Original Article

Evolution of Hematological Parameters in Patients with Vasoplegia Following Coronary Artery Bypass Graft Surgery

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Abstract

Background: The utilization of extracorporeal circulation during a coronary artery bypass graft (CABG) surgery induces the secretion of inflammatory mediators associated with the onset of vasoplegic syndrome (VS). Blood cells contribute to the amplification of enzymatic mechanisms related to the development of VS, which is responsible for high mortality rates.

Objectives: To investigate possible changes in hematological ratios to evaluate the evolution of VS in patients undergoing CABG.

Methods: Analytical observational study of the retrospective cohort type, utilizing data collected from medical records in a reference cardiology hospital.

Results: VS was associated with decreased monocyte rates (p = 0.02) 24 hours before the CABG, as well as elevated lymphocyte/monocyte ratio (LMR) (p = 0.01) and neutrophil/monocyte ratio (NMR) (p = 0.01) on the same period. Twenty-four hours after the procedure, increased neutrophil counts (p = 0.05) and platelet/lymphocyte ratio (PLR) (p = 0.03), as well as neutrophil/lymphocyte ratio (NLR) (p = 0.04), were associated with VS. Between 24 and 48 hours after CABG, neutrophil ratios (p = 0.01), PLR (p = 0.02), MLR (p = 0.04), and systemic inflammation response index (SIRI) (p = 0.02) were lower in patients who developed vasoplegia.

Conclusion: A decreased monocyte count 24 hours before CABG was associated with the development of VS, as well as an elevated neutrophil count 24 hours after the procedure. Higher LMR and NMR 24 hours before the surgery, as well as PLR and MLR after the cardiac surgery were also associated with VS. Our data show different hematological changes at different times after CABG and highlight that new studies are essential to allow the use of hematological ratios in the monitoring of patients undergoing CABG.

Keywords: Vasoplegia; Inflammation; Neutrophils; Monocytes; Leukocytes.

Introduction

Worldwide, 17.9 million people die due to Cardiovascular Diseases (CVDs).[1] In severe cases, coronary artery disease (CAD), the most prevalent form of CVD, can be managed with coronary artery bypass grafting surgery (CABG), with or without cardiopulmonary bypass (CPB). While the combination of CABG/CPB generally leads to a positive prognosis, studies have also shown an association with systemic inflammatory response syndrome (SIRS).[2,3]

SIRS is characterized by an inflammatory reaction stemming from infectious, metabolic, or traumatic origins. Blood contact with the CPB circuit triggers immuno-inflammatory pathways, with high levels of nitric oxide (NO) produced via induced nitric oxide synthase (iNOS) contributing to vasodilation and increased vascular permeability.[4] One of the consequences of SIRS is vasoplegic syndrome (VS), which manifests as refractory hypotension with a mean arterial pressure (MAP) below 65 mmHg that does not respond to fluid therapy, being associated with a cardiac index ≥ 2.2 L/kg/m^2. VS is characterized by normal or increased cardiac output and low systemic vascular resistance, leading to hypoperfusion. It can occur during or up to 24 hours after CPB.[5,6] VS is associated with high morbidity and mortality, affecting 5 to 50% of all patients undergoing CABG.[7] Risk factors for developing vasoplegia include undergoing combined cardiac surgeries, prior use of antihypertensive or antiarrhythmic medications, left ventricular ejection fraction < 35%, prolonged CPB and/or aortic clamping times, receiving blood products, and experiencing increased core temperatures during bypass.[8,9]

The scientific community has been actively exploring methods to assess patients' inflammatory status to predict major adverse cardiac events and death in those undergoing CABG/CPB.[10] As such, calculating various hematological ratios—such as the neutrophil-lymphocyte ratio (NLR),

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platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), neutrophil-monocyte ratio (NMR), monocyte-lymphocyte ratio (MLR), aggregate index of systemic inflammation (AISI = platelet x monocyte x neutrophil/lymphocyte), and systemic immune inflammation index (SII = platelet x neutrophil/lymphocyte)—is being explored, given their potentially favorable cost/benefit ratio.[11,12] Therefore, this study conducted retrospective analyses to assess the predictive potential of leukocyte counts and hematological ratios for VS and its post-CABG/CPB complications.

Method

Study design

The study was conducted in the Cardiac Intensive Care Unit of a tertiary reference hospital specializing in the treatment of cardiovascular diseases in the microregion of Alto Vale do Itajaí, Santa Catarina, Brazil, in the period between April 2018 and October 2022.

Patients aged 18 years or older who underwent CABG/CPB were included. Patients with previous use of corticosteroids or immunomodulators, previous revascularization, and/or combined cardiac surgical procedures were excluded. The study was approved by the UNIDAVI Human Research Ethics Committee (opinion 5.727.585).

Data collection

Data collection was made from electronic medical records (Tasy®; Philips®, Amsterdam, Netherlands), accessed from the report of patients undergoing CABG. Subsequently, these patients were identified by the service number, maintaining confidentiality and anonymity.

Research instrument

The research instrument developed by the authors is described in Supplementary Material 1.1.

Surgical procedure

Although the authors did not directly monitor the cardiac surgeries, the standard methodology used is described in Supplementary Material 1.2.

Vasoplegic syndrome

At the institution, the standard treatment for VS is administered with methylene blue, defined as the diagnostic criterion for VS in this study.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences software (SPSS®, version 26.0; IBM®, Armonk, NY, USA). The normality of quantitative variables was analyzed using the Kolmogorov-Smirnov test. Then, if the data distribution was normal, the comparison between two groups was performed using the Student's t test for independent samples or the corresponding non-parametric Mann-Whitney U test. For qualitative variables, the Pearson Chi-Square test (if test $n > 5$) or Fisher's Exact test (if test $n < 5$) were used. Furthermore, adjusted residuals were analyzed ($ra > 1.96$). Finally, variables with statistical significance were candidates for the linear logistic regression model. Values of $p \leq 0.05$ were considered statistically significant.

Results

Six-hundred and eight (608) digital records were analyzed and, according to Strobe Guideline 5,[13] 507 records were considered (Figure 1). Of these, 98.0% (n = 501) did not develop VS, while 2.0% (n = 6) developed VS during the period analyzed.

The majority of participants were men (74%) and white (95.3%). The average age was 62.0 ± 9.3 years. The body mass index (BMI) was calculated according to the Guidelines for the Treatment of Overweight and Obesity in Adults.[14] No differences were observed between the age and BMI of patients with or without VS. With the exception of dyslipidemia ($p = 0.02$), all other comorbidities described were equivalent between the groups studied (Table 1).

The main indication for CABG among patients without VS was unstable angina (34.3%). In patients with VS, it was acute non-ST segment elevation myocardial infarction (STEMI; 66.7%; $p = 0.05$). Although patients in the VS group underwent cardiac surgery earlier, there was no statistical difference between the groups according to the average time between coronary syndrome diagnosis and the procedure (Table 2).

Hematological ratios were calculated to evaluate the probability of developing VS in patients undergoing MVR surgery. Twenty-four hours before CABG/CPB, the monocyte count was reduced ($p = 0.02$) and the LMR and NMR ratios were increased ($p = 0.01$ and $p = 0.01$, respectively) in the VS group (Table 3). To validate the findings 24 hours before surgery, linear regression analyses were performed, confirming the reduced number of monocytes and increased LMR and NMR (Supplementary Material – Supplementary Table 2).

Increased neutrophil counts ($p = 0.05$) and increased NLR ($p = 0.04$) and PLR ($p = 0.03$) were observed up to 24 hours after CABG/CPB in VS patients compared to the non-VS group (Table 3).

Between 24 and 48 hours after CABG/CPB, decreased neutrophil counts ($p = 0.01$) and reduced ratios of PLR ($p = 0.02$), MLR ($p = 0.04$) and SIRI ($p = 0.02$) were observed in VS patients compared to non-VS patients (Table 3). Reduced neutrophil count and SIRI ratio were confirmed by simple linear regression analyses ($\beta = -0.2$ and $p = 0.01$; $\beta = -0.1$ and $p = 0.05$, respectively).

During the surgical procedure, patients who developed VS had significantly longer times on CPB ($p = 0.02$) and aortic clamping ($p = 0.02$) compared to those who did not develop the condition (Table 4). Linear regression analyses supported these findings, showing values of $\beta = 0.10$ and

