Inflammatory Profile in Left Ventricular Apical Thrombus

Ismet Zengin[1] and Hakan Erkan[1]

ABSTRACT

Objective: To investigate the relationship between systemic immune inflammation index (SII), C-reactive protein/albumin ratio (CAR), lymphocyte/CRP ratio (LCR), and apical thrombus development.

Study Design: Observational, cross-sectional study.

Place and Duration of the Study: Bursa City Hospital, Turkey, from 1st January to 31st March 2023.

Methodology: Twenty-two patients with a clinical presentation of acute anterior myocardial infarction and diagnosed with LVAT during follow-up were included. Sixty-eight patients with acute anterior myocardial infarction (AMI) were selected as the control group (comparison). Clinical and demographic characteristics, laboratory data, echocardiographic findings, coronary angiography, and percutaneous coronary intervention data were recorded. SII was calculated by the formula Neutrophil (N) × Platelet (P) / Lymphocyte (L). CAR and LCR values were also determined.

Results: While there was no significant difference between the two groups in terms of SII, CAR was significantly higher and LCR was significantly lower in the apical thrombus group. The cut-off value for CAR was 0.165 (sensitivity=63.64%, specificity=74.60%, AUC=0.718; p <0.05). For LCR, the AUC value of 0.382 and below was found to indicate the presence of apical thrombus with a probability of 69.8% (sensitivity=68.18%, specificity=67.16%, p= 0.002).

Conclusion: No significant relationship was found between SII and apical thrombus in the detection of LVAT, whereas high CAR and low LCR were associated with the presence of apical thrombus.

Key Words: *Left ventricular apical thrombus, Apical aneurysm, C-reactive protein/albumin ratio, Lymphocyte/C-reactive protein ratio, Systemic immune inflammation index.*

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INTRODUCTION

Left ventricular apical thrombus (LVAT) is an important complication of previous anterior myocardial infarction (MI), and its consequences can be devastating. Its incidence has decreased with the widespread use of percutaneous coronary intervention (PCI), but it still maintains its clinical importance, especially in terms of thromboembolism. The incidence varies between 2.7 and 19.2% in different series. Although LVAT is associated with parameters such as differences in coronary anatomy, intervention time for MI, and left ventricular ejection fraction, there is not yet a method to accurately predict LVAT.[1,2]

Several parameters can be used to determine the inflammatory state in the body. This can usually be determined using haematological and biochemical parameters. There are various studies on Systemic Immune Inflammation Index (SII), C-reactive protein/albumin ratio (CAR), and lymphocyte/C-reactive protein (LCR) ratio as inflammatory parameters and data on cardiovascular diseases are also increasing day by day.

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The development of acute MI and LVAT, which occur as a result of an inflammatory and pro-thrombotic pathophysiology, may also be associated with SII, CAR, and LCR. In the context of the disastrous consequences, it is clear that predicting apical thrombus formation will have a beneficial impact on patient outcomes. The aim of this study was to evaluate the relationship between these markers and the formation of an apical thrombus after a previous anterior myocardial infarction.

METHODOLOGY

This observational, cross-sectional study was conducted between January and March 2023. Six hundred and twenty-three consecutive patients, admitted to Bursa City Hospital, Turkey, with acute anterior MI who underwent PCI were reviewed. Acute anterior myocardial infarction was diagnosed in accordance with the 2017 European Society of Cardiology guidelines for ST elevation myocardial infarction.[3] Twenty-two patients with an LVAT identified by transthoracic echocardiography (TTE) within 6 months of acute anterior MI were enrolled. A group of 68 patients with similar clinical and demographic characteristics who had suffered an acute anterior MI were included as a control group. Patients with active infection, haematologic or inflammatory disease, hypo/hyperthyroidism, fibrinolytic therapy, severe liver disease, severe valvular disease, active malignancy, need for anticoagulant medication such as atrial fibrillation (AF), and pregnancy were excluded. Patients with apical akinesia/dyskinesia and/or apical aneurysm due to previous anterior MI were also excluded.

