Relationship between systemic inflammation indices and time of symptom onset in cardiac remodeling after first ST-segment elevation myocardial infarction

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ABSTRACT

Background: Circadian variations play a pivotal role in both leukocyte trafficking and inflammatory response. This may affect the course of cardiac healing after myocardial infarction (MI).

Aims: The present study investigated the relationship between the systemic immune inflammation (SII) index and the systemic inflammation response index (SIRI), two new inflammation indices integrating white blood cell subsets and platelets, and the time of onset of symptoms in left ventricular adverse remodeling (LVAR) after ST-segment elevation MI (STEMI).

Methods: In this retrospective study, we included 512 patients with first-time STEMI. The time of onset of symptoms was divided into 4 intervals: 06:00–11:59, 12:00–17:59, 18:00–23:59, and 00:00–05:59. The endpoint was LVAR, defined as an increase in left ventricular end-diastolic and end-systolic volume by ≥12% at 6 months.

Results: The time of onset of chest pain most often occurred between 06:00 and 11:59 AM. In this window of time, median SII and SIRI indices were higher than in other time intervals. An increased SIRI level (odds ratio [OR], 3.03; P <0.001), symptom onset in the morning hours (OR, 2.92; P = 0.03), and an increased Global Registry of Acute Coronary Events (GRACE) score (OR, 1.16; P <0.001) were determined as independent predictors of LVAR. The threshold value of the SIRI to discriminate between patients with and without LVAR was >2.5 (area under the curve [AUC], 0.84; P <0.001). The SIRI showed superior diagnostic performance compared to the SII index.

Conclusions: In STEMI patients, an increased SIRI was independently associated with LVAR. This was more pronounced between 06:00 and11:59 AM. Despite differences across circadian periods, the SIRI may be a potential screening tool for identifying LVAR patients at long-term risk of heart failure.

Key words: biomarker, cardiac remodeling, inflammation, myocardial infarction

INTRODUCTION

Acute myocardial infarction (MI) arises as a result of sudden occlusion of the coronary artery and results in necrotic tissue damage [1]. Cellular necrosis and degradation of the matrix cause rapid activation of the complement cascade, which is an important component of the immune-inflammatory response (IIR) [2]. Complement cascade activation allows leukocytes to infiltrate the infarct area to scavenge dead cells and matrix residues [3]. This inflammatory phase ends with repair pathways replacing dead cardiomyocytes with scar tissue. An excessive IIR can determine the extent of changes in ventricular size, shape, and function and can also play pathological roles, such as in the case of left ventricular (LV) adverse remodeling (LVAR) that can cause heart failure [4].

The circadian clock may play a prognostic role in the increased inflammatory response observed in the development of LVAR after acute MI. Epidemiological research has confirmed the association of acute MI development with a day/night pattern [5, 6]. Furthermore, studies have suggested that onset time in cases of acute MI independently predicts LV function, infarct size, and mortality rates [7, 8].

WHAT'S NEW?

This study provides new findings showing that the severity of inflammation, which plays an important role in cardiovascular events, is associated with circadian clock variations. In ST-segment elevation myocardial infarction (STEMI), increased systemic immune inflammation (SII) and response (SIRI) indices at presentation were independently associated with development of left ventricular adverse remodeling (LVAR) after STEMI. This association was more pronounced between 06:00 and 11:59 AM. Circadian clock variations may increase the severity of inflammation and thus contribute to the development of LVAR, which carries a long-term risk of heart failure.

The circadian clock can affect the infiltration of leukocytes into tissues [9, 10]. A population-based study of adults has shown that a blunted rest-activity rhythm is associated with an increase in leukocyte-based inflammatory indices [11]. Therefore, given the potential role of increased IIR in the development of LVAR after acute MI, we hypothesized that there might be an association between leukocyte-based inflammatory indices and the circadian clock. Among these indices, we evaluated the systemic immune inflammation (SII) index and systemic inflammation response index (SIRI), which have not yet been investigated in the context of LVAR but are claimed to have better prognostic roles in predicting cardiovascular events including acute MI [12–14]. The SII index, which is an indicator of inflammatory status, is calculated by platelet count × neutrophil count/lymphocyte count [15], while the SIRI, which is an indicator of the balance between the inflammatory response and immune status, is calculated by neutrophil count × monocyte count/lymphocyte count [16].

This study aimed to investigate the relationships between the SII index and SIRI and the time of onset of symptoms in the development of LVAR after acute MI.

