Original Article

Leucoglycemic index predicts post-operative vasopressor-inotropic requirement after adult cardiac surgery (LEUCOGLYPTICS): A retrospective single-center study

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Abstract

Background and Aims: Cardiac surgery often necessitates considerable post-operative vasoactive-inotropic support. