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Resistin as a predictive marker for myocardial injury in patients with acute myocardial infarction

La resistina como marcador predictivo de lesión miocárdica en el infarto agudo de miocardio

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SUMMARY

High-sensitivity troponin I (hs-TnI) has recently been used as a reference marker to detect myocardial injury in acute myocardial infarction (AMI). Atherosclerotic plaque is the primary cause of AMI. Resistin plays a role in endothelial injury processes, inflammatory responses, lipid accumulation, progression of atherosclerotic plaque, plaque rupture, and cardiac remodeling after myocardial infarction, suggesting its potential relationship to the extent of myocardial injury. We aimed to assess whether resistin is comparable to hs-TnI in diagnosing acute myocardial injury. This study used a cross-sectional design conducted from March to May 2024. Resistin levels were measured using the ELISA method. Data were analyzed statistically using the Kolmogorov-Smirnov, Mann-Whitney, and Spearman's correlation tests. The total sample included 88 patients with either ST-segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI). The sample group predominantly included men and individuals over 50 years of age. A total of 56 patients had a history of coronary angiography, which revealed severe degrees of stenosis. There was a significant difference in resistin levels between STEMI and NSTEMI patients ($p=0.037$, $p<0.05$), and a positive correlation ($r=0.266$, $p=0.012$) was found between resistin and hs-TnI across all participants. However, no correlation was observed in the subgroup analysis.

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Although the correlation with hs-TnI is weak, resistin remains a predictive marker comparable to hs-TnI for detecting myocardial injury in acute myocardial infarction patients.

Keywords*: Resistin, myocardial injury, Hs-TnI, acute myocardial infarction.*

RESUMEN

Recientemente, la troponina I de alta sensibilidad (hs-TnI) se ha utilizado como marcador de referencia para detectar lesiones miocárdicas en el infarto agudo de miocardio (IAM). La placa aterosclerótica es la causa principal del IAM. La resistina desempeña un papel en los procesos de lesión endotelial, respuestas inflamatorias, acumulación de lípidos, progresión de la placa aterosclerótica, ruptura de la placa y remodelación cardíaca después del infarto de miocardio, lo que sugiere su posible relación con la magnitud de la lesión miocárdica. El objetivo fue evaluar si la resistina es comparable a la hs-TnI en el diagnóstico de lesión miocárdica aguda. Este estudio utilizó un diseño transversal, llevado a cabo de marzo a mayo de 2024. Los niveles de resistina se midieron utilizando el método ELISA. Los datos se analizaron estadísticamente utilizando las pruebas de Kolmogorov-Smirnov, Mann-Whitney y correlación de Spearman. La muestra total incluyó a 88 pacientes con infarto de miocardio con elevación del segmento ST (STEMI) o infarto de miocardio sin elevación del segmento ST (NSTEMI). El grupo de muestras incluyó predominantemente a hombres y personas mayores de 50 años. Un total de 56 pacientes tenían antecedentes de angiografía coronaria, que reveló grados severos de estenosis. Hubo una diferencia significativa en los niveles de resistina entre los pacientes con STEMI y NSTEMI (p=0,037, p<0,05), y se encontró una correlación positiva (r=0,266, p=0,012) entre la resistina y la hs-TnI en todos los participantes. Sin embargo, no se observó correlación en el análisis de subgrupos. Aunque la correlación con hs-TnI es débil, la resistina sigue siendo un marcador predictivo comparable a hs-TnI para detectar lesiones miocárdicas en pacientes con infarto agudo de miocardio.

Palabras clave*: Resistina, lesión miocárdica, hs-TnI, infarto agudo de miocardio.*

INTRODUCTION

Cardiovascular disease is the leading cause of mortality worldwide. According to data from the World Health Organization (WHO) in 2019, the three highest causes of death globally are cardiovascular diseases, respiratory diseases, and neonatal conditions (1). Heart disease remains the primary cause of death in Indonesia, as indicated by the 2014-2019 Global Burden of Disease report (2). Indonesian Basic Health Research data from 2018 shows that cardiovascular diseases are increasing annually in Indonesia, with the highest incidence among those aged over 75 years and a higher prevalence in urban areas (3). Data from the Institute for Health Metrics and Evaluation (IHME) indicates that deaths caused by ischemic heart disease accounted for 28.3 % of total deaths in Indonesia in 2019 (4). Acute myocardial infarction (AMI) is a major cause of death in developed countries, with the global prevalence of this disease approaching three million people (5).

The onset of myocardial ischemia marks the initial stage in the development of myocardial injury, characterized by an imbalance between oxygen supply and demand in heart muscle cells. Myocardial injury can present with atypical symptoms such as palpitations or cardiac arrest, or it can occur without any symptoms at all (6). Rapid episodes of myocardial ischemia can cause necrosis, resulting in the release and elevation of troponin levels. The affected heart muscle cells can die due to apoptosis (7). Myocardial injury is defined as an increase in cardiac troponin levels, with or without ischemic symptoms (8). AMI is a component of Acute Coronary Syndrome (ACS), which is characterized by ischemic symptoms and elevated cardiac biomarkers. AMI is categorized into two types: ST-elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), which are distinguished based on electrocardiography findings. Non-ST-segment elevation myocardial infarction (NSTEMI) is a type of heart attack in which a minor artery of the heart is completely blocked, or a major artery of the heart is partially blocked. It is less serious than a "classic" heart attack, known as an ST-segment elevation myocardial infarction (STEMI). The term AMI is applicable when there is evidence of myocardial injury accompanied by consistent clinical symptoms of ischemia or necrosis (9).

Human resistin is an adipokine, which has been suggested to be an inflammatory marker,

with possible links to atherosclerosis and coronary heart disease. It is expressed in humans by a number of cells, including adipocytes, peripheral blood mononuclear cells, macrophages, and bone marrow cells. Serum resistin concentration has been correlated with risk factors for coronary heart disease, renal dysfunction, and outcomes among stroke patients. Recent studies have drawn attention to the potential role of resistin as a biomarker that can predict mortality in patients with cardiovascular disease, in close connection with the ability of resistin to influence glucose and insulin metabolism, thrombosis, angiogenesis, and smooth muscle cell dysfunction, but as a factor regulating expression of Vascular Cell Adhesion Molecule-1 (VCAM-1) on endothelial cells, and as a marker of inflammation that can predict survival in critically ill patients (10,11). There is evidence that resistin levels are positively correlated with cardiac troponin I, particularly during the acute period of STEMI, making resistin beneficial for predicting myocardial infarction size and prognosis in patients with ACS (12). Other studies indicate that increases in resistin and troponin I are associated with decreased left ventricular ejection fraction (LVEF) and the incidence of systolic heart failure in patients with STEMI (13,14). Research on resistin in the cardiovascular field is compelling. Resistin plays multiple roles in endothelial injury, inflammatory response, and lipid accumulation, influencing the progression of atherosclerotic plaque and cardiac remodeling after myocardial infarction. Therefore, understanding the relationship between resistin and myocardial injury is particularly interesting.

METHODS

This research is an observational study with a cross-sectional design. The study population comprised 88 patients clinically diagnosed with STEMI (n=47) or NSTEMI (n=41). The inclusion criteria for this study were patients diagnosed with STEMI and NSTEMI by cardiologists at the Makassar Cardiac Center, Dr. Wahidin Sudirohusodo General Teaching Hospital, from March to May 2024. Exclusion criteria included subjects with diabetes mellitus, acute and/or chronic kidney disorders, sepsis, rheumatoid arthritis, and malignancy. Lipemic, icteric, or hemolyzed serum samples that could not be re-sampled were excluded. The serum resistin levels were quantified at the Hasanuddin University Medical Research Center using the ELISA method.

Data Analysis

Statistical analysis was performed using Statistical Package for the Special Sciences (SPSS) version 24.0. Data are presented as numbers and frequencies for categorical variables. Statistical analyses were performed using the Mann-Whitney Test or Spearman-Correlation tests. The level of significance (p-value) used was $p < 0.05$.

Ethical consideration

The Ethical Board Committee for Health Research, Faculty of Medicine, Hasanuddin University approved this study under assignment letter no. 120/UN4.6.4.5.31/PP36/2024. Written informed consent was obtained from all participants.

RESULTS

Of the 88 patients with AMI, 47 (53.4 %) were diagnosed with STEMI and 41 (46.6 %) with NSTEMI. Table 1 presents the baseline characteristics of the study participants. The table shows that most patients who experienced AMI were male (81.8 %). The incidence of AMI most often occurs in individuals aged over 50 years (71.6 %). More than half of the patients with AMI had a history of hypertension (59.1 %) and smoking (54.5 %). Additionally, coronary angiography revealed severe stenosis in 55.7 % of the patients.

Table 2 shows that resistin levels were significantly higher in STEMI compared to NSTEMI patients (p=0.037). Similarly, high-sensitivity troponin I levels in this study demonstrated a significantly higher difference in STEMI compared to the NSTEMI group ($p<0.0001$).

Table 1. Baseline Characteristic of Study Participants (n=88)

Variables	n (%)	Mean ± SD
STEMI	47 (53.4)	
NSTEMI	41 (46.5)	
Male	72 (81.8)	
• STEMI	39	
• NSTEMI	33	
Female	16 (18.2)	
• STEMI	8	
• NSTEMI	8	
Age		57.7 ± 11.6
≤ 50 years old	25 (28.4)	
• STEMI	16	
• NSTEMI	9	
> 50 years old	63 (71.6)	
• STEMI	31	
• NSTEMI	32	
Hypertension	52(59.1)	
Smoking	48(54.5)	
Severe Stenosis (CA)	49 (55.7)	

STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction, SD: Standard Deviation, CA: Coronary Angiography

Table 3. Correlation between Resistin and hs-TnI in AMI patients

Parameters	n	r	p-value
Total			
Resistin (pg/mL) Hs-TnI (ng/L)	88	0.266	0.012*
NSTEMI			
Resistin (pg/mL) Hs-TnI (ng/L)	41	0.186	0.244
STEMI			
Resistin (pg/mL) Hs-TnI (ng/L)	47	0.087	0.560

*p<0.05. Analyses using Spearman's Correlation test, r = Correlation coefficient.

Table 2. Comparisons of Resistin and hs-TropI I in the STEMI and NSTEMI

Parameters	Median	Min-max	p-value
Resistin (pg/mL)			
STEMI	1 962.8	603.8 – 88 381.8	0.037*
NSTEMI	1 595.5	571.1 – 59 852.7	
High-Sensitivity Troponin I (ng/L)			
STEMI	44 303.4	60.9 – 50 000.0	<0.0001*
NSTEMI	888.1	50.1 – 50 000.0	

*p<0.05. Analyses using the Mann-Whitney test.
STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction, Min-max = Minimum-Maximum

Table 3 shows the correlation between resistin and hs-TnI in AMI patients. We found a significant (p = 0.012), although weak, positive correlation (r = 0.266) between resistin levels and hs-TnI in all AMI patients, as illustrated in Figure 1. However, in the subgroup analysis, there was no significant correlation within each group (p>0.05).

DISCUSSION

This study found that most AMI patients were male in both STEMI and NSTEMI groups. This finding aligns with previous studies on AMI patients (15,16). Gender is a risk factor for AMI, linked to the pathomechanism of atherosclerosis

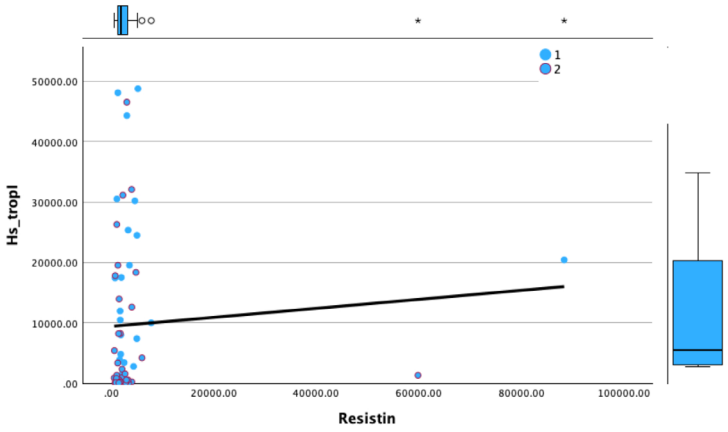

Figure 1. Correlation between Resistin and hs-TnI in AMI patients.

and the role of estrogen. While estrogen is traditionally considered to have a protective effect on the heart, androgens also play a role in cardiovascular disease. Elevated testosterone levels are associated with increased HDL levels and decreased levels of oxidized LDL, total cholesterol, and triglycerides. Consequently, a decrease in testosterone levels may increase the risk of cardiovascular events (17,18).

Age over 50 years is associated with a higher risk of developing AMI compared to younger individuals. Aging is a significant risk factor for cardiovascular disease, primarily due to its relationship with oxidative stress, which leads to myocardial damage and cellular degeneration. As individuals age, the incidence of heart muscle cell degeneration increases (19). A meta-analysis has shown that the prevalence of AMI is notably higher in patients over 60 years old (20). This study's findings are consistent with this pattern, as shown in Table 1. Older age often coincides with additional risk factors that contribute to a higher incidence of AMI. This is in line with the results of Rashid et al., who showed in 100 consented patients with diagnosed STEMI and NSTEMI in the age range 40 to 70 years, that AMI is more prevalent in males aged> 50 years, where most patients are non-smokers but hypertensive (16).

In the present study population, more than half of the participants had hypertension and were smokers. Hypertension is a well-known risk factor for AMI due to its chronic damaging effects on the endothelial cells of coronary vessels. This damage leads to inflammation, atherosclerosis, and plaque formation in the blood vessels. Smoking also has toxic and pro-inflammatory effects, exacerbating cardiovascular risk (19). Coronary angiography, an invasive procedure, provides detailed information on the presence and severity of coronary artery disease. Stenosis of more than 50 % in diameter or a reduction of more than 75 % in the cross-sectional area can result in chest pain. The severity of stenosis is categorized based on the percentage of luminal diameter reduction: mild (30 % - 40 %), moderate (50 % - 70 %), and severe (greater than 70 %) (21). In this study, 56 % of participants exhibited severe coronary stenosis.

Our study found that resistin levels were significantly higher in STEMI patients compared to those with NSTEMI. Additionally, resistin levels were generally higher in male patients with STEMI. This finding aligns with several studies indicating that men experience a higher incidence of STEMI and exhibit elevated resistin levels compared to NSTEMI patients. This association is likely related to risk factors such as hypertension and smoking, which are more prevalent among male patients. Furthermore, it was shown that the levels of resistin and cardiac biomarkers cardiac troponin T (cTnT) and cardiac troponin I (cTnI) were significantly raised in STEMI patients as compared to NSTEMI

patients (16). The significant difference in resistin levels between STEMI and NSTEMI groups can be attributed to resistin's role as a pro-inflammatory agent. In STEMI, total occlusion caused by atherosclerotic plaque is accelerated by inflammation, which contributes to the higher resistin levels observed. It was suggested that resistin could stimulate endothelial cells and encourage the process of inflammation via chemokines and cytokines, thus accelerating the dysfunction of endothelium, in addition to the blockade of the expression of endothelial nitric oxide and increasing the production of superoxide anion in endothelial cells, which declines the relaxation of the endothelial-dependent vascular system and altered the process of relaxation and contraction in vessels of the heart (16).

Resistin is a 12 kDa (kiloDalton) protein primarily secreted from macrophages, monocytes, and adipocytes. Resistin is thought to be involved in metabolic signals that lead to inflammation and atherosclerosis (23). This pro-inflammatory adipocytokine, predominantly secreted by macrophages, plays a role in regulating the expression of other pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), Interleukin-1β (IL-1β), and monocyte chemoattractant protein-1, through the Nuclear Factor Kappa B (NF-$\varkappa$B) signaling mechanism, resulting in an inflammatory process (14). Resistin is associated with various functions in the process of endothelial injury, inflammatory response, and lipid accumulation. Specifically, it exacerbates atherosclerotic plaque vulnerability, plaque rupture, and cardiac remodeling after myocardial infarction (24).

Resistin levels increase significantly within the first 24 hours of disease onset and persist for one week. Thus, resistin levels can serve as a predictor of myocardial injury and are related to disease severity (16,25). The correlation between coronary artery disease and resistin levels shows a gradual increase, influenced by the number of segments or arteries experiencing stenosis. Resistin is thought to act as a pro-inflammatory agent, increasing inflammation in blood vessels and playing a role in smooth muscle cell proliferation and angiogenesis. This process results in endothelial dysfunction, vasorelaxation, increased thrombosis, increased membrane permeability, and increased cell adhesion, ultimately contributing to atherosclerosis (16).

Resistin levels are higher in unstable atherosclerotic plaques compared to stable plaques and are associated with more than 50 % stenosis in coronary arteries (24,26). Unstable angina plaques are characterized by cap infiltration, inflammation, protruding necrotic cores, extensive hemorrhage, thrombi, and plaque rupture. While several biomarkers are available for coronary heart disease, resistin stands out due to its unique mechanism of action. It directly influences vascular endothelial injury, foam macrophage formation, and smooth muscle cell proliferation, making it a valuable biomarker with significant sensitivity and specificity (24).

Elevated high-sensitivity troponin I (hs-TnI) levels are a crucial biomarker for assessing myocardial damage and detecting early myocardial cell injury (27). This study supports the notion that STEMI is associated with a greater extent of myocardial injury compared to NSTEMI, as demonstrated by significantly higher hs-TnI levels in STEMI patients. This finding aligns with previous research, which reported higher average hs-TnI levels in STEMI than in NSTEMI (14). Research involving 92 patients with STEMI found a significant positive correlation between serum resistin levels and hs-TnI (28). In line with this, our study found a significant, although weak, positive correlation between resistin levels and hs-TnI in all AMI patients. However, the significance of the correlation between hs-TnI and resistin disappeared in the subgroup analysis. This may be due to potential variations or lack of clinical relevance in different patient groups, possible confounding factors or interactions with other variables, or smaller subgroup sizes leading to wider confidence intervals, affecting statistical significance.

This study showed no significant correlation between patients with resistin and hs-TnI levels in STEMI ($p=0.224$) or NSTEMI ($p=0.560$). These findings contrast with previous research, which reported a significant positive correlation between resistin and hs-TnI levels in STEMI patients (16), and in a study in AMI patients where serum resistin is positively correlated with cardiac troponin I, suggesting that values

of serum resistin during the acute period of STEMI are valuable for predicting the size of myocardial infarction and prognosis in patients with ACS (12). Despite high hs-TnI levels, some patients exhibited low resistin levels, potentially due to treatments administered before hospital admission. Conversely, high resistin levels were noted in patients with relatively low hs-TnI levels. This discrepancy might be influenced by Toll-like receptor 4 (TLR4) binding to resistin, which is associated with innate and adaptive immune responses stimulated by lipopolysaccharides and may not have been detected in these patients (24).

CONCLUSIONS

Despite the weak positive correlation with hs-TnI, resistin is a predictive marker comparable to hs-TnI for detecting myocardial injury in patients with acute myocardial infarction.

ABBREVIATIONS

ACS:	Acute Coronary Syndrome
AMI:	Acute Myocardial Infarction
ECG:	Electrocardiography
ELISA:	Enzyme-Linked Immunosorbent Assay
HDL:	High-Density Lipoprotein
Hs-TnI:	High-Sensitivity Troponin I
IL-1β:	Interleukin-1 β
IL-6:	Interleukin-6
kDa:	kilo Dalton
LDL:	Low-Density Lipoprotein
LVEF:	Left ventricular ejection fraction
NF-KB:	Nuclear Factor Kappa B
NSTEMI:	Non-ST segment elevation myocar dial infarction
STEMI:	ST-segment elevation myocardial infarction
TLR:	Toll-like receptor 4
TNF-α:	Tumor Necrosis Factor-alpha

DECLARATION

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Author's contribution

Conceptualization: CP,ATL,RS; Methodology: CP, ATL, RS; Formal analysis and investigation: CP, AQ; Writing-original draft: CP; Writing, review, and editing: AQ; Resources and supervision: ATL, RS, AS, MZ, UB; Validation: ATL, RS, AS, MZ, UB. The authors read and approved the final manuscript.

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Availability of Data and materials

Applicable upon request

Ethics approval and consent to participate

This research was approved by The Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. Based on a letter of recommendation number: 120/UN4.6.4.5.31/PP36/2024

Consent for publication

Not Applicable

Competing interest

The authors state that no potential conflicts of interest exist in this work, authorship, or publication.

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