METHODS

Patients diagnosed with first ST-segment elevation MI (STEMI) in a cardiac center between January 2018 and January 2020 were enrolled in this study. The study received the local ethics committee's approval (date: September 12, 2022, decision no. 146/19) and was conducted in compliance with the relevant ethical guidelines and the Declaration of Helsinki (2013 Brazilian revision). The local ethics committee waived the requirement for informed consent due to the retrospective nature of the research.

Study population

A total of 2182 STEMI patients undergoing primary percutaneous coronary intervention (pPCI) no later than 12 hours after the onset of chest pain were assessed retrospectively. STEMI in these patients was diagnosed according to the fourth universal definition of myocardial infarction [17], with management procedures following the latest guidelines of the European Society of Cardiology [18]. One thousand six hundred and seventy patients who were not diagnosed with STEMI upon applying those criteria were excluded. The following exclusion criteria were then also applied: a history of any systemic inflammatory or autoimmune diseases, history of myocardial infarction or heart failure, any mechanical complications (ventricular septal and/or free wall rupture, papillary muscle rupture, or cardiac tamponade), thyroid dysfunction, liver diseases, active hepatitis, malignancy, renal failure, history of anti-inflammatory or chronic corticosteroid drugs, sepsis, atrial fibrillation, elective or emergency coronary artery bypass grafting following an angiography procedure, major bleeding events, cardiogenic shock, requirement for an intra-aortic balloon pump, history of silent ischemia/infarct or right coronary artery occlusion, pregnancy or delivery in the last 90 days, lactation, and missing clinical data. After this exclusion process, 512 patients who had experienced STEMI for the first time were enrolled in this study.

Study protocol

The hospital's electronic information system and patient files were used to gather demographic and clinical data. Following the index event, echocardiographic evaluations were conducted for all patients at day 7 (baseline) and 6 months. Global Registry of Acute Cardiac Events (GRACE) risk scores were calculated using the official GRACE calculator (www.gracescore.org). Blood samples of all patients were taken on admission. We divided the 24 hours of the day into 4 intervals to evaluate the time of onset of symptoms, designating these windows of time as morning (06:00-11:59), daytime (12:00–17:59), evening (18:00–23:59), and nighttime hours (00:00–05:59).

Laboratory parameters

A Beckman Coulter LH 780 device (Mervue, Galway, Ireland) and Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., Indianapolis, IN, US) were used to evaluate patients' venous blood samples. Levels of hemoglobin (photometrically), platelet count (impedance method), high sensitivity C-reactive protein (hs-CRP) (immunoturbidimetric method), albumin (bromocresol green method), triglycerides, and total cholesterol (enzymatic colorimetry), and high-density lipoprotein cholesterol (HDL-C) (homogeneous enzymatic colorimetry) were determined. The Friedewald formula was used to determine low-density lipoprotein cholesterol (LDL-C) [19]. The SII index and SIRI were respectively calculated as follows: SII = platelet count × neutrophil count/lymphocyte count

and SIRI = neutrophil count × monocyte count/lymphocyte count.

Echocardiographic evaluation

Echocardiographic data were obtained when patients underwent transthoracic echocardiographic evaluations with the Vivid 7 Dimension Cardiovascular Ultrasound System (General Electric Vingmed, Horten, Norway). All data were collected during hospital stays within 1 week following acute coronary syndrome destabilization in accordance with the relevant guidelines [20]. LV volumes were measured based on apical 4- and 2-chamber views, and the modified Simpson method was applied to calculate left ventricular ejection fraction (LVEF) as per the recommendations of the American Society of Echocardiography. Papillary muscles were excluded, and manual tracing began at the endocardial boundaries of the end-systolic and end-diastolic phases of the short-axis stack images, covering the left ventricle to the apex from the mitral annular line. LV stroke volume (SV) was obtained with the following formula: SV = LVEDV – LVESV, where LVEDV is the LV end-diastolic volume and LVESV is the LV end-systolic volume. For LVEF, the following formula was applied: EF = [(LVEDV – LVESV)/LVEDV] × 100.

LVAR was defined as a ≥12% increase in baseline LVEDV or LVESV at 6 months of follow-up [21].

Statistical analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, US). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests were given as mean (standard deviation [SD]) values while non-normally distributed variables were given as median (interquartile range [IQR]) values. For comparisons between groups, Student's t-test and Mann-Whitney U test were used in line with the normality of the considered distribution. Categorical variables were given as numbers and percentages, and inter-group comparisons were conducted with χ^2 and Fisher's exact tests. Spearman correlation analyses were applied to evaluate the relationships between numerical variables. Spearman correlation coefficients <0.10 were evaluated as negligible correlations, 0.10–0.39 as weak correlations, 0.40–0.69 as moderate correlations, 0.70–0.89 as strong correlations, and 0.90–1.00 as very strong correlations [22]. Changes in echocardiographic parameters were evaluated with paired-sample t-tests or Wilcoxon tests. The differences in these changes (Δ) between groups were evaluated by mixed-model repeated-measures analysis. Multivariable logistic regression analysis with the backward Wald method was subsequently performed to identify any possible independent predictors of LVAR. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance. Threshold values were determined by the Youden index method. Comparison of the AUCs was performed with a nonparametric approach using the theory of generalized U-statistics to generate an estimated covariance matrix previously reported by DeLong et al. [23]. Significance was accepted at P <0.05 (*) for all statistical analyses.

RESULTS

The study population included 512 patients at a mean age of 55.8 (10.2) years, and these STEMI patients were mostly male. All patients received acetylsalicylic acid (ASA) plus ticagrelor, and they continued their current discharge treatment routinely for 6 months. Their basic characteristics are shown in Table 1. Patients' angiographic and echocardiographic findings are presented in Supplementary material, *Table S1*. The time of STEMI symptom onset was associated with circadian variations. The peak incidence of STEMI was seen in the morning hours, while the second highest frequency was observed at nighttime. At 6 months after STEMI, the number of patients who had developed LVAR was 25.4%. In the LVAR group, the rate of symptom onset in the morning hours, median SII index, and SIRI were higher compared to patients without LVAR (Table 1).

The median GRACE score was higher in the LVAR group compared to patients without LVAR, while other baseline echocardiographic parameters were similar between the groups (Supplementary material, *Table S1*). Baseline mean LVEF levels and median LV volumes were similar in the groups with and without LVAR. At 6 months after STEMI, median LV volumes increased, and mean LVEF levels decreased in the LVAR group (Supplementary material, *Table S2*).

Demographic and clinical findings did not differ significantly according to time of symptom onset. The median cardiac troponin, median SII index and SIRI were higher in patients who experienced symptom onset during the morning hours (Table 2). Mean door-to-balloon time and mean symptom-to-balloon time did not differ by time of symptom onset. The median GRACE score was higher in patients with symptom onset in the morning hours (Table 3).

For the considered circadian time windows, the median SII index and SIRI were higher in the LVAR group than in the group without LVAR (Figure 1). In the morning hours, there was a moderate positive correlation between the SII index and SIRI and the ΔLVEDV and ΔLVESV levels, while a moderate negative correlation was found with the ΔLVEF levels. In other time intervals, there was a weak correlation between the SII index and SIRI and the ΔLVEDV, ΔLVESV, and ΔLVEF levels (Supplementary material, *Table S3*).

Among the potential confounding factors associated with LVAR (Table 1 and Supplementary material, *Table S1*), time of onset of symptoms, cardiac troponin I, white blood counts, SII, SIRI, HDL-C, hs-CRP, and GRACE scores were included in the multivariable logistic regression model. The components of SII and SIRI were not included in the multivariable regression model because of their multicollinearity. An increased SIRI level, morning hours of symptom onset, and an increased GRACE score were

Table 1. Distribution of demographic and clinical findings by cardiac remodeling groups

Variables	All population n = 512	LVAR		*P*-value
		No n = 382	Yes n = 130	
Demographic findings				
Age, years	55.8 (10.2)	56.00 (9.3)	55.4 (8.3)	0.80
Male sex, n (%)	442 (88.0)	332 (86.9)	110 (84.6)	0.51
BMI, kg/m^2	27.5 (4.1)	27.6 (4.5)	27.2 (3.9)	0.34
Active smoking, n (%)	280 (54.7)	205 (53.7)	66 (57.7)	0.42
Hypertension, n (%)	240 (46.9)	180 (47.1)	60 (46.2)	0.86
Diabetes mellitus, n (%)	144 (28.1)	104 (27.2)	40 (30.8)	0.43
Clinical findings				
Symptoms, n (%)				
Chest pain	512 (100.0)	382 (100)	130 (100)	–
Shoulder or back pain	288 (56.3)	208 (54.5)	80 (61.5)	0.32
Arm pain	228 (44.5)	168 (44.0)	60 (46.2)	0.77
Dyspnea	192 (37.5)	132 (34.6)	60 (46.2)	0.10
Fatigue	320 (62.5)	230 (60.2)	90 (69.2)	0.24
Time of onset of symptoms, n (%)				
Morning hours	212 (41.4)	140 (36.6)	72 (55.4)	0.04[a]
Daytime hours	90 (17.6)	68 (17.8)	22 (16.9)	
Evening hours	70 (13.7)	56 (14.7)	14 (10.8)	
Night hours	140 (27.3)	118 (30.9)	22 (16.9)	
SBP, mm Hg	123.4 (17.9)	124 (17.5)	121.7 (18.9)	0.42
DBP, mm Hg	76.2 (12.3)	76.5 (11.9)	75.4 (13.4)	0.60
HR, bpm	76.8 (16.0)	76.1 (16.9)	78.6 (13.5)	0.30
LVEF, %	46.1 (10.1)	45.7 (9.3)	47.3 (11.5)	0.26
Laboratory findings				
cTn-I, ng/l	47 (39–59.6)	40.8 (32.5–50.9)	51 (40–58.3)	0.03[a]
Glucose, mg/dl	115 (96–149)	114.5 (96–146)	115 (97–163)	0.67
Hemoglobin, g/dl	14.1 (1.5)	14.1 (1.5)	14.0 (1.7)	0.21
WBC, ×10^9/l	11.6 (9.3–14.3)	10.6 (8.6–12.4)	12.2 (10.2–14.8)	0.03[a]
Neutrophils, ×10^9/l	7.5 (6.1–9.3)	7.2 (5.9–9.3)	8.4 (7.5–9.4)	<0.001[a]
Lymphocytes, ×10^9/l	2.4 (1.8–3.1)	2.5 (2–3.2)	2 (1.6–2.7)	<0.001[a]
Platelets, ×10^9/l	278.1 (69.5)	273.0 (68.0)	293.2 (72.3)	0.04[a]
Monocyte, ×10^9/l	0.7 (0.2)	0.7 (0.2)	0.8 (0.2)	<0.001[a]
SII	931 (658–1156)	858 (547–1023)	1257 (961–1523)	<0.001[a]
SIRI	2.2 (1.5–3.4)	1.9 (1–2.6)	3.5 (2.6–4.3)	<0.001[a]
Total cholesterol, mg/dl	199.0 (49.0)	198.1 (47.0)	201.4 (54.6)	0.64
HDL-cholesterol, mg/dl	42.2 (10.4)	43.5 (10.7)	38.1 (8.2)	<0.001[a]
LDL-cholesterol, mg/dl	137 (110–166)	137 (109–163)	140 (115–170)	0.52
Triglycerides, mg/dl	133 (100.5–184)	116 (90–183)	145 (116–190)	0.07
Creatinine, mg/dl	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.21
hs-CRP, mg/l	20.8 (13.5–28)	17.2 (10.7–24.8)	25.1 (19.7–32.7)	0.04[a]
Discharge therapy, n (%)				
Aspirin	512 (100.0)	382 (100.0)	130 (100.0)	1.00
Ticagrelor	512 (100.0)	382 (100.0)	130 (100.0)	1.00
ACEi/ARBs	500 (97.7)	372 (97.4)	128 (98.5)	0.98
Beta-blockers	492 (96.1)	366 (95.8)	126 (96.9)	0.97
Statins	504 (98.4)	376 (98.4)	128 (98.5)	0.99

Categorical variables were shown as number percentages. Numerical variables are mean (SD) or median (IQR)
[a]*P*-value <0.05 shows statistical significance

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; cTn-I, cardiac troponin I; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVAR, left ventricular adverse remodeling; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; WBC, white blood counts

Table 2. Distribution of demographic and clinical findings by time of onset of symptoms groups

Variables	Morning hours n = 212	Daytime hours n = 90	Evening hours n = 70	Night hours n = 140	*P*-value
Demographic findings					
Age, years	54.7 (9.3)	54.1 (8.4)	54.3 (7.1)	53.0 (8.9)	0.44
Male sex, n (%)	180 (84.9)	79 (87.8)	60 (85.7)	125 (89.2)	0.73
BMI, kg/m^2	27.8 (3.6)	27.8 (5.1)	26.8 (6.5)	27.6 (2.8)	0.54
Active smoking, n (%)	114 (53.8)	48 (53.3)	36 (51.4)	82 (58.6)	0.77
Hypertension, n (%)	104 (49.1)	40 (44.4)	32 (45.7)	64 (45.7)	0.92
Diabetes mellitus, n (%)	58 (27.4)	26 (28.8)	20 (28.6)	40 (28.6)	0.79
Clinical findings					
Symptoms, n (%)					
Shoulder or back pain	102 (52.8)	56 (62.2)	38 (54.3)	82 (58.6)	0.71
Arm pain	90 (42.5)	36 (40.0)	34 (48.6)	68 (48.6)	0.74
Dyspnea	84 (39.6)	34 (37.8)	28 (40.0)	46 (32.9)	0.81
Fatigue	140 (66.0)	46 (51.1)	48 (68.6)	86 (61.4)	0.31
SBP, mm Hg	122.2 (17.3)	121.5 (15.2)	127.6 (21.9)	124.6 (18.7)	0.56
DBP, mm Hg	75.2 (12.6)	74.2 (10.0)	77.3 (13.8)	78.4 (12.3)	0.37
HR, beat per minute	77.1 (15.4)	75.5 (13.5)	78.6 (22.0)	76.2 (15.5)	0.85
Laboratory findings					
cTn-I, ng/l	55 (42.6–68.4)	38 (32–42)	36 (30–42)	47 (41–53)	0.004[a]
Glucose, mg/dl	128 (97–148)	120 (96–152)	114 (85–175)	116 (100–148)	0.69
Hemoglobin, g/dl	14.1 (1.6)	14.2 (1.7)	14.1 (1.4)	13.9 (1.5)	0.86
WBC, ×10^9/l	13.2 (10.2–14.9)	10.4 (8.4–12.3)	10.1 (8–12.1)	11.3 (8.6–13.2)	<0.001[a]
Neutrophils, ×10^9/l	8.6 (7.5–10.1)	6.5 (5.9–8.1)	6.1 (5.7–7)	7.3 (5.4–9.3)	<0.001[a]
Lymphocytes, ×10^9/l	2 (1.6–2.6)	2.8 (2.2–3.3)	2.6 (2.1–3)	2.8 (2.1–3.5)	<0.001[a]
Platelets, ×10^9/l	298.1 (68.2	264.1 (63.6	260.4 (58.5	270.2 (72.8)	<0.001[a]
Monocyte, ×10^9/l	0.8 (0.3)	0.7 (0.2)	0.7 (0.2)	0.7 (0.3)	<0.001[a]
SII	1213 (1008–1544)	759 (587–876)	547 (388–810)	796 (466–923)	<0.001[a]
SIRI	3.2 (2.0–4.1)	2.2 (1.5–2.5)	1.9 (0.9–2.2)	1.7 (0.9–2.3)	<0.001[a]
Total cholesterol, mg/dl	191.6 (49.4)	194.8 (43.1)	202.4 (47.1)	211.2 (51.3)	0.11
LDL-cholesterol, mg/dl	42.0 (9.8)	42.8 (10.7)	42.4 (9.4)	42.8 (11.5)	0.63
HDL-cholesterol, mg/dl	135 (96–157)	134 (105–166)	133.5 (125–163)	141 (128–179)	0.28
Triglycerides, mg/dl	120.5 (89–182.5)	125 (95.5–204)	164 (127–182)	162 (107–184)	0.12
Creatinine, mg/dl	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.66
hs-CRP, mg/l	24.6 (11.7–32.2)	19.3 (13–31.4)	20 (13.5–25.5)	19.4 (14.3–26)	0.80
Discharge therapy, n (%)					
ACEi/ARBs	208 (98.1)	88 (97.8)	66 (94.3)	138 (98.6)	0.57
Beta-blockers	204 (96.2)	90 (100.0)	68 (97.1)	130 (92.9)	0.30
Statins	208 (98.1)	88 (97.8)	70 (100.0)	138 (98.6)	0.99

Categorical variables were shown as number percentages. Numerical variables are mean (SD) or median (IQR)
[a]*P*-value <0.05 shows statistical significance. Bold characters show the difference between groups

Abbreviations: see Table 1

determined as independent predictors of LVAR. Accordingly, a 1% increase in the SIRI increased the risk of LVAR by 3.03-fold (odds ratio [OR], 3.03; *P* <0.001) (Table 4). The threshold value of the SIRI was found to be >2.5, with 78.5% sensitivity and 74.3% specificity. The threshold value of the SII index was found to be >1204.2, with 55.4% sensitivity and 87.4% specificity. The SIRI showed superior diagnostic performance compared to the SII index in predicting LVAR (Figure 2) (Supplementary material, *Table S4*).

DISCUSSION

To our knowledge, this is the first study in the literature to report the association between the SII index, SIRI, and the time of onset of symptoms in LVAR after STEMI. SII index and SIRI on admission were generally higher in patients who developed LVAR, but this difference was particularly pronounced in the morning hours between 06:00 and 11:59 AM. The SIRI was found to be an independent predictor of LVAR and showed superior diagnostic performance compared to the SII index.

Previous studies demonstrated that increased SII index and SIRI were important predictors of cardiovascular events [12–14]. Increased SII index and SIRI were related to increased risk of LVAR in patients experiencing STEMI for the first time. Immune system activation starting from the onset of acute MI allows neutrophils, as the first line of defense against inflammation, to gather in the ischemic zone to scavenge dead cell debris following this cardiac event [24]. Protein heteromers of neutrophil and platelet cells promote monocyte recruitment [25]. Moreover, neutrophils have the potential to modulate macrophages to the anti-inflammatory phenotype, while platelets can

Table 3. Distribution of angiographic and echocardiographic findings by time of onset of symptoms groups

Variables	Time of onset of symptoms				*P*-value
	Morning hours n = 212	Daytime hours n = 90	Evening hours n = 70	Night hours n = 140	
Angiographic findings					
Door-to-balloon time, min	43.2 (7.0)	44.1 (8.6)	41.5 (7.2)	42.6 (12.0)	0.39
Symptom-to-balloon time, min	310.2 (56.4)	307.2 (54.1)	237.8 (48.6)	306.2 (50.5)	0.41
GRACE score	142 (102–152)	118 (102–130)	112 (102–130)	128 (88–140)	0.02[a]
IRA, n (%)					
LAD	80 (37.7)	30 (33.3)	22 (31.4)	52 (37.1)	0.89
Cx	132 (62.3)	60 (66.7)	48 (68.6)	88 (62.9)	
Number of diseased vessels, n (%)					
1	144 (67.9)	74 (82.2)	46 (65.7)	102 (72.9)	0.27
≥2	68 (32.1)	16 (17.8)	24 (34.3)	38 (27.1)	
Pre-PCI TIMI flow, n (%)					
0	140 (66.0)	62 (68.9)	40 (57.1)	86 (61.4)	0.41
1	24 (11.3)	2 (2.2)	8 (11.4)	18 (12.9)	
2	18 (8.5)	8 (8.9)	10 (14.3)	22 (15.7)	
3	30 (14.2)	18 (20.0)	12 (17.1)	14 (10.0)	
Post-PCI TIMI flow >2, n (%)	200 (94.3)	86 (95.6)	70 (100.0)	132 (94.3)	0.60
Number of stents	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0.87
Echocardiographic findings					
Baseline					
LVEF, %	48.5 (9.1)	49.7 (9.9)	50.1 (7.3)	48.4 (9.8)	0.10
LVEDV, ml	150 (130–171)	142 (126–167)	140 (113–165)	146 (129–171)	0.13
LVESV, ml	74 (60–104)	70 (57–98)	72 (49–94)	74 (62–97)	0.11
Stroke volume, ml	70.0 (16.1)	69.7 (17.0)	70.8 (15.8)	70.2 (17.6)	0.99
6 months					
LVEF, %	48.3 (9.9)	51.2 (10.0)	54.2 (8.4)	49.6 (10)	0.01[a]
LVEDV, ml	154 (128–171)	140 (132–150)	138 (117–151)	143 (129–160)	0.04[a]
LVESV, ml	76 (55–95)	65 (54–82)	63 (50–72)	68 (53–99)	0.05[a]
Stroke volume, ml	73.7 (16.1)	75.9 (18.3)	74.8 (13.3)	73.3 (17.1)	0.84
LVAR, n (%)	72 (34.0)	22 (24.4)	14 (20.0)	22 (15.7)	0.04[a]

Categorical variables were shown as number percentages. Numerical variables are mean (SD) or median (IQR)
[a]*P*-value <0.05 shows statistical significance. Bold characters show the difference between groups

Abbreviations: Cx, circumflex artery; IRA, infarct-related artery; LAD, left anterior descending artery; LVAR, left ventricular adverse remodeling; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction

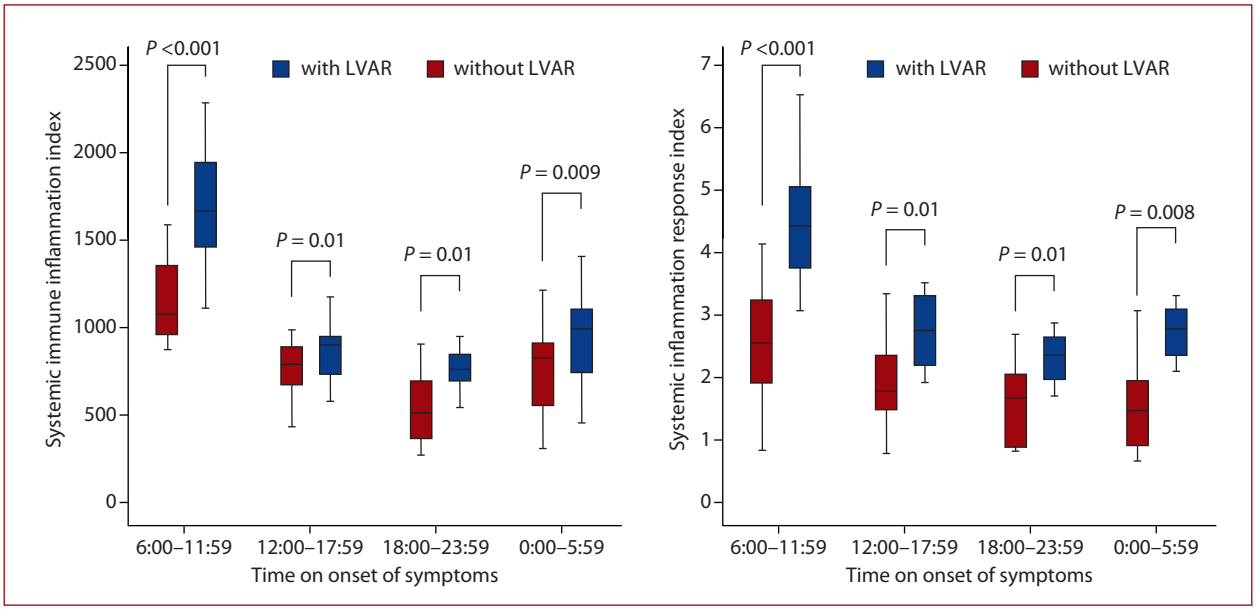

Figure 1. Box and whisker plots of SII and SIRI levels by time of onset of symptoms. Data are presented as median (interquartile range [IQR])

Table 4. Independent predictors of LVAR

Variables	Univariable regression				Multivariable regression			
	OR	95% CI		*P*-value	OR	95% CI		*P*-value
		Lower	Upper			Lower	Upper	
Time of onset of symptoms								
Morning hours	2.76	1.29	5.89	0.009[a]	2.92	1.32	6.10	0.03[a]
Daytime hours	1.74	0.68	4.43	0.25	1.89	0.75	4.80	0.32
Evening hours	1.34	0.47	3.83	0.58	1.45	0.53	4.04	0.62
Night hours	ref				ref			
cTn-I	1.08	1.01	1.16	0.03[a]	–	–	–	–
WBC	1.04	1.01	1.08	0.04[a]	–	–	–	–
Neutrophils	1.30	1.12	1.50	<0.001[a]	–	–	–	–
Lymphocytes	0.46	0.31	0.68	<0.001[a]	–	–	–	–
Platelets	1.04	1.01	1.08	0.04[a]	–	–	–	–
Monocyte	25.34	6.73	95.43	<0.001[a]	–	–	–	–
SII	1.02	1.01	1.03	<0.001[a]	–	–	–	–
SIRI	3.00	2.21	4.07	<0.001[a]	3.03	1.46	6.28	<0.001[a]
HDL	0.94	0.91	0.97	<0.001[a]	–	–	–	–
hs-CRP	1.04	1.01	1.08	0.04[a]	–	–	–	–
Grace score	1.14	1.05	1.23	0.003[a]	1.16	1.06	1.25	0.01[a]
						C-Statistics = 0.85; *P* <0.001[a]		

[a]*P*-value <0.05 shows statistical significance. The reference category (ref) for the time of onset of symptoms variable was "Night hours"

Abbreviations: CI, confidence interval; cTn-I, cardiac troponin I; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; WBC, white blood cell counts

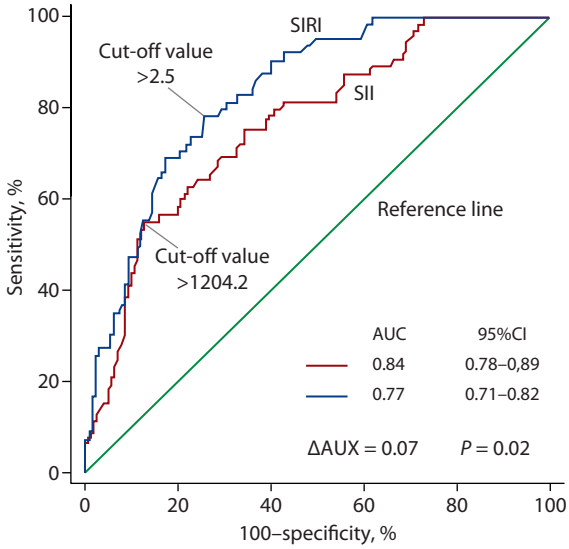

Figure 2. Diagnostic performance of SII and SIRI in predicting LVAR

Abbreviations: AUC, area under the curve; CI, confidence interval; SII, systemic immune inflammation index; SIRI, systemic inflammation response index

affect neutrophil functions [26]. This can release proteolytic enzymes and reactive oxygen species and cause an exacerbation of cardiac damage by damaging surviving myocytes [27]. This may also favor long-term tissue damage, resulting in poor wound healing due to exaggerated inflammation [28].

The relationships between LVAR and IIR indices are not surprising, as previous limited studies reported that increased values of the neutrophil count/lymphocyte count ratio (NLR) or leukocyte components were predictive of LVAR [29, 30]. The current findings both support and expand this literature. This study is the first to report the relationship between LVAR and SII and SIRI indices. The SII index and SIRI have been shown to be better prognostic markers as they contain all components of both the NLR and platelet count/lymphocyte count ratio [31, 32]. These inflammatory indices peaked between the morning hours of 06:00 and 11:59 AM. This suggests that the circadian clock may play a role in IIR and LVAR.

Some important mechanisms of the active phase of the circadian cycle may explain the potential role of IIR indices in the development of LVAR. In a healthy physiological state, circulating neutrophil and monocyte counts peak in the resting phase and are minimal in the active phase [33]. However, circadian variations in leukocyte trafficking due to MI-induced IIR are sensitive to acute inflammatory impulses from the first moment of the acute phase [34]. This sensitivity can result in higher infiltration of neutrophils and monocytes into the myocardium. In addition to this trafficking of neutrophils and monocytes, increased platelet aggregation in the morning phase may exacerbate inflammation [35]. This sequence of events may suggest that neutrophils, which play a role in the modulation of other subtypes of leukocytes, are more affected by the circadian clock, which can result in increasing inflammation or cardiac events. In the morning hours, excessive leukocyte activation may cause increased levels of reactive oxygen species and nitric oxide synthase activity, which play roles in the pathology of LVAR [36]. In nighttime hours, melatonin may play a role in the regulation of these factors [37].

Melatonin is known to influence the regulation of IIR responses, platelet aggregation, and leukocyte trafficking into damaged tissue [38]. Therefore, melatonin secreted in nighttime hours may cause both a more stable IIR and may protect cardiomyocytes from infarction. Administration of melatonin on admission in patients with early STEMI symptom onset was shown to result in reduced infarct size after pPCI [39].

In previous human studies, increased infarct size and mortality rate were associated with different circadian clocks [5–8]. The differences between studies may be due to patient selection. Previous studies included patients at elevated prognostic risk, such as those with a prior history of MI. When patients were evaluated in terms of the first incidence of STEMI, we found that the LVAR rate and IIR indices were higher in the morning hours. These findings are consistent with previous experimental studies that found that MI occurring in the active phase caused increased inflammation or infarct size and worse cardiac repair outcomes [9, 40]. Additionally, neutrophil modulation was shown to reduce infarct size and improve cardiac function [9]. In another MI study in a mouse model, the daily rhythm was randomized to a normal diurnal rhythm or disrupted environment for 5 days after MI. Disruption of the circadian rhythm caused further increases in cytokines, neutrophil and macrophage infiltration, and altered innate immune responses. As a result, poor cardiac healing and exacerbated LVAR were observed [41].

All patients received antiplatelet therapy in accordance with the guidelines [42]. Despite similar treatment protocols, patients with STEMI in the morning hours had elevated LV volumes at 6-month follow-up in the present study. In addition, there was a positive correlation between baseline IIR indices and change in LV volumes, and this relationship was more pronounced for the patients from the morning interval. These findings suggest that there may be a vicious circle between IIR indices, LV volumes, and the circadian clock in the development of LVAR.

Limitations of the study

The present study has some limitations. First, magnetic resonance imaging, the gold standard method in evaluating cardiac remodeling, could not be performed due to the retrospective nature of the study. Therefore, infarct size could not be measured. Second, complete blood counts at the time of admission to the hospital were evaluated but were not taken into account after the acute phase. In addition, cytokines or chemokines that may play a role in leukocyte trafficking were not analyzed. Evaluation of subtypes of leukocytes by flow cytometry analysis may be more revealing in the development of LVAR. Evaluations of these factors in future studies might further highlight the role of IIR indices varying throughout the circadian cycle in cases of LVAR.

CONCLUSIONS

In patients experiencing STEMI for the first time, an increased SIRI was independently associated with LVAR development. This relationship was more pronounced in the morning hours between 06:00 and 11:59 AM. Circadian variation in the onset of STEMI may play an important role in the severity of inflammation. Despite differences across the circadian periods, the SIRI may be a potential screening tool for identifying LVAR patients at long-term risk of heart failure.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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