The first step was to identify the protocol numbers of the cases and enter them into the hospital's information management

system. Demographic information such as age and sex, risk factors such as hypertension, diabetes, smoking, clinical features, laboratory, ECG, and TTE findings were then obtained from these records. Hypertension was a diagnosis of systolic ≥140 mm/hg, diastolic ≥90 mm/hg, or taking antihypertensive medication; diabetes mellitus was a diagnosis of fasting blood glucose ≥126 mg/dl or glycated haemoglobin (HgbA1c) ≥6.5% or treating with antidiabetic medication. Smoking was described as active smoking or quitting within the past one-year. The necessary approval for the study was obtained from the Clinical Ethics Research Committee of Bursa City Hospital on 04.01.2023 with the registration number 2023-1/8 and in accordance with the tenets of the Declaration of Helsinki as a human study.

The initial blood drawn from the peripheral venous system during the MI was the preferred time for blood sampling. Haemogram parameters were measured by fluorescence flow cytometry method, serum albumin was measured by bromine cresol violet method, and CRP levels in serum were assayed by the turbidimetric technique. SII was determined using the equation "Neutrophil (N) × Platelet (P)/ Lymphocyte (L)". CAR was determined by the ratio of CRP (mg/L) to serum albumin (g/L). LCR was obtained as the ratio of lymphocyte count (10^3/μL) to the concentration of CRP (mg/L).

The TTE was carried out by the same person, unaware that the subject was a study patient, to avoid interobserver variability. After the primary PCI, TTE was performed within the first 24 hours with the Vivid S5 device (GE Vingmed Ultrasound AS) and 3S cardiac sector probe using standard echocardiographic windows. Subsequent TTEs after 48-72 hours were also evaluated for the presence of apical thrombus and recorded. Apical thrombus was determined as a mass separated from the left ventricle with clear boundaries from the endocardium and accompanied by left ventricular segmental and/or global wall motion abnormality. Measures of ejection fraction computed by the modified Simpson method were recorded. The occurrence of apical thrombus and ejection fraction values at months 1, 3, and 6 were also recorded from the patients' retrospective records.

On diagnosis of acute anterior MI, patients were immediately transferred to the haemodynamic unit for urgent coronary angiography. Coronary angiography was performed *via* femoral or radial access according to the operator's choice, parenteral anticoagulant therapy with the appropriate agent at an adequate dose (70-100 U/kg if glycoprotein 2b-3a was not used, targeting activated clotting time >250 msec) and PCI was performed according to the operator's selection. TIMI (*T*hrombolysis *I*n *M*yocardial *I*nfarction) scores, responsible lesion sites, the status of other vessels, presence of no-reflow, and use of glycoprotein 2b-3a antagonists were recorded. No-reflow was defined as the presence of insufficient myocardial blood flow in a given segment in the absence of angiographic signs of persistent physical obstruction of the epicardial vessels.[4] Loading doses of clopidogrel, prasugrel, and ticagrelor, whichever was preferred, was administered before the procedure and maintenance therapy was organised. In individuals in whom apical thrombus was detected, use of oral anticoagulant was recommended for at least 3-6 months in addition to the use of dual antiaggregant therapy for a certain period of time.

The data obtained from the study were described using descriptive statistics such as mean and standard deviation for numerical variables and analyses of frequencies and percentages for categorical variables. The Shapiro-Wilk test was used to analyse whether the variables obtained corresponded to a normal distribution. These variables were compared between study groups using Student's t-test or Mann-Whitney U test. Chi-square analysis was also used to test for differences between categorical variables. Receiver operating characteristic (ROC) analysis was also used to estimate the cut-off point of the SII, CAR, and LCR variables according to the presence of apical thrombus. Analyses were performed using SPSS 22.0. A significance level of $p<0.05$ was accepted.

RESULTS

Table I shows the detailed demographic and clinical characteristics of the patients. The results of the baseline laboratory tests are shown in Table II. The levels of leukocytes, neutrophils, and CRP were significantly higher in the group with an apical thrombus. Furthermore, the apical thrombus group had a higher incidence of no-reflow during PCI. New cerebrovascular events occurred statistically more frequently in patients with apical thrombus. Other parameters were not significantly different between the two groups. At the end of the first month, 64.29% of patients in the apical thrombus group had an apical thrombus, compared to 71.43% at 3 months and 33.3% at 6 months.

While SII was not significantly different between the two groups (3258.85 ± 6943.42 *vs.* 1345.76 ± 1006.17; p=0.066), CAR was significantly higher (1.05 ± 2.45 *vs.* 0.29 ± 0.66; p=0.002) and LCR was significantly lower (0.41 ± 0.19 *vs.* 1 ± 0.56; p=0.005) in the apical thrombus group.

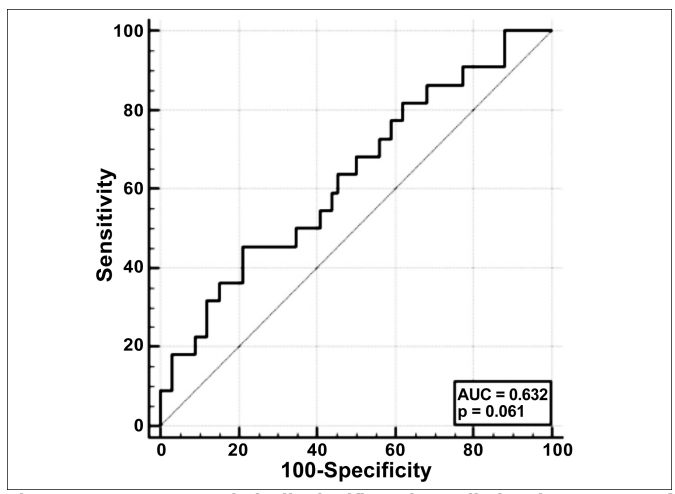

Figure 1: SII was not statistically significant in predicting the presence of apical thrombus (area under the curve: 0.632, p = 0.06).

Table I: Clinical and demographic data of study groups.

		Apical thrombus n (%)	No apical thrombus n (%)	p
Gender	Female	1 (4.5)	15 (22.1)	0.062
	Male	21 (95.5)	53 (77.9)	
Hypertension	+	8 (36.4)	34 (50)	0.265
	-	14 (63.6)	34 (50)	
DM	+	9 (40.9)	22 (32.4)	0.463
	-	13 (59.1)	46 (67.6)	
Hyperlipidaemia	+	1 (4.5)	2 (2.9)	0.716
	-	21 (95.5)	66 (97.1)	
Smoking	+	8 (36.4)	16 (23.5)	0.237
	-	14 (63.6)	52 (76.5)	
Previous Stent	+	1 (4.5)	13 (19.1)	0.101
	-	21 (95.5)	55 (80.9)	
CKD	+	1 (4.5)	11 (16.2)	0.163
	-	21 (95.5)	57 (83.8)	
Coronary Angiography				
LAD	Total	17 (77.3)	52 (76.5)	0.938
	Subtotal	5 (22.7)	16 (23.5)	
LAD	Osteal	4 (18.2)	8 (11.8)	0.702
Segment	Proximal	13 (59.1)	37 (54.4)	
	Mid	5 (22.7)	22 (32.4)	
	Distal	0 (0)	1 (1.5)	
RCA	>%50	6 (27.3)	24 (35.3)	0.772
	<%50	12 (54.5)	34 (50)	
	Normal	4 (18.2)	10 (14.7)	
CX	>%50	6 (27.3)	24 (35.3)	0.046*
	<%50	10 (45.5)	39 (57.4)	
	Normal	6 (27.3) *	5 (7.4)	
CTO	+	0 (0)	11 (16.2)	0.059
	-	22 (100)	57 (83.8)	
No-reflow	+	5 (22.7) *	3 (4.4)	0.019*
	-	17 (77.3)	65 (95.6) *	
Coronary Disection	+	1 (4.5)	0 (0)	0.244
	-	21 (95.5)	68 (100)	
Coronary Thrombus	+	5 (22.7)	11 (16.2)	0.485
	-	17 (77.3)	57 (83.8)	
Stent thrombosis	+	1 (4.5)	7 (10.3)	0.410
	-	21 (95.5)	61 (89.7)	
GP2b3a	+	9 (40.9)	15 (22.1)	0.082
	-	13 (59.1)	53 (77.9)	
HF	+	3 (13.6)	5 (7.4)	0.368
	-	19 (86.4)	63 (92.6)	
New CVE	+	3 (13.6) *	0 (0)	0.013*
	-	19 (86.4)	68 (100) *	

*DM: Diabetes mellitus, CKD: Chronic kidney disease, LAD: Left anterior descending coronary artery, RCA: Right coronary artery, Cx: Circumflex coronary artery, CTO: Chronic total occlusion, HF: Heart failure, CVE: Cerebrovascular event. *p<0.05; Chi-square test.*

Table II: The baseline laboratory findings of study groups.

	Apical thrombus	No Apical thrombus	p
HGB, g/dl	15.01 ± 1.61	14.53 ± 2.11	0.333§
HCT, %	43.07 ± 4.52	41.71 ± 5.71	0.310§
PLT, $x10^3$	259 (213-361)	236 (203-295)	0.188‡
WBC, $x10^3$	14.67 ± 3.22	11.71 ± 3.48	0.001*§
NEU, $x10^3$	11.34 ± 3.14	8.6± 3.4	0.001*§
LYM, $x10^3$	1.79 (1.33-3.02)	1.97 (1.29-2.91)	0.711‡
Creatinine, mg/dl	0.85 (0.79-0.97)	0.89 (0.74-1.04)	0.573‡
GFR, ml/dk/1.73 m^2	94.45 (84.25-101.5)	92.95 (69.0-100.3)	0.315‡
Na, mEq/L	135.64 ± 3.13	136.87 ± 3.02	0.104§
K, mEq/L	4.12 ± 0.55	4.01 ± 0.58	0.446§
AST, IU/L	90.5 (40.7-181.5)	50.5 (25.7-139.2)	0.072‡
ALT, U/L	33.5 (29.2-48.0)	23.5 (18.0-41.0)	0.032*‡
Hs-Troponin^X, ng/L	1127 (167-4907)	701 (71-2630)	0.244‡
Hs-Troponin^{XX}, ng/L	5930 (3375-10000)	4962 (2295-9564)	0.331‡
D-dimer, ug FEU/ml	0.46(0.25-0.77)	0.34 (0.2-0.55)	0.279‡
Albumin, g/L	38.93 ± 4.14	39.72 ± 3.85	0.420§
CRP, mg/L	8 (3.7-24.5)	3.5 (2.2-6.7)	0.002*‡
NT Pro-BNP, ng/L	705 (135-5053)	469 (162-2685)	0.782‡

All data were presented as mean±SD or median (Q1-Q3). HGB: Haemoglobin, HCT: Haematocrit, PLT: Platelet, WBC: White blood cell, NEU: Neutrophile, LYM: Lymphocyte, GFR: Glomerular filtration rate, Na: Sodium, K: Potassium, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive Protein, NT Pro-BNP: N-Terminal-Pro-brain Natriuretic Peptide. X: Baseline value, XX: Peak value.
**p<0,05; ‡Mann-Whitney U test, §Student's t-test.*

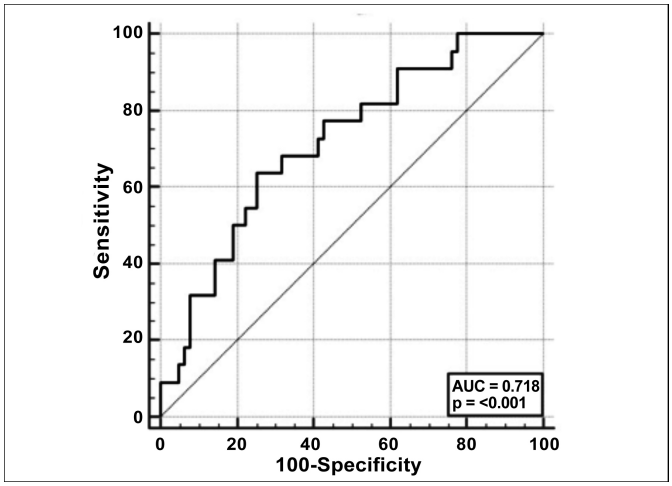

Figure 2: ROC analysis to determine the association between presence of apical thrombus and CRP/Albumin ratio. Cut-off value of >0,165 demonstrated a sensitivity of 63.6% and a specificity of 74.6% (area under the curve: 0.718, p = 0.001).

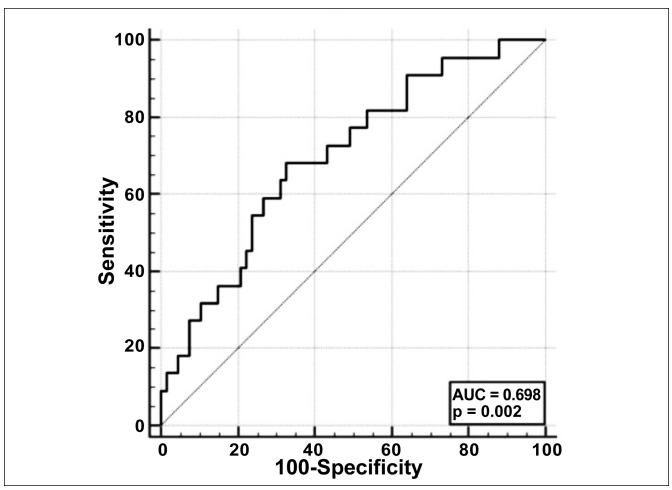

Figure 3: ROC analysis to determine the association between presence of apical thrombus and Lymphocyte/CRP ratio. Cut-off value of ≤0.382 demonstrated a sensitivity of 68.1% and a specificity of 67.1% (area under the curve: 0.698, p = 0.002).

When 2100 was taken as the cut-off value, the sensitivity and specificity of SII were found to be 45.45% and 78.79%, respectively, in the detection of apical thrombus. As a result, it was determined that the SII value was not statistically significant in predicting the presence of apical thrombus (p >0.05, Figure 1).

The cut-off value for CAR is found as 0.165 (sensitivity = 63.64%; specificity = 74.60%). The sensitivity and specificity of the cut-offs are statistically significant and on good levels (AUC = 0.718; p<0.05, Figure 2). The AUC for LCR of 0.382 and below indicated the presence of apical thrombus with a probability of 69.8% (sensitivity = 68.18%, specificity = 67.16%, p = 0.002, Figure 3).

DISCUSSION

In this study, a statistically significant relationship was found between CAR and LCR and apical thrombus development, whereas SII, used as an inflammatory marker, was not associated with apical thrombus development.

During an MI, the pro-inflammatory state, increase in fibrinogen and neutrophils, platelet accumulation, and triggering of the coagulation cascade lead to hypercoagulability, resulting in an impaired flow pattern, impaired left ventricular contraction, and blood stasis in the apical/anterior aneurysm.[1] Inflammation appears to play an important role in LVAT formation. For instance, the neutrophil/lymphocyte ratio has been found to be associated with the development of apical thrombus.[5] In addition, the number of inflammatory platelets has been shown to be associated with the development of left ventricular apical aneurysm, which is one of the components in the pathophysiology of LVAT.[6] Previous studies reported that elevated CRP levels are associated with the development of apical thrombus.[7]

SII is an inflammatory biomarker that is linked with poor clinical outcomes in cancer patients and had been studied in some cardiac conditions.[8] For instance, SII predicted major cardiovascular events in coronary artery disease (CAD) after PCI to be better than the traditional risk factors.[9] High SII was found to predict a high risk of MACE with high 30-day, 90-day, and in-hospital mortality in critically-ill patients with heart failure.[10] In STEMI, patients undergoing primary PCI, SII was shown to be a more powerful predictor of in-hospital and long-term outcomes than the traditional risk factors.[11] In the patients with advanced aortic stenosis undergoing TAVI, a high pre-procedural SII was found to be predictive of MACEs and short-term mortality.[12]

According to the study by Tok *et al.*, 1753 people with previous anterior MI were retrospectively reviewed, and apical thrombus was found in 99 patients. Patients with apical thrombus had lower LVEF, longer time from symptoms to treatment, higher rate of TIMI score ≤1 after PCI, higher mean high-sensitivity CRP and SII levels, and lower lymphocyte count.[8] In this study, CRP, white blood cell, and neutrophil counts were found to be higher. Unlike this study, SII was not found to be associated with apical thrombus development in the current study.

