VASOplegia is Predicted by Preoperative Platelet-LEucocyte conGlomerate Indices in Cardiac Surgery (VASOPLEGICS): A Retrospective Single-Center Study

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ABSTRACT

Background: Post-cardiotomy vasoplegia syndrome (VS) is often linked to an exaggerated inflammatory response to cardiopulmonary bypass (CPB). At the same time, the prognostic role of platelet-leucocyte indices (PLIs) and leucocyte indices (LIs), (platelet-lymphocyte ratio [PLR], systemic immune-inflammation index [SII = platelet neutrophil/lymphocyte], aggregate index of systemic inflammation [AISI = platelet monocyte neutrophil/lymphocyte], and neutrophil-lymphocyte ratio [NLR], systemic inflammation response index [SIRI = monocyte neutrophil/lymphocyte], respectively) has been recently described in diverse inflammatory settings.

Methods: The retrospective study was conducted to evaluate the VS predictive performance of PLIs and LIs in 1,045 adult patients undergoing elective cardiac surgery at a tertiary care center. VS was defined by mean blood pressure <60 mmHg, low systemic vascular resistance (SVRI <1,500 dynes.s/cm²/m²), a normal or high CI (>2.5 L/min/m²), and a normal or reduced central filling pressure despite high-dose vasopressors.

Results: About 205 (19.61%) patients developed VS postoperatively. On univariate analysis, age, diabetes, dialysis-dependent renal failure, preoperative congestive heart failure (CHF), the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, ejection fraction, NLR, PLR, SII, AISI, CPB, and aortic cross clamp (ACC) duration, packed red blood cell (PRBC) transfusion, and time-weighted average blood glucose predicted VS. Subsequent to the multivariate analysis, the predictive performance of EuroSCORE II (OR: 3.236; 95% CI: 2.345–4.468; P < 0.001), CHF (OR: 1.04; 95% CI: 1.02–1.06; P = 0.011), SII (OR: 1.09; 95% CI: 1.02–1.18; P = 0.001), AISI (OR: 1.11; 95% CI: 1.05–1.17; P < 0.001), PRBC (OR: 4.747; 95% CI: 2.443–9.223; P < 0.001), ACC time (OR: 1.003; 95% CI: 1.001–1.005; P = 0.004), and CPB time (OR: 1.016; 95% CI: 1.004–1.028; P = 0.001) remained significant. VS predictive cut-offs of SII and AISI were 1,045 10⁹/mm³ and 137532×10⁹/mm³, respectively. AISI positively correlated with the postoperative vasoactive-inotropic score (R = 0.718), lactate (R = 0.655), mechanical ventilation duration (R = 0.837), and ICU stay (R = 0.757).

Conclusions: Preoperative elevated SII and AISI emerged as independent predictors of post-cardiotomy VS.

Keywords: Aggregate index of systemic inflammation, cardiac surgery, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index, vasoplegia syndrome

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INTRODUCTION

The platelet-leucocyte interactions are being increasingly implicated as pivotal perpetrators of an ongoing systemic inflammatory state. As an extension of the aforementioned, there is an ever-growing interest in evaluating the prognostic role of various novel platelet-leucocyte indices (PLIs, including the platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII = platelet × neutrophil/lymphocyte), aggregate index of systemic inflammation (AISI = platelet × monocyte × neutrophil/lymphocyte)) in diverse clinical settings predisposed to inflammation.

While a systemic inflammatory-response syndrome is inexorably associated with the conduct of cardiopulmonary bypass (CPB), the burden of the resultant inflammatory complications can be significant. In this context, post-CPB vasoplegia syndrome (VS) is a peculiar hemodynamic complication with a wide reported incidence ranging from 9 to 40% and is heralded by systemic hypotension accompanied by a low vascular resistance, normal to augmented cardiac index, and poor response to volume therapy. Vascular hyporesponsiveness, accentuated vasopressor requirements, and heightened operative morbidity-mortality frequently compound such clinical scenarios.

Ahead of the range of demographic, pharmacological, and perioperative factors which have been described to be related to an escalated risk of post-CPB VS, the inflammatory links of VS continues to be strengthened in the recent literature. Herein, the description of the association of post-cardiac transplant VS with an elevated preoperative neutrophil-lymphocyte ratio (NLR) by Ahmed et al. and the elucidation of higher post-coronary artery bypass grafting vasoactive-inotropic scores (VIS) in patients with an elevated pre-grafting SII is intriguing. Therefore, we conducted the present retrospective analysis aimed at evaluating the potential of novel PLIs (PLR, SII, and AISI) and leucocyte indices (LIs, including NLR and systemic inflammation response index [SIRI = monocyte × neutrophil/lymphocyte]) in predicting post-cardiotomy VS.

METHODS

After obtaining clearance from the institutional ethics committee (No. 454 (103/2020) IEC/ABVIMS/RMLH), the study was conducted at our tertiary care cardiac center. A total of 1,316 consecutive patients (age >18 years) undergoing elective cardiac surgery on CPB between January 1, 2015, and December 31, 2019, were primarily included. The patients with the presence of any one of the following conditions were excluded: anemia with hemoglobin (Hb) <10 g/dL on admission, multiple organ dysfunction syndrome (MODS defined as the development of physiologic derangement involving two or more organ systems), presence of an active infection and unavailability of complete hemogram within 48 h prior to surgery. During the intraoperative period, 86 patients required either intra-aortic balloon pump (IABP) (n = 68) or extracorporeal membrane oxygenation (ECMO) (n = 18) to assist the separation from CPB and were excluded from the analysis. Patients requiring deep hypothermic circulatory arrest during the procedure were also excluded. Another 37 patients were lost due to the unavailability of adequate postoperative data. Finally, 1,045 patients were evaluated for the outcome and their data were extracted from an electronic database and/or hospital record archive files. The flow chart for patient enrolment is illustrated in Figure 1.

Preoperative characteristics of the patients such as age, sex, body surface area (BSA), smoking history, pre-existing comorbidities (hypertension, diabetes mellitus [DM]),...
ventilation was gradually started, and the patient was weaned following the operative procedure, the ACC was removed and blood cell (PRBC) when required. Maintenance during CPB with the addition of packed red cells when required. Heparinization was achieved with 4 mg/kg heparin and a target ACT >380 s. After aortic and venous cannulation, an aortic cross-clamp (ACC) was placed and the heart was arrested with del Nido cardioplegia (20 mL/kg). A maximum flow of 2.2–2.5 L/min/m² of BSA was employed and a target perfusion pressure of 60–80 mmHg was maintained with mild-to-moderate hypothermia. A hematocrit of 24% was maintained during CPB with the addition of packed red blood cell (PRBC) when required.

Following the operative procedure, the ACC was removed and after adequate it is deairing and rewarming (temperature ≥35°C), ventilation was gradually started, and the patient was weaned off CPB slowly with the support of inotropes and vasopressor infusions. While a combination of 5 µg/kg/min dobutamine and 0.05 µg/kg/min adrenaline was initiated at rewarming, the subsequent inotrope and vasopressor management was aided by the transesophageal echocardiographic examination and/or minimally-invasive cardiac output evaluation (FloTrac™, Edwards Lifesciences, Irvine, CA, USA) with the objective of maintaining the biventricular performance and systemic perfusion. Temporary epicardial pacing was instituted as and when required. After hemodynamic stability was achieved, protamine (dose @ 1:1 of heparin) was administered. Blood and blood products were transfused to maintain Hb ≥10 g/dL. Post-sternal closure, all patients were shifted to the postoperative intensive care unit (ICU) for elective mechanical ventilation.

The following perioperative variables were recorded: cardiac index (CI), systemic vascular resistance index (SVRI), intraoperative blood glucose (time-weighted average of blood glucose [TWAG] calculated as the area under the curve of all intraoperative glucose measurements divided by the time between the first and last measurements), number of PRBC units transfused, blood lactate, dose of the vasopressors and inotropes (calculated as VIS = Dopamine (µg/kg/min) + dobutamine (µg/kg/min) + milrinone (µg/kg/min) × 10 + epinephrine (µg/kg/min) × 100 + norepinephrine (µg/kg/min) × 100 + vasopressin (units/kg/min) × 10,000), duration of CPB, ACC time, duration of mechanical ventilation (DO-MV), length of ICU stay (LOS-ICU), and length of hospital stay (LOS-H). Hemodynamic parameters were recorded at every 15-min interval intraoperatively and on an hourly basis in the ICU.

VS (within the first 24 postoperative ICU hours) was defined by the constellation of the following hemodynamic criteria: hypotension (defined by systemic mean blood pressure <60 mmHg), low systemic vascular resistance (SVRI <1,500 dynes.s/cm²/m²), a normal or high CI (>2.5 L/min/m²), and a normal or reduced central filling pressure (central venous pressure <10 mmHg) despite high-dose vasopressors (typically 0.5 µg/kg/min of norepinephrine equivalents). Other outcomes including mortality, atrial fibrillation (AF), and acute kidney injury (AKI defined in accordance with the Acute Kidney Injury Network [AKIN] criteria) developed during the hospital stay were also noted.

Statistical analysis
The categorical variables were expressed as the number of patients and percentage of patients and compared between the subgroups using the Chi-square test. The continuous variables were compared using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. The categorical outcomes were compared using the Fisher's exact test. The p-values were adjusted for multiple comparisons using the Bonferroni correction. The statistical significance level was set at p < 0.05.
variables were reported as mean and standard deviation and compared between the VS and non-VS groups using the unpaired t-test. The correlation between the continuous variables was measured with the help of Pearson’s correlation analysis. The non-parametric receiver operating characteristic (ROC) curve analysis was performed to evaluate the accuracy of various variables to predict VS indicated by their respective area under the curve (AUC). The “optimum cut-off point” was determined as the cut-off point with the highest [(sensitivity + specificity)/2] ratio, at which there was a maximal correct classification of developing VS. The sensitivity, specificity, and predictive values were depicted using these generated cut-offs. The multivariate analysis was performed using the binary logistic regression method. The statistical software SPSS version 20 (IBM Corp., Armonk, NY, USA) was used for the analysis. An alpha level of 5% has been considered with any P value < 0.05 considered as significant (a Bonferroni correction was done for testing the five indices together during the multivariate analysis and P value < 0.01 was taken as significant).

RESULTS

The study included a total of 1,045 patients out of which 205 patients developed VS (19.6%). The patient demographics, comorbid conditions, and perioperative variables have been compared in Table 1 between VS and non-VS groups. The patients in the VS group were significantly older than the non-VS group (P < 0.001). A higher proportion of the vasoplegic patients were diabetic, suffering from dialysis-dependent renal failure and preoperative CHF had significantly poorer LVEF and higher EuroSCORE II as compared to the non-vasoplegics [Table 1]. Among the intraoperative variables, significantly higher CPB, and ACC time, higher CI, PRBC requirement, and TWAG were noted among the VS group whereas the SVRI was significantly lower in the same [Table 1]. Subsequently, univariate analysis revealed both the causative and protective factors for developing VS [Table 2A].

After adjusting all these factors in the multivariate analysis, the following variables remained significantly associated with the development of VS: EuroSCORE II (OR: 3.236; 95% CI: 2.345–4.468; P < 0.001), history of preoperative CHF (OR: 1.04; 95% CI: 1.02–1.06; P = 0.011), preoperative SII (OR: 1.09; 95% CI: 1.02–1.18; P = 0.001), and AISI (OR: 1.11; 95% CI: 1.05–1.17; P < 0.001), PRBC used (OR: 4.747; 95% CI: 2.443–9.223; P < 0.001), ACC time (OR: 1.003; 95% CI: 1.001–1.005; P = 0.004), and CPB time (OR: 1.016; 95% CI: 1.004–1.028; P = 0.001) [Table 2B]. Preoperative β-blocker usage was found to be protective against the development of VS (OR: 0.893; 95% CI: 0.803–0.987; P = 0.026) [Table 2B]. Metoprolol was used predominantly in our institution. However, the dosage required to protect from vasoplegia could not be determined due to the unavailability of data.

Subsequently, the ROC analysis for the hematological parameters revealed the cut-off values for predicting the development of post-CPB VS with AISI having the highest AUC (0.965) as depicted in Figure 2. The derived cut-off values of the hematological parameters for the development of VS were the following: NLR = 4.125 (94.6% sensitivity, 76.9% specificity); PLR = 152.635 (97.1% sensitivity, 80.9% specificity); SII = 845 (94.7% sensitivity, 85.3% specificity); SIRI = 1045 (90.7% sensitivity, 93.3% specificity), and AISI = 137,532 (90.2% sensitivity, 96% specificity).

In addition, evaluation of the postoperative variables outlined a significantly higher incidence of postoperative AF (16.58% vs. 9.84%, P value = 0.006), AKI (12.68% vs. 8.23%, P value = 0.048), higher mortality rate (11.7% vs. 3.49%, P value < 0.001), a higher postoperative maximum lactate level (12.41 ± 2.03 vs. 10.47 ± 1.21, P value < 0.001), and VIS (24.64 ± 2.81 vs. 18.06 ± 1.44, P value < 0.001) and a significantly higher DO-MV (19.96 ± 6.82 vs. 15.35 ± 3.52, P value < 0.001) and LOS-ICU (4.77 ± 1.43 vs. 2.96 ± 0.84, P value < 0.001) in the VS group as compared to the non-VS group [Table 3A]. The two hematological indices which emerged as independent predictors of VS (SII and AISI) strongly positively correlated with the postoperative outcomes. The Pearson’s correlation coefficients were higher for AISI (R = 0.837 for correlation with DO-MV; R = 0.757 for correlation with LOS-ICU; R = 0.718 for correlation with VIS and R = 0.655 for correlation with lactate level) [Table 3B].

DISCUSSION

The findings of the index study regarding the VS risk factors are largely in agreement with the seminal meta-analysis in this research area by Dayan and colleagues.[29] Alongside the commonly implicated demographic, comorbid status, pharmacological and intraoperative surgical duration, the present study also discovered the role of the modifiable factors such as TWAG and PRBC transfusion in modulating the subsequent risk of developing VS [Table 2A and B]. With respect to the prognostic inflammatory hematological indices, we delineated the LIs and PLIs as important predictors of post-cardiotomy VS wherein the predictive
potential of SII and AISI was robust to multivariate analysis in our evaluation.

Talking of the VS risk predictive potential of hematological inflammatory indices, the findings of the study by Ahmed et al.[15] involving heart transplant recipients (a cohort highly predisposed to VS) deserve a mention. The retrospective study evaluated 70 patients undergoing a heart transplant with 25.7% developing vasoplegia postoperatively. Pre-transplant NLR emerged as an independent risk factor (OR 2.47) for developing VS with a mean NLR value of 6.72 among their patients manifesting VS.[15] Our study also derived an NLR cut-off value of 4.125 for predicting post-cardiotomy VS. While Ahmed

### Table 1: Patient characteristics and perioperative variables for VS and non-VS groups

| Variables                     | Non-VS | VS    | P     |
|-------------------------------|--------|-------|-------|
| n=840                         | n=205  |       |       |
| **Patient characteristics**   |        |       |       |
| Age (years)                   | 66.4±7.4 | 69.6±9.4 | <0.001 |
| Male sex                      | 574 (71.57) | 154 (75.12) | 0.311 |
| BMI (kg/m²)                   | 25.07±2.28 | 24.87±2.16 | 0.271 |
| BSA (m²)                      | 1.62±0.08 | 1.62±0.08 | 0.931 |
| Smoker                        | 421 (52.49) | 109 (53.17) | 0.862 |
| HTN                           | 556 (69.33) | 133 (64.88) | 0.221 |
| COPD                          | 41 (5.11) | 13 (6.34) | 0.486 |
| DM                            | 27 (28.3) | 78 (38.05) | 0.007 |
| Hyperlipidemia                | 424 (52.87) | 110 (53.66) | 0.840 |
| CAD                           | 110 (13.72) | 26 (12.68) | 0.699 |
| PVD                           | 138 (17.21) | 36 (17.56) | 0.905 |
| Dialysis-dependent renal failure | 27 (3.35) | 16 (7.75) | 0.055 |
| CRF                           | 86 (10.72) | 18 (8.78) | 0.415 |
| H/o stroke                    | 78 (9.73) | 20 (9.76) | 0.990 |
| Preop CHF                     | 195 (24.31) | 75 (36.59) | <0.001 |
| H/o MI                        | 109 (13.59) | 31 (15.09) | 0.489 |
| LVEF (%)                      | 55.4±7.67 | 50.2±9.34 | <0.001 |
| EuroSCORE II                  | 4.23±0.93 | 6.5±1.75 | <0.001 |
| **Type of surgery**           |        |       |       |
| Mitral valve Sx               | 322 (40.2) | 87 (41.95) | 0.649 |
| Aortic valve Sx               | 203 (25.4) | 56 (26.83) | 0.676 |
| Double valve Sx               | 57 (7.14) | 18 (8.29) | 0.574 |
| CABG                          | 183 (22.9) | 34 (16.58) | 0.058 |
| CABG+valve                    | 37 (4.61) | 12 (5.68) | 0.521 |
| Resternotomy                  | 52 (6.49) | 18 (8.16) | 0.397 |
| **Laboratory parameters**     |        |       |       |
| Hb (g/dL)                     | 12.6±0.36 | 11.9±0.69 | <0.001 |
| NLR                           | 3.4±0.95 | 5.3±1.04 | <0.001 |
| PLR                           | 120.5±37.5 | 191.6±31.9 | <0.001 |
| SII (/mm³)                    | 632.3±196.57 | 1105.5±232.13 | <0.001 |
| SIRI                          | 452.2±128.88 | 909.5±211.59 | <0.001 |
| AISI (mm³)                    | 83531.49±26430.28 | 187245.52±46516.96 | <0.001 |
| BUN (mg/dL)                   | 22.8±3.76 | 23.2±3.75 | 0.137 |
| Cr (mg/dL)                    | 0.9±0.22 | 0.9±0.22 | 0.568 |
| AST (U/L)                     | 68.1±9.23 | 67.9±8.53 | 0.649 |
| ALT (U/L)                     | 67.7±9.63 | 68.1±9.49 | 0.605 |
| **Intraoperative variables**  |        |       |       |
| DO-SX (min)                   | 90.2±7.98 | 311.1±52.32 | <0.001 |
| CPB time (min)                | 64.6±7.6 | 78.9±9.51 | <0.001 |
| ACC time (min)                | 49.6±6.33 | 64.2±9.23 | <0.001 |
| PRBC (units)                  | 2.5±0.62 | 3.1±0.75 | <0.001 |
| SVRI (dynes.s/cm²/m²)         | 2184.8±152.56 | 1114.0±239.12 | <0.001 |
| CI (L/min/m²)                 | 2.4±0.27 | 3.5±0.37 | <0.001 |
| TWAG (mg/dL)                  | 132.1±8.96 | 169.4±22.14 | <0.001 |

Data are presented as mean±SD and n (%); P<0.05 in bold are statistically significant Abbreviations: BMI: body mass index; BSA: body surface area; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HTN: hypertension; CAD: coronary artery disease; PVD: peripheral vascular disease; CRF: chronic renal failure; H/O STROKE/TIA: history of stroke/transient ischemic attack; Preop CHF: preoperative congestive heart failure; H/O MI: history of myocardial infarction; LVEF: left ventricular ejection fraction; EuroSCORE II: European System for Cardiac Operative Risk Evaluation; CABG: coronary artery bypass grafting; Hb: hemoglobin; NLR: neutrophil to lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; AISI: aggregate index of systemic inflammation; BUN: blood urea nitrogen; CR: creatinine; AST: aspartate transaminase; ALT: alanine transaminase; DO-SX: duration of surgery; CPB time: cardiopulmonary bypass time; ACC time: aortic cross clamp time; PRBC: packed red blood cell; SVRI: systemic vascular resistance index; CI: cardiac index; TWAG: time-weighted average blood glucose

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Table 2A: Univariate association of variables with the development of vasoplegia

| Variables                      | Odds Ratio | 95% CI for Odds Ratio Lower | 95% CI for Odds Ratio Upper | P    |
|--------------------------------|------------|-----------------------------|-----------------------------|------|
| Patient characteristics        |            |                             |                             |      |
| Age                            | 1.051      | 1.031                       | 1.072                       | <0.001|
| Sex                            | 1.199      | 0.844                       | 1.705                       | 0.311 |
| BMI                            | 0.961      | 0.897                       | 1.029                       | 0.253 |
| BSA                            | 0.871      | 0.134                       | 5.668                       | 0.885 |
| HTN                            | 0.817      | 0.591                       | 1.130                       | 0.222 |
| COPD                           | 1.257      | 0.660                       | 2.392                       | 0.487 |
| SMOKER                         | 1.028      | 0.756                       | 1.397                       | 0.862 |
| DM                             | 1.556      | 1.128                       | 2.145                       | 0.007 |
| Hyperlipidemia                 | 1.032      | 0.759                       | 1.404                       | 0.840 |
| CAD                            | 0.914      | 0.578                       | 1.444                       | 0.699 |
| PVD                            | 1.025      | 0.684                       | 1.535                       | 0.905 |
| Dialysis-Dependent Renal failure | 1.80      | 1.29                        | 2.52                        | 0.005 |
| Preoperative medication intake  |            |                             |                             |      |
| Nitrates                       | 0.854      | 0.545                       | 1.337                       | 0.490 |
| B-Blockers                     | 0.875      | 0.860                       | 0.890                       | 0.029 |
| DHPCCB                         | 0.950      | 0.638                       | 1.413                       | 0.798 |
| NDHPCCB                        | 0.987      | 0.608                       | 1.605                       | 0.959 |
| ACEI/ARB                       | 0.958      | 0.702                       | 1.307                       | 0.785 |
| Heparin                        | 0.865      | 0.556                       | 1.346                       | 0.520 |
| Statin                         | 1.124      | 0.823                       | 1.536                       | 0.462 |
| Hydralazine                    | 0.990      | 0.662                       | 1.481                       | 0.961 |
| Steroids                       | 1.182      | 0.672                       | 2.079                       | 0.562 |
| Digoxin                        | 1.047      | 0.590                       | 1.859                       | 0.876 |
| Diuretics                      | 1.342      | 0.815                       | 2.211                       | 0.247 |
| Aspirin                        | 5.808      | 4.179                       | 8.070                       | 0.568 |
| LT4                            | 1.307      | 0.750                       | 2.279                       | 0.345 |
| Type of surgery                |            |                             |                             |      |
| Mitrval valve Sx               | 0.65       | 0.35                        | 1.21                        | 0.649 |
| Aortic valve Sx                | 0.98       | 0.52                        | 1.83                        | 0.676 |
| Double valve Sx                | 0.89       | 0.67                        | 1.17                        | 0.574 |
| CABG                           | 0.653      | 0.519                       | 0.822                       | 0.049 |
| CABG + valve                   | 1.10       | 0.78                        | 1.54                        | 0.66  |
| Resternotomy                   | 1.034      | 0.646                       | 1.654                       | 0.397 |
| Intraoperative variables       |            |                             |                             |      |
| DO-SX                          | 1.325      | 0.992                       | 2.090                       | 0.985 |
| CPB time                       | 1.151      | 1.131                       | 1.172                       | <0.001|
| ACC time                       | 1.214      | 1.185                       | 1.245                       | <0.001|
| PRBC                           | 4.183      | 3.248                       | 5.386                       | <0.001|
| TWBG                           | 1.124      | 1.108                       | 1.141                       | <0.001|
| Laboratory parameters          |            |                             |                             |      |
| Hb                             | 0.098      | 0.070                       | 0.137                       | 0.089 |
| NLR                            | 5.359      | 4.299                       | 6.682                       | <0.001|
| PLR                            | 1.050      | 1.043                       | 1.057                       | <0.001|
| SII                            | 1.009      | 1.008                       | 1.010                       | <0.001|
| SIRI                           | 1.013      | 1.012                       | 1.015                       | <0.001|
| AISI                           | 1.000      | 1.000                       | 1.000                       | <0.001|

Table 2A: Contd...

| Variables                      | Odds Ratio | 95% CI for Odds Ratio Lower | 95% CI for Odds Ratio Upper | P  |
|--------------------------------|------------|-----------------------------|-----------------------------|----|
| BUN                            | 1.032      | 0.990                       | 1.075                       | 0.134|
| Cr                             | 1.224      | 0.616                       | 2.430                       | 0.564|
| AST                            | 0.997      | 0.980                       | 1.014                       | 0.710|
| ALT                            | 1.004      | 0.988                       | 1.020                       | 0.637|

P-values in bold are statistically significant. Abbreviations: BMI: body mass index; BSA: body surface area; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HTN: hypertension; CAD: coronary artery disease; PVD: peripheral vascular disease; CRF: chronic renal failure; H/D STROKE/TIA: history of stroke/transient ischemic attack; Preop CHF: preoperative congestive heart failure; H/O MI: history of myocardial infarction; LVEF: left ventricular ejection fraction; Euro SCORE II: European System for Cardiac Operative Risk Evaluation; DHP CCB: dihydropyridine calcium channel blocker; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; LT4: levothyroxine; CABG: coronary artery bypass grafting; Hb: hemoglobin; NLR: neutrophil to lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SII cut-off value of 1,045 × 10^3 /mm^3; AISI: aggregate index of systemic inflammation; BUN: blood urea nitrogen; Cr: creatinine; AST: aspartate transaminase; ALT: alanine transaminase; DO-SX: duration of surgery, CPB time: cardiopulmonary bypass time; ACC time: aortic cross clamp time; PRBC: packed red blood cell; SVRI: systemic vascular resistance index; CI: cardiac index; TWBG: time-weighted average blood glucose

Magoon, et al. attributed the high NLR value in the VS group to a pre-existing low-grade inflammation inextricably linked to a pre-transplant heart failure setting, the index study also discovered preoperative CHF as an independent predictor of developing VS. Moreover, the patients with preoperative CHF in the present study also had a significantly higher mean preoperative AISI and SII values as compared to the rest of the patient cohort (mean AISI [CHF: 155,321.89, non-CHF: 76,241.72], P value < 0.001; mean SII [CHF: 987.25 × 10^3 /mm^3, non-CHF: 620.48 × 10^3 /mm^3], P value = 0.002).

At the same time, the literature is accumulating on the role of LIs and PLIs in predicting poor outcome following adult cardiac surgery. Herein, Rosalia et al. in their retrospective analysis of a large adult cardiac surgical cohort revealed the association of an elevated SII with postoperative outcomes albeit failed to account for the extent of poor outcome related to the development of VS. Our description of the VS risk prediction potential of SII and AISI highlights vasoplegia as an important harbinger of the prognostic links of these novel LIs and PLIs with inflammation being the common denominator. Nevertheless, our VS predictive SII cut-off value of 1,045 × 10^3 /mm^3 was higher than the Dey et al. and Rosalia et al. outcome predictive SII cut-off of 878.057 × 10^3 /mm^3 and 647, respectively.

The interaction of the corpuscular lineages with each other and the endothelium as the perpetrators of an ongoing inflammatory process continue to captivate
Table 2B: Multivariate analysis of the significant variables for the development of vasoplegia

| Variables          | Odds Ratio | 95% CI for Odds Ratio | P     |
|--------------------|------------|------------------------|-------|
| Age                | 1.009      | 0.959 - 1.062          | 0.722 |
| DM                 | 0.522      | 0.198 - 1.381          | 0.190 |
| EuroSCORE II       | 3.236      | 2.345 - 4.468          | <0.001|
| Preop CHF          | 1.04       | 1.02 - 1.06            | 0.011 |
| β-Blocker          | 0.893      | 0.803 - 0.987          | 0.026 |
| NLR                | 0.974      | 0.279 - 3.468          | 0.678 |
| PLR                | 1.006      | 0.986 - 1.026          | 0.557 |
| SII                | 1.09       | 1.02 - 1.18            | 0.001 |
| SIRI               | 1.000      | 0.993 - 1.007          | 0.933 |
| AISI               | 1.110      | 1.05 - 1.17            | <0.001|
| PRBC               | 4.747      | 2.443 - 9.223          | <0.001|
| ACC time           | 1.003      | 1.001 - 1.005          | 0.004 |
| CPB time           | 1.016      | 1.004 - 1.028          | 0.001 |

P<0.05 in bold are statistically significant. Abbreviations: ACC time: aortic cross clamp time; AISI: aggregate index of systemic inflammation; CPB time: cardiopulmonary bypass; DM: diabetes mellitus; EuroSCORE II: European System for Cardiac Operative Risk Evaluation II; NLR: neutrophil to lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PRBC: packed red blood cell; Preop CHF: preoperative congestive heart failure; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index.

Table 3A: Comparison of postoperative outcomes among the VS and non-VS groups

| Postoperative outcomes | VS     | Non-VS | P     |
|------------------------|--------|--------|-------|
| AF                     | 34 (16.58) | 79 (9.84) | 0.006 |
| AKI                    | 26 (12.68) | 66 (8.23) | 0.048 |
| Mortality              | 24 (11.7)  | 66 (8.23) | 0.048 |
| Lactate                | 12.4±2.03 | 10.47±1.21 | <0.001|
| VIS                    | 24.64±2.81 | 18.06±1.44 | <0.001|
| DO-MV                  | 19.96±6.82 | 15.35±3.52 | <0.001|
| LOS-ICU                | 4.77±1.43 | 2.96±0.84 | <0.001|

P<0.005 in bold are statistically significant. Abbreviations. AKI: acute kidney injury; DO-MV: duration of mechanical ventilation; LOS-ICU: length of stay in Intensive Care Unit; AF: atrial fibrillation; VIS: vasoactive-inotropic score.

Figure 2: Receiver operating characteristic (ROC) curves of LIs and PLIs for predicting postoperative vasoplegia. (a) The comparison of the ROC curves of the LIs (NLR and SIRI) with respect to the area under the curve (AUC). (b) The comparison of the ROC curves of the PLIs (PLR, SII, and AISI) with respect to the area under the curve (AUC). The cut-off values, sensitivity, specificity, AUC, and 95% confidence intervals (CI) of the different hematological indices are displayed in the lower right corner of the respective figures.

To the best of our knowledge, the present study is a maiden endeavor at analyzing the vasoplegia predictive performance of LIs and PLIs in a cardiac surgical subset. First, the inclusion of a large sample size from a single tertiary cardiac care center constitutes a major strength of the study. Future prospective evaluation is warranted to extrapolate the findings to the highly predisposed settings like mechanical circulatory assistance. Moreover, the heterogeneity of the VS definition employed in the literature presents a unique impediment to the sound extrapolation of a novel finding in this dynamic research area. Second, the categorization of the patients as vasoplegic on the persistence of the VS-defining hemodynamic criteria in the ICU, is a positive study attribute, particularly when an isolated immediate post-CPB evaluation is precluded by a weaning-associated dynamic preload and pharmacological alterations. Third, the cost-effective readily available hematological VS risk prediction can aid in the VS risk stratification and clinical decision-making. However, the prognostic assessment in...
Table 3B: Correlation study of SII and AISI with lactate, VIS, DO-MV, and LOS-ICU

| Postoperative outcomes | SII | AISI |
|------------------------|-----|------|
|                        | R   | P    | R   | P    |
| DO-MV                  | 0.746 | <0.001 | 0.837 | <0.001 |
| LOS-ICU                | 0.581 | <0.001 | 0.757 | <0.001 |
| VIS                    | 0.637 | <0.001 | 0.718 | <0.001 |
| Lactate                | 0.576 | <0.001 | 0.655 | <0.001 |

P-values < 0.05 in bold are statistically significant. Abbreviations: AISI: aggregate index of systemic inflammation; DO-MV: duration of mechanical ventilation; LOS-ICU: length of stay in intensive care unit; SII: systemic immune-inflammation index; VIS: vasoactive-inotropic score.

the present retrospective analysis could have been limited by the residual confounding.[29]

CONCLUSION

Preoperative PLIs can potentially stratify the adult cardiac surgical subset with regards to their risk of developing post-cardiotomy VS. The aforementioned parsimonious risk stratification reemphasizes the inflammatory association of this intriguing hemodynamic syndrome.

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Conflicts of interest

There are no conflicts of interest.

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