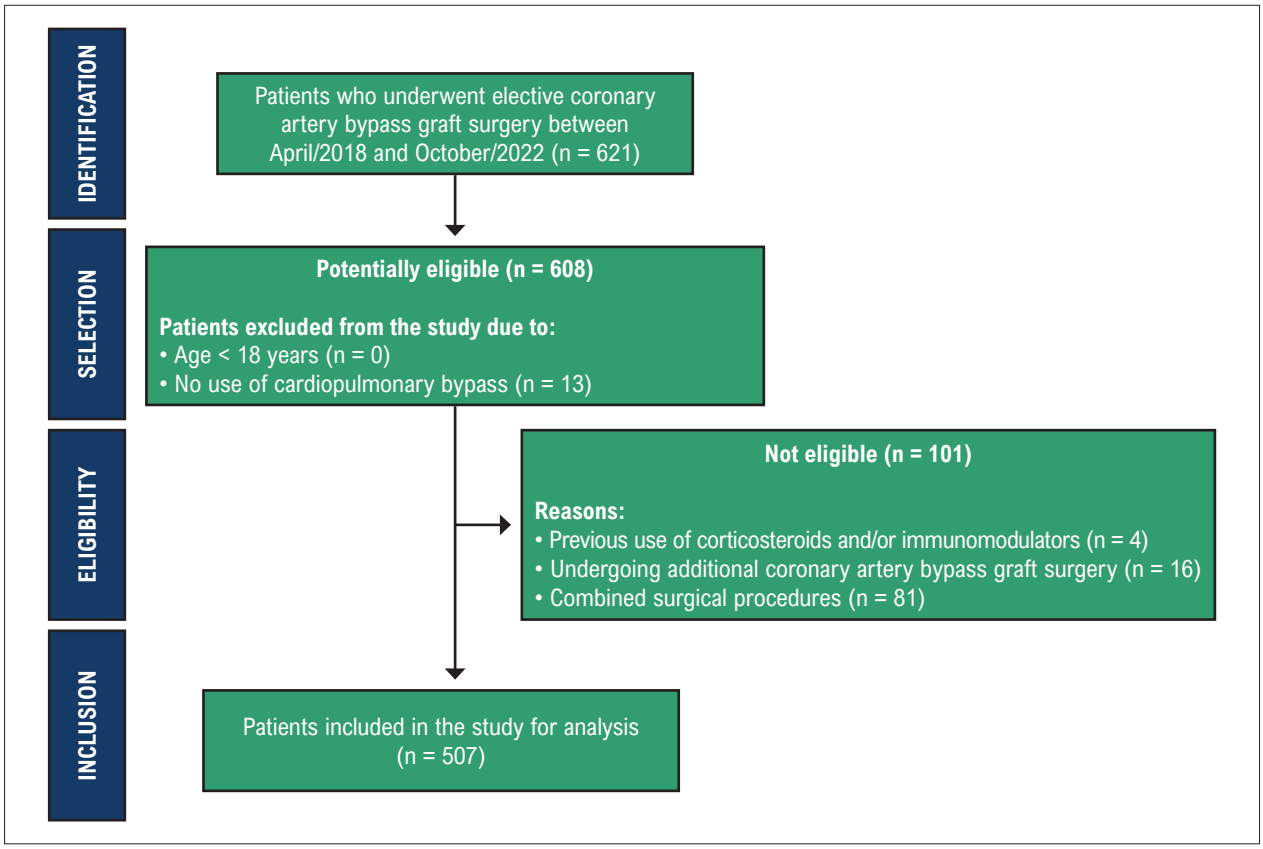

Figure 1 – *Sample eligibility flowchart.*

p = 0.03 for CPB time and β = 0.10 and p = 0.02 for aortic clamping time. However, there was no difference between the groups in terms of the number of bypasses performed, use of blood products, VAD, and ECV during surgery (Table 4).

During the hospitalization period in the cardiac ICU, there were no differences between the VS and non-VS groups in terms of the use of VAD development of AF, thrombocytopenia, delirium, acute renal failure, and/or the need for mechanical ventilation (Supplementary Material - Supplementary Table 3).

At the end of hospitalization, 95.8% (n = 480) of non-VS patients and 83.3% (n = 5) in the VS group (p = 0.2) were discharged from hospital. The variation in length of stay after CABG until hospital discharge was similar in the groups analyzed (Supplementary Material - Supplementary Table 4).

Discussion

Vasoplegia is a significant complication of cardiac surgery, with a prevalence ranging from 5 to 50% and possibly fatal. Our study indicates that a decreased number of monocytes and increased hematological ratios of LMR and NMR are associated with the development of vasoplegic syndrome (VS) 24 hours before undergoing CABG/CPB. Additionally, within 24 hours of the surgical procedure, coinciding with the onset of VS, an increased number of neutrophils and elevated NLR and PLR ratios were observed. Moreover, during CABG, the durations of both CPB and aortic clamping were prolonged in the VS group.

The patient population in our study aligns with literature, indicating that individuals with CVDs requiring CABG/CPB are predominantly male, elderly, white, overweight, and hypertensive.[15] However, the well-established relationship between diabetes mellitus and smoking as risk factors for cardiac comorbidities[16] did not correlate with the emergence of VS in our study. Interestingly, a prior diagnosis of dyslipidemia was considered a protective factor against developing this complication. Research has shown a preference for statins in treating lipid imbalances, with additional benefits including improved endothelial function and reduced inflammatory markers. Therefore, prior statin use may be associated with a lower incidence of VS in patients with dyslipidemia.[17,18] Despite smoking, hypertension, and diabetes not being associated with VS in our findings, patients with VS were typically older and exhibited similar gender distribution, consistent with existing literature.[19]

In our study, the main indication for surgical revascularization of VS patients was STEMI. No data were found that could elucidate this condition. In cases of transmural involvement (STEMI), which entails greater tissue damage and subsequent

Table 1 – Sociodemographic characteristics and comorbidities of patients

Variables	(-) VS	(+) VS	p
	Mean ± SD or n (%)	Mean ± SD or n (%)	
	n = 501	n = 6	
Age (years)	62.0 ± 9.3	65.3 ± 6.1	0.38
Sex			
Female	130 (25.9)	2 (33.3)	0.65
Male	371 (74.1)	4 (66.7)	
Race			
Black	2 (0.4)	0 (0.0)	1.00
White	477 (95.2)	6 (100.0)	
Mixed	19 (3.8)	0 (0.0)	
Asian	3 (0.6)	0 (0.0)	
BMI (kg/m²)	27.6 ± 4.1	24.5 ± 2.9	0.08
Diabetes mellitus	178 (35.5)	0 (0.0)	0.10
Systemic arterial hypertension	450 (89.8)	4 (66.7)	0.12
Dyslipidemia	445 (88.8) ra = 2.9	3 (50.0)*	0.02*
Cardiac insufficiency	112 (22.4)	0 (0.0)	0.35
Chronic obstructive pulmonary disease	80 (16.0)	0 (0.0)	0.59

*The table above outlines the data of patients who presented the respective comorbidities. Data shows the mean ± standard deviation (SD) or the number of patients (n). (-) VS: absence of vasoplegic syndrome; (+) VS: presence of vasoplegic syndrome. BMI: body mass index. *p ≤ 0.05 vs (-) VS. ra: standardized adjusted residuals. Source: authors.*

Table 2 – CABG referral

CABG referral	(-) VS	(+) VS	p
	Mean ± SD or n (%)	Mean ± SD or n (%)	
	n = 501	n = 6	
Stable Angina	159 (31.7)	1 (16.7)	0.67
Unstable Angina	172 (34.3)	1 (16.7)	0.67
STEMI	37 (7.4)	0 (0.0)	1.00
NSTEMI	132 (26.3)	4 (66.7)*	0.05*
△t AMI-CABG (days)	65.3 ± 128.0	42.7 ± 45.4	0.88

*Data shows the mean ± standard deviation (SD) or number of patients (n). (-) VS: absence of vasoplegic syndrome; (+) VS: presence of vasoplegic syndrome. STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; Δt AMI-CABG: time variation between acute myocardial infarction diagnosis and coronary artery bypass graft surgery. *p ≤ 0.05 vs (-) VS. Source: authors.*

inflammation, there is an increased recruitment of leukocytes.[20] Therefore, our study suggests that STEMI patients who undergo surgery earlier may experience a more intense inflammatory response, potentially increasing the risk of developing VS. Additionally, we observed a trend towards a reduction in the time interval between the diagnosis of AMI and CABG/CPB in patients with VS, suggesting that any delay in surgical management following diagnosis did not impact the patient's outcome. However, no studies have explored this relationship thus far.

While leukocyte ratios have been extensively studied for the diagnosis and prognosis of various tumors and, to a lesser extent, limb amputation cases, [21-23] their use in CVDs is less documented. NLR, for example, has been associated with a poor prognosis in conditions such as atrial fibrillation, acute kidney injury, low output syndrome, and prolonged mechanical ventilation following cardiac surgeries.[24] High PLR and red cell distribution width (RDW) values have also been identified as useful and independent risk factors for predicting postoperative ischemic stroke in CPB patients.[25] In our study, LMR and NMR were able to predict the occurrence of VS 24 hours before CABG/CPB. The reduction in LMR and NMR values was dependent on decreased circulating monocytes and related to the development of VS.

Table 3 – Hematological ratios before and after cardiac surgery

Hematological parameters	24 hours before CABG		24 hours after CABG		Up to 48 hours after CABG	
	(-) VS Mean ± SD n = 501	(+) VS Mean ± SD n = 6	(-) VS Mean ± SD n = 501	(+) VS Mean ± SD n = 6	(-) VS Mean ± SD n = 501	(+) VS Mean ± SD n = 6
Neutrophils (%)	57.4 ± 10.0	59.3 ± 6.9	76.7 ± 8.0	83.0 ± 5.1*	81.8 ± 6.5	68.7 ± 34.0*
Lymphocytes (%)	29.8 ± 8.7	28.5 ± 7.9	16.1 ± 7.0	11.0 ± 4.1	9.6 ± 4.7	9.0 ± 5.5
Monocytes (%)	8.3 ± 2.2	6.2 ± 4.1*	5.7 ± 2.5	5.0 ± 2.1	7.9 ± 2.4	5.5 ± 3.1
Platelets (x10³)	209.4 ± 63.02	220.8 ± 63.2	163.3 ± 77.7	187.8 ± 38.5	170.4 ± 80.5	162.4 ± 82.6
NLR	2.3 ± 2.3	2.3 ± 1.0	6.2 ± 4.5	8.6 ± 3.8*	11.4 ± 7.7	7.1 ± 4.5
LMR	3.8 ± 2.4	9.4 ± 10.6*	3.8 ± 3.5	3.0 ± 3.0	1.3 ± 0.9	1.4 ± 0.8
NMR	7.4 ± 3.7	17.6 ± 19.1*	17.7 ± 13.0	20.4 ± 11.1	12.2 ± 8.2	11.3 ± 7.2
PLR (x10³)	7.68 ± 4.62	7.91 ± 1.9	15.0 ± 52.34	20.12 ± 10.41*	22.74 ± 16.76	16.83 ± 11.15*
MLR	0.3 ± 0.1	0.2 ± 0.2	0.4 ± 0.3	0.5 ± 0.2	0.9 ± 0.5	0.6 ± 0.1*
SIRI	18.5 ± 15.5	16.8 ± 17.3	36.1 ± 31.0	42.6 ± 19.2	82.4 ± 49.1	43.6 ± 24.5*
AISI (x10³)	379.3 ± 298.3	318.6 ± 295.3	596.7 ± 640.7	842.4 ± 448.3	1392.3 ± 983.4	849.2 ± 479.7
SIII (x10³)	46.8 ± 39.6	46.7 ± 12.6	101.8 ± 96.0	171.3 ± 98.0	192.4 ± 156.1	141.6 ± 100.01
Troponin (ng/mL)	46.2 ± 234.0	35.5 ± 0.00	7073.3 ± 8022.3	-	3917.4 ± 5536.4	-

*Data shows the mean ± standard deviation (SD) or number of patients (n). (-) VS: absence of vasoplegic syndrome; (+) VS: presence of vasoplegic syndrome. CABG: coronary artery bypass graft; NLR: neutrophil/lymphocyte ratio; LMR: lymphocyte/monocyte ratio; NMR: neutrophil/monocyte ratio; PLR: platelet/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; SIRI: systemic inflammatory response index; AISI: aggregate index of systemic inflammation; SII: systemic immuno-inflammation index. *p ≤ 0.05 vs (-) VS. Source: authors.*

Table 4 – Surgery characteristics

Surgery characteristics	(-) VS Mean ± SD or n (%) n = 501	(+) VS Mean ± SD or n (%) n = 6	p
Time on extracorporeal circulation (minutes)	63.0 ± 17.8	79.5 ± 14.0	0.02*
Aortic clamping time (minutes)	44.2 ± 13.4	56.7 ± 13.5	0.02*
Number of bypasses revascularized	3.3 ± 0.7	3.8 ± 0.8	0.06
Blood products	137 (27.3)	2 (33.3)	0.67
Vasoactive drug(s)	145 (28.9)	3 (50.0)	0.36
Electrical Cardioversion	37 (7.4)	0 (0.0)	1.00

*Data shows the mean ± standard deviation (SD) or number of patients (n). (-) VS: absence of vasoplegic syndrome; (+) VS: presence of vasoplegic syndrome. *p≤0.05 vs (-) VS. Source: authors.*

The literature highlights the significant role of monocytes in CVD development, particularly in patients with comorbidities like hypertension and atherosclerosis.[26] Chronic systemic inflammation alters endothelial physiology, leading to increased secretion of pro-inflammatory cytokines such as TNF-alpha, IL-1, and IL-6, which activate circulating monocytes. Additionally, activated monocytes express inducible iNOS.[27] In inflammatory states, high levels of NO produced by iNOS contribute to protein nitration and nitrosylation, potentially contributing to cardiovascular disease development.[28] Also, neutrophils were found to be predictors of vasoplegic complications as early as the next day following surgery. Our study revealed increased neutrophil levels in the VS group compared to the non-VS group, along with decreased lymphocyte counts in both evaluation periods. The immediate immune response to cardiac surgery involves neutrophil mobilization. In SIRS, there is suppression of neutrophil apoptosis with a consequent increase in neutrophils.[29] In this context, our study found that NLR was able to predict the main outcome after 24 hours of CABG/CPB, but not beyond such

period. These findings align with studies by Cooper et al.[30] and Gurm et al.,[31] who demonstrated a significant association between increased neutrophil levels, reduced lymphocyte counts, and adverse outcomes including death and cardiac complications. No data regarding the development of VS and hematological ratios were found in the literature.

Recently, Magoon et al. demonstrated an association between PLR and the development of VS, 24 hours before surgery.[19] However, our study revealed that this was associated with the development of vasoplegia only one day after CABG/CPB. Platelet count decreased on the first day after surgery and alternately increased on the second day for the VS group. This alternation can be reasoned by the use of intraoperative anticoagulant, as well as heparinization of the CPB circuit. However, during surgery, even in smaller numbers, platelets are activated by the secretion of pro-inflammatory cytokines, releasing the contents of α-granules. Thus, activated platelets stimulate the formation of thrombi, commonly associated with post-surgical complications.[32]

Finally, we evaluated leukocyte parameters within 48 hours after CABG. Although the concept of VS is restricted to occurrence within 24 hours of cardiac surgery, we seek to understand the patient's inflammatory status for yet another 24 hours. In this context, neutrophils, PLR, MLR, and SIRI reflected an exacerbated inflammatory condition after CPB surgery. Patients with CVDs show chronic systemic inflammation, characterized by ongoing endothelial damage and leukocyte activation due to the impact of pre-existing comorbidities.[33]

In accordance with recent studies, we found that prolonged CPB and aortic clamping times are associated with VS.[6,19] Vasoplegia may result from prolonged exposure of plasma proteases to the unlined CPB tubing, leading to activation of the inflammatory cascade.[6] Patients with comorbidities have heightened secretion of pro-inflammatory cytokines and increased iNOS expression, predisposing them to a state of vasoplegia proportional to CPB and aortic clamping times.[34,35]

While conditions like acute kidney injury, arrhythmias (especially atrial fibrillation), thrombocytopenia, invasive mechanical ventilation use, and delirium are common after cardiac surgery,[36-38] none were observed in our study's VS patients.

Conclusion

Our study underscores the prognostic role of monocytes and the role of neutrophils in the evolution of VS in CABG/CPB patients for the first time in the literature. Increased hematological LMR and NMR were associated with vasoplegia 24 hours pre-surgery. Additionally, increased NLR and PLR 24 hours post-surgery were also related to VS.

Considering the low cost, the use of hematological ratios in the postoperative period of cardiac surgeries appears essential. Moreover, our study provides new insights into the discussion of this topic. It is important to note that while our study is unprecedented, it remains preliminary, and further studies should be conducted to strengthen our findings.

Study limitations

The small sample size of patients who developed VS in our study may have been a limiting factor, as well as the incomplete recording of medical records. Furthermore, the lack of adequate materials for hemodynamic diagnosis of VS and the absence of practical management protocols for the condition are also factors that could compromise our results.

Author Contributions

Conception and design of the research: Ramos N, Hebeda CB; Acquisition of data: Ramos N; Analysis and interpretation of the data: Ramos N, Faé MT, Hebeda CB, Rocha FR; Statistical analysis: Ramos N, Rocha FR; Writing of the manuscript: Ramos N, Faé MT, Hebeda CB; Critical revision of the manuscript for important intellectual content: Ramos N, Hebeda CB, Bacca COF, Gambetta MV.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Centro Universitário para o Desenvolvimento do Alto Vale do Itajaí under the protocol number 5.727.585. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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***Supplemental Materials**

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