CAR is used as a prognostic marker in noncardiac conditions, and there had been many studies on cardiac pathologies. For instance, CAR had been reported to be a more effective prognostic marker than CRP and albumin in ST-elevation MI.[13] It was concluded that CAR can be used as a reliable predictor of CAD severity in non-ST elevation MI.[14] In addition, in a study, high CAR level was found to be associated with apical thrombus development. Cirakoglu *et al*. included 955 patients and apical thrombus was found in 126 patients in this study. Similar to the current study, white blood cell, neutrophil counts, and CRP levels were found to be high, and no-reflow apical thrombus was significantly higher in cases. They concluded that CAR could be a simple and useful tool for predicting apical thrombus in patients with acute anterior MI.[15] CRP is an acute phase reactant. CRP may also activate complement through the classical pathway.[16] CRP may act as a local pro-inflammatory mediator during MI by activating

complement, as demonstrated in a post-mortem study of infarcted human myocardium.[7,13-17] Albumin is one of the negative acute phase reactants. Its level is expected to decrease in the blood during the inflammation process. Thus, as found in this study, elevated CAR level could be associated with the development of apical thrombus.

Data on LCR, another marker of inflammation, are limited, especially in clinical cardiac conditions. LCR was found to be an independent predictor of in-hospital and long-term MACEs, including cardiovascular death, new-onset non-fatal MI, revascularisation for unstable angina, malignant arrhythmia, heart failure, and new-onset AF in patients undergoing primary PCI for STEMI in a retrospective study of 382 patients with ST-elevation MI. It was concluded that pre-procedural LCR could be one potential biomarker for worse prognosis in STEMI after primary PCI. LCR was also associated with the no-reflow phenomenon and severity of coronary artery lesion.[18] Lymphocytes play an essential role in systemic immunoregulatory networks. An increased inflammatory state and elevated levels of catecholamines and cortisol under stressed situations can exacerbate lymphocyte apoptosis, leading to a reduction in peripheral blood lymphocyte counts.[19,20] Furthermore, as mentioned above, CRP is a characteristic marker of the inflammatory response and is involved in the pathogenesis of acute MI, leading to vascular endothelial dysfunction, and complement activation.[21] Thus, LCR may reflect both the systemic inflammatory response and immune status. High CRP and low lymphocyte count are associated with low LCR. This is indicative of impaired immune response and exacerbated systemic inflammation.[18] In this study, LCR level was found to be lower in patients with apical thrombus, supporting this pathophysiology. The no-reflow phenomenon was also observed more in the apical thrombus group in which LCR was lower.

In the present study, the incidence of no-reflow was higher in the apical thrombus group. The higher incidence of no-reflow phenomenon in the apical thrombus group may be due to both the presence of a prothrombotic environment and the more advanced level of left ventricular regional wall motion defect due to insufficient myocardial perfusion, negative remodelling, and apical aneurysm development. Moreover, LCR was found to be higher in patients with no-reflow, suggesting an association between inflammation and no-reflow.

There are several limitations to this study. Firstly, it was a unicentric, cross-sectional, observational study, and another limitation was the relatively small sample size. More enlightening results may be obtained in larger populations and multi-centre studies. Thirdly, only initial blood samples were used to calculate these rates. Subsequent repeat blood samples may yield different results. Fourth, long-term outcomes in patients with apical thrombus were not available from this study. Fifth and finally, apical thrombus was diagnosed by TTE and the sensitivity of apical thrombus diagnosis by this method was low.[1] The use of contrast media during TTE or imaging with cardiac MR in cases of poor or suspicious image quality may change the diagnosis and treatment planning. Beyond these limitations, to the best of the authors' knowledge, the present study was the first to specifically investigate the inflammatory panel in patients with LVAT.

CONCLUSION

There was no statistically significant correlation between SII and apical thrombus development, whereas a significant correlation was found among CAR, LCR, and apical thrombus presence. In light of these data, CAR and LCR may be considered for use in the detection of apical thrombus in a clinical practice because they are relatively easily accessible and calculable.

ETHICAL APPROVAL:
The ethics committee approval was obtained from the Clinical Research Ethics Committee of Bursa City Hospital, Bursa, Turkey on 04.01.2023 with registration number 2023-1/8.

PATIENTS' CONSENT:
Informed consent was obtained from the patients for publication of the case data used in the study.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
IZ: Study design, material and data collection or processing, literature review, and manuscript preparation.
IZ, HE: Study conception, critical review and supervision.
HE: Statistical analysis and/or data interpretation.
All authors approved final version of the manuscript to be published.

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