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The Prognostic Value of Systemic Inflammation Immune Index in Acute Myocardial Infarction Patients Treated by Renin Angiotensin System Blockers

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ABSTRACT

Background: One mechanism that regulates several cellular activities is the renin-angiotensin-aldosterone system (RAAS). The vast array of peptides that make up this system encompass chemicals that regulate inflammatory processes, cellular progression, electrolyte and water balance, vascular integrity and signaling activation across several organs in both physiological and pathological states.

Objectives: This study aimed to assess the value of using RAS blockers on lowering the inflammatory indices in acute myocardial infarction (AMI) patients and to assess the impact of low inflammatory indices on short-term outcome after myocardial infarction

Subjects and methods: This prospective cohort research included 125 AMI patients and was conducted in Cardiology Department, Zagazig University Hospital.

Result: Functional capacity, EF, and creatinine levels were statistically significant independent predictors ($p<0.05$). Among them, functional capacity had the strongest standardized effect ($\beta = 0.45$, $p = 0.002$), followed by EF ($\beta = 0.30$, $p = 0.015$) and creatinine ($\beta = 0.25$, $p = 0.037$). However, symptoms did not reach statistical significance ($p = 0.32$), indicating that it was not an independent determinant in this model. The levels of BNP continued to have a role in systemic immune-inflammation (SII) as independent variables. The sole independent determining factor influencing SIRI was creatinine levels.

Conclusion: This study demonstrated that cases with AMI who were previously managed by Renin-Angiotensin System Blockers (RASB) had significantly lower systemic immune-inflammation index (SII) values, suggesting a potential anti-inflammatory benefit of this therapy. Furthermore, lower inflammatory indices were linked to better functional capacity, preserved ejection fraction and improved renal function, which collectively contribute to favorable short-term outcomes. While SII and systemic inflammatory response index (SIRI) appear to be promising markers for risk stratification in AMI, their predictive value is influenced by cardiac and renal parameters. Incorporating inflammatory indices alongside conventional clinical and biochemical predictors may enhance early prognostic assessment in myocardial infarction.

Keywords: Systemic inflammation immune index, Acute myocardial infarction, Renin angiotensin system blockers.

INTRODUCTION

Several cellular activities are regulated by the RAAS. This system is composed of a diverse array of peptides that have many functions, such as regulating cellular development, electrolyte and water balance, inflammation, and signaling activation in various organs under physiological and pathological states [(1)].

Angiotensin receptor antagonists (ARAs) and angiotensin converting enzyme inhibitors (ACEIs) help mitigate the consequences of RAAS overactivation. In addition to renal disorders, they are utilized to treat conditions including arterial hypertension, left ventricular dysfunction, heart failure , and myocardial infarction [(2)]. ACEI increases glucose uptake and decreases total, LDL, and triglyceride cholesterol [(3)].

Atherosclerosis is mostly an inflammatory process. The complicated inflammatory response includes several mediators. These parameters have been found to be important bad prognostic indicators in patients with stable coronary artery disease (CAD) & ST-elevation myocardial infarction (STEMI) [(4)]. Among them, the inflammatory parameters that may be obtained from a basic complete blood count have garnered attention due to their simplicity, accessibility, and affordability as biomarkers. In the case of AMI, for instance, the following changes occur in the blood: The number of neutrophils rises early and peaks within a day or three, monocytes and platelets also rise and finally, the number of lymphocytes falls. Study after study has shown that calculated biomarkers, for example the monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are sourced from simple routine blood counts, can be utilized as indicators of prognosis for CAD patients**.** Two new indices, the systemic inflammatory response index (SIRI) and the SII, have recently been suggested as additive inflammation-related instruments that may be utilized to evaluate the immunological and inflammatory status at the same time [(4, 5)]**.**

The inclusion of three inflammatory indicators in SII and SIRI suggests that they may be more effective than the prior three indices (NLR, PLR, and MLR). In particular, both SII and SIRI incorporate neutrophil and lymphocyte counts into their calculations, with platelets serving as an additional biomarker in SII index, and monocytes forming an integral part of SIRI index. An elevated SIRI level suggests a robust pro-inflammatory

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response, carried out by neutrophils and monocytes, while the anti-inflammatory impact, mediated by lymphocytes, is diminished. This is due to the fact that SIRI incorporates the two previously suggested inflammatory indicators, NLR & MLR, into a composite index. However, the SII index takes into account platelets, which are critical components that enhance cell recruitment at lesion sites and release several inflammatory mediators, thereby magnifying the inflammatory environment, and combines the predictive potential of PLR and NLR [5].

This study assessed the value of using RAS blockers on lowering the inflammatory indices in AMI patients and assessed the effect of low inflammatory indices on short-term outcome after myocardial infarction.

PATIENTS AND METHODS

This prospective cohort research was performed on 125 AMI patients at Cardiology department, Zagazig University Hospital.

Sample: It was calculated using open epi according to the following expected small effect size CI 95%, power 80 % and df =1, the sample size was calculated to be 125 cases

Inclusion criteria: Adult cases (age ≥18 years) hospitalized after being initially diagnosed with AMI, who underwent primary or urgent coronary angiography&percutaneous coronary intervention (PCI) and who were prescribed a RAS blocker (ACE inhibitor or ARB) at hospital discharge.

Exclusion criteria: Cases with severe valvular heart disease requiring surgery, Patients with non-obstructive CAD (CAD < 50% stenosis), Patients with elevated creatinine level (e.g.,> 2.0 mg/dL or on dialysis).

Methods: All studied patients were subjected to the following:

Complete history taking including sex, age, risk factors for CAD as hypertension, smoking status, diabetes mellitus, previous history for ACS or myocardial revascularization, dyslipidemia and family history of premature CAD.

Comprehensive clinical examination: Vital signs (BP & HR), signs of heart failure (Killip class), jugular venous pressure, and cardiac auscultation (murmurs, gallops, heart sounds).

Laboratory examination: Prior to angiography, venous blood samples were taken upon admission to measure complete blood count (CBC), which was used to calculate indices. SII = (Neutrophil count × Platelet count)/Lymphocyte count. SIRI = (monocyte count × neutrophil count)/Lymphocyte count. Renal function tests (Serum creatinine). Cardiac biomarkers (Peak Troponin I/T. Lipid Profile: LDL-C, HDL-C and triglycerides).

Electrocardiographic examination: As an evidence of ischemic heart disease (A 12-lead ECG was performed at admission to confirm ischemic changes (ST-elevation, ST-depression, T-wave inversion).

Echocardiography: Transthoracic echocardiography was performed during hospitalization to measure left ventricular ejection fraction (LVEF) using Simpson's biplane method & to rule out significant valvular disease.

Study procedures

Coronary angiography: All procedures was carried either using radial or femoral access using Judkins standard techniques for 3 months follow up. The number of diseased vessels (single, double, or triple-vessel disease) and the success of the PCI procedure were documented.

Ethical approval: The study protocol was reviewed and approved by The Ethics Committee of Zagazig University Hospitals, Egypt. After obtaining ethics committee approval, written informed consent was obtained from each participant. The study followed the rules of Helsinki Declaration through its execution.

Statistical analysis

Data analysis was done utilizing SPSS version 25, which stands for the Statistics Package for the Social Sciences. Frequency and percentage were the metrics employed to represent qualitative data. The mean ± standard deviation (Mean ± SD) was utilized to represent continuous quantitative data. The categorical variables were contrasted utilizing the chi-square test, while the continuous variables were analyzed utilizing the independent sample t-test. P value ≤ was deemed significant.

RESULTS

Table (1) showed that the mean age of the examined group was 68.3 ± 10.8 years. The majority of participants were males, accounting for 69.6% (87 patient), while females represented 30.4% (38 patient). The mean BMI of the examined group was 28.1 ± 4.3 (kg/m^2).

Table (1): Distribution of demographic data in the examined group

	Examined group (N=125)
Age (years)	68.3 ± 10.8
Gender	
Male	87 (69.6%)
Female	38 (30.4%)
BMI (kg/m^2)	28.1 ± 4.3

Table (2) and figure (1) showed that the mean LVEF of the examined group was 49.5 ± 8.3%. The mean BNP level was 143 ± 146.2 ng/L, with a median value of 130 ng/L (interquartile range: 52–247).

Table (2): Distribution of instrumental data in the examined group

	Examined group (N=125)
LVEF (%)	49.5 ± 8.3
BNP (ng/L) Median (Q1-Q3)	143 ± 146.2 130 (52-247)

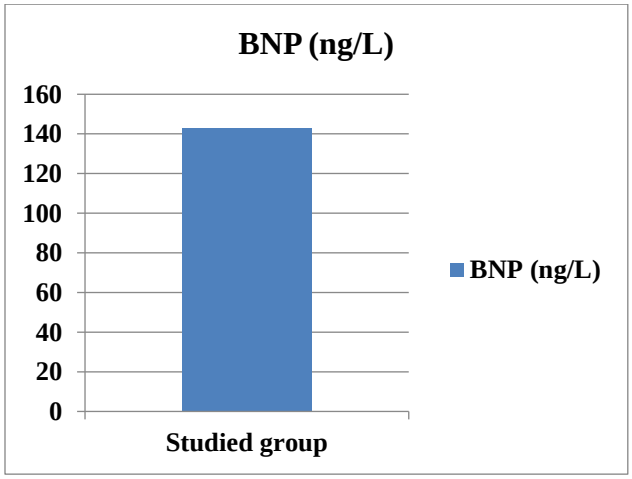

Figure (1): Instrumental data in the examined group.

This table showed that the mean of creatinine was 1.02 ± 0.4, mean of Neutrophils was 6.2 ± 2.5 with a median value of 6.2 (interquartile range: 4.6–8), mean of Lymphocytes was 1.7 ± 0.45, mean of Monocytes was 0.8 ± 0.3 with a median value of 0.8 (interquartile range: 0.6–1) and mean of Creatinine was 238.8 ±77.03 (table 3).

Table (3): Distribution of laboratory data in the examined group

	examined group (N=125)
Creatinine (mg/dL)	1.02 ± 0.04
Neutrophils (10^3/µL) Median (Q1-Q3)	6.2 ± 2.5 6.2 (4.6-8.0)
Lymphocytes (10^3/µL)	1.7 ±0.45
Monocytes (10^3/µL) Median (Q1-Q3)	0.8 ± 0.3 0.8 (0.6-1.0)
Platelets (10^3/µL)	238.8 ± 27.03
SII	1125.3 ± 658.3
SIRI	3.8 ±3.1

Table (4) showed that functional capacity, EF, and creatinine levels were statistically significant independent predictors ($p<0.05$). Among them, functional capacity had the strongest standardized effect ($\beta = 0.45$, $p = 0.002$), followed by EF ($\beta = 0.30$, $p = 0.015$) and creatinine ($\beta = 0.25$, $p = 0.037$). However, symptoms did not reach statistical significance ($p = 0.32$), indicating that it was not an independent determinant in this model.

Table (4): Multiple regressions among RASB and variant risk factors

	Standard coefficient	**t-value**	**p-value**
Functional capacity	0.45	3.2	**0.002**
EF	0.3	2.5	**0.015**
Creatinine	0.25	2.1	**0.037**
Symptoms	0.1	1	0.32

Table (5) showed that, the levels of BNP continued to have a role in SII as independent variables.

Table (5): Multiple regression among SII levels and variant risk factors

	Standard Coefficient	**t-value**	**p-value**
Age	0.20	0.9	0.28
BNP	**0.29**	**2.4**	**0.03***
Creatinine	0.18	1.7	0.32

Table (6) showed that levels of creatinine stayed being the one variable that can be relied on to influence SIRI.

Table (6): Multiple regression among SIRI levels and variant risk factors

	Standard Coefficient	**t-value**	**p-value**
Age	0.21	0.8	0.31
BNP	0.18	1.2	0.22
Creatinine	0.38	2.9	**0.001***

DISCUSSION

Our results revealed a statistically significant reduction in SII levels in the RASB group contrary to the no-RASB group indicating a potential anti-inflammatory effect of RASBs. In contrast, neither group revealed a statistically significant variance in SIRI levels. The SII, BNP, and creatinine levels were positively correlated with one another. Age, BNP, and creatinine were also positively correlated with SIRI. The data showed that heart stress indicators (BNP) and renal failure markers

(creatinine) are linked with SII and SIRI, which supports the idea that SI may take part in the pathophysiology and risk stratification of AMI. In harmony with our results, **Kim *et al.*** [6] demonstrated that when individuals with AMI and concurrent AKI were treated with RASBs, the results were better for patients with less severe AKI, but not for those with greater levels of AKI. The use of RASBs during the discharge process was shown to reduce 5-year all-cause mortality in the whole group, except for those with AKI. In cases with AKI stages II and III, subgroup analysis showed that the higher hazard of poor outcomes with RASBs was the main factor causing this difference. Also, a meta-analysis by **Awad *et al.*** [7] who contributed data about the anti-inflammatory benefits of ACEIs and ARBs. The levels of CRP, IL-6, and TNF-α were all positively impacted by ACEIs, whereas ARBs reduced IL-6 alone. The evidence for the ACEIs' ability to reduce CRP levels was stronger with enalapril and perindopril, in patients with CAD, and for therapy durations less than 24 weeks. Similarly, **Park *et al.*** [8] reported significantly fewer serious adverse cardiac events occurred in the RAS inhibition group among STEMI patients who had PCI. Even in low-risk patients with largely maintained LVEF, RAS inhibition enhanced long-term clinical consequences following a successful PCI in post-STEMI cases who were admitted to the hospital thereafter.

Our results demonstrated that functional capacity, EF, and creatinine levels were statistically significant independent predictors. Among them, functional capacity had the strongest standardized effect, followed by EF and creatinine, suggesting that RASBs were preferentially used in patients with better preserved physical status and cardiac function. However, symptoms did not reach statistical significance ($p = 0.32$) indicating that it was not an independent determinant in this model.

Our findings demonstrated that BNP levels continued to play a significant role in determining SII, reinforcing the link between cardiac dysfunction and heightened systemic inflammation. While, only creatinine levels could be identified as an independent predictor of SIRI further highlighting the central role of renal function in modulating inflammatory responses in AMI. In agreement with our results, **Zhu *et al.*** [9] determined the prognosis of patients with acute STEMI using the systemic SII & NT-proBNP values, either alone or in combination. They found a significant correlation among NT-proBNP and SII and both were independent markers of clinical prognosis in individuals with acute STEMI. Clinical prognosis might be improved by combining these elements. Similarly, our findings are consistent with **Marchi *et al.*** [10] who studied the factors that influence SII and SIRI and the capability of SIRI and SII to predict outcomes in cases with STEMI. Their findings demonstrated a positive & statistically significant association among SIRI and SII. Overall, there was a positive & statistically significant correlation among SII and BNP and creatinine levels. Moreover, there was a positive trend among SII & age although it did not achieve statistical significance. In the whole population, a direct correlation was discovered among SIRI and age, creatinine ($r = 0.34$, $p<0.01$) & BNP levels ($r = 0.28$, $p<0.01$). According to their findings, creatinine and BNP are linked to the outcome and the hazard variables of interest (SIRI & SII), which weakens the ability to forecast SII & SIRI for mortality in STEMI cases. Also, **Samedov *et al.*** [11] demonstrated that in patients with ACS, SII were discovered to be strong indicators of mortality. To differentiate among patients who did not survive and those who did, multivariate regression analysis revealed that SIRI and AISI levels were significantly and independently correlated.

SII incorporates additional indicators of inflammation and immunity that reflect the body's condition. Patients' inflammatory&immune system condition can be more accurately reflected by it [12]. An abnormal increase in platelets could be a result of inflammation following it has occurred in the human body. Additionally, abnormally aggregated platelets adhere to the body's endothelial cells, creating hypoxia, microthrombosis and ultimately the blockage of blood vessels. This can lead to stroke, peripheral vascular disorders, ischemic MI & other malignant clinical outcomes [13].

Ischemic heart disease, ACS, CVD& stroke are all elevated risk factors for SII when measured in serum [14]. **Dziedzic *et al.*** [15] have stated that following the use of SII in STEMI patients, when looking at the short-term prognosis, the group with a bad prognosis had significantly greater SII levels contrasted with the group with a favorable prognosis.

NT-proBNP is the byproduct that remains after the BNP precursor (pro BNP) cleaves into BNP. Mainly produced by ventricular cells, this hormone has a wide range of biological effects, including vasodilation, regulation of sodium &water metabolism, inhibition of the renin-angiotensin&sympathetic nervous system pathways and many more. The left heart's dysfunction or an increase in ventricular volume and pressure burden can quickly manifest and reflect the heart's function [16, 17]. An early warning and diagnostic indication for STEMI, according to certain research, can be NT-proBNP [18].

CONCLUSION

This study demonstrated that patients with AMI who were previously treated with RAS blockers had significantly lower systemic SII values, suggesting a potential anti-inflammatory benefit of this therapy. Furthermore, lower inflammatory indices were linked to better functional capacity, preserved ejection fraction, and

improved renal function, which collectively contribute to favorable short-term outcomes. While, SII and SIRI appear to be promising markers for risk stratification in AMI, their predictive value is influenced by cardiac and renal parameters. Incorporating inflammatory indices alongside conventional clinical and biochemical predictors may enhance early prognostic assessment in myocardial infarction. Future large-scale research is required to validate these results and investigate the long-term effects of RASB therapy on inflammation and cardiovascular outcomes.

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