	276 ± 59	243 ± 52	<0.001
Systemic immune-inflammation index	821 (638–1105)	487 (365–669)	<0.001
High-sensitivity C-reactive protein, mg/L	3.7 (2.2–5.9)	2.0 (1.1–3.5)	<0.001
Fasting blood glucose, mg/dL	111.8 ± 29.4	102.6 ± 24.1	0.038
Coronary flow reserve	1.70 ± 0.27	2.69 ± 0.47	<0.001
Index of microvascular resistance	31 (26–39)	18 (14–21)	<0.001

Table 3: Multivariable predictors of coronary microvascular dysfunction

Variable	Adjusted odds ratio	95% confidence interval	p-value
Age, per year	1.05	1.01–1.09	0.022
Female sex compared with male sex	1.55	0.76–3.17	0.231
Body mass index, per kg/m ²	1.09	0.99–1.19	0.071
Hypertension	1.29	0.61–2.72	0.503
Diabetes mellitus	2.12	0.91–4.94	0.081
High-sensitivity C-reactive protein, per mg/L	1.13	1.01–1.26	0.032
Systemic immune-inflammation index, per 100 units	1.18	1.09–1.28	<0.001

The systemic immune-inflammation index was shown to be a significant independent predictor of coronary microvascular dysfunction in addition to age, gender, body mass index, hypertension, diabetes mellitus, smoking, and high-sensitivity C-reactive protein. According to Table 3, the probability of dysfunction rose by 18% for every 100 units.

Receiver-operating-characteristic (ROC) analysis yielded an area under the curve (AUC) of 0.83, with a 95% confidence interval (CI) between 0.76 and 0.89. Employing a systemic immune-inflammation index threshold of 620, the sensitivity for identifying coronary microvascular dysfunction was 80.6%, while the specificity was 73.9%. The occurrence of dysfunction was 68.5% among individuals with scores ≥ 620 compared to 15.6% in those with values < 620 ($p < 0.001$).

DISCUSSION

The present research demonstrated a strong association between the systemic immune-inflammation index and coronary microvascular dysfunction in individuals devoid of obstructive coronary artery disease¹. The systemic immune-inflammation index levels were markedly elevated in individuals with compromised coronary microvascular function compared to those with intact microvascular function. The index exhibited a negative correlation with coronary flow reserve and a positive correlation with the index of microvascular resistance, indicating that increased systemic inflammatory activity was associated with diminished vasodilatory capacity of the coronary arteries and elevated microvascular resistance².

A considerable proportion of the individuals had coronary microvascular dysfunction in the absence of obstructive epicardial coronary disease³. This discovery supports the idea that a significant clinical cause of ischaemia is not ruled out by a nonobstructive coronary angiography. Standard angiography may fail to identify functional irregularities in the coronary microcirculation, which might be associated with persistent chest discomfort, decreased exercise tolerance, and recurrent visits to healthcare facilities⁴.

The systemic immune-inflammation index (SII) is an integrated inflammatory metric including neutrophils, lymphocytes, and platelets⁵. The results indicating elevated

neutrophils, heightened platelets, and diminished lymphocytes support the hypothesis of an augmented inflammatory and thrombo-inflammatory condition in individuals with microvascular dysfunction. Neutrophil activation may lead to oxidative stress, endothelial damage, and reduced availability of nitric oxide. Platelets may engage with leukocytes and endothelial cells to enhance inflammation, whereas relative lymphopenia might correlate with physiological stress and compromised immunological control⁶.

These results suggest an inverse relationship between the systemic immune-inflammation index and coronary flow reserve, indicating that systemic inflammation may hinder coronary flow reserve during hyperaemia⁷. This decline might be attributed to endothelial impairment, malfunction in vascular smooth muscle relaxation, oxidative stress, and/or microvascular restructuring. The affirmative association with microvascular resistance indicates that inflammation is connected to the constriction of tiny coronary resistance arteries regarding their structure and/or function⁸.

Individuals exhibiting coronary microvascular dysfunction presented with elevated age and body mass index, and a greater prevalence of diabetes mellitus⁹. These are all acknowledged elements that contribute to endothelial dysfunction, oxidative stress, insulin resistance, and chronic inflammation. Following the consideration of these variables, the systemic immune-inflammation index remained independently linked to microvascular dysfunction, indicating that it provides additional insights beyond conventional cardiovascular risk factors¹⁰.

Microvascular impairment was seen in both genders, and the correlation between the systemic immune-inflammation index and microvascular dysfunction was identified in both males and females¹¹. Although the prevalence of dysfunction was greater in females, sex did not serve as an independent predictor after multivariable adjustment. This finding raises doubts about the potential influence of systemic inflammatory processes on coronary microvascular dysfunction in both genders¹².

Coronary microvascular dysfunction served as an autonomous predictor of high-sensitivity C-reactive protein¹³. Nonetheless, a superior connection was seen

between the systemic immune-inflammation index and both coronary flow reserve and microvascular resistance. This might indicate its capacity to connect pathways associated with inflammation, immunity, and platelets, rather than just hepatic inflammatory processes¹⁴.

Employing receiver-operating-characteristic analysis, the systemic immune-inflammation index exhibited strong selective capacity for diagnosing coronary microvascular dysfunction¹⁵. The suggested cut-off value demonstrated satisfactory sensitivity and specificity outcomes, indicating its potential as an initial screening indicator. The index is obtained from a standard complete blood count and is accessible, economical, and user-friendly in clinical settings¹⁶.

A systemic immune-inflammation index must not to be regarded as a replacement for invasive coronary functional assessments¹⁷. Infection, obesity, tobacco use, pharmacological treatments, blood problems, and many inflammatory conditions might influence its measurements. It may be most effective when integrated into a thorough risk-assessment strategy to pinpoint a patient with a non-obstructive coronary artery who might gain most from an in-depth physiological evaluation¹⁸.

This research has some constraints¹⁹. The results could be relevant just to one location, and the sample size was average. The cross-sectional analysis is unable to establish a causal relationship between systemic inflammation and coronary microvascular dysfunction. The index was evaluated at a single moment and may not accurately reflect prolonged inflammatory exposure. Provocation testing was not conducted for endothelial dysfunction and coronary vasospasm. Additionally, no clinical monitoring was performed, therefore preventing any association from being established between the index and subsequent cardiovascular occurrences²⁰.

Further multicenter and longitudinal investigations are required to validate the proposed cut-off value and to ascertain whether the systemic immune-inflammation index might serve as a predictor for symptom persistence, treatment efficacy, hospitalisation, or significant cardiovascular incidents⁶. Subsequent studies need to explore if the integration of this score with clinical attributes, imaging, and other inflammatory indicators might improve diagnostic precision¹⁴.

CONCLUSION

The systemic immune-inflammation index (sIII) was autonomously linked to coronary microvascular impairment in individuals with non-obstructive coronary arteries. In both male and female subjects, elevated index values correlated with decreased CFR and increased microvascular resistance. This is an accessible and

inexpensive biomarker of inflammation that may assist in identifying individuals requiring further coronary functional evaluation. It need to be used as a supplementary risk-stratification instrument rather than a solitary diagnostic evaluation.

DECLARATION

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

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Author's Contribution: All authors contributed equally in the complication of current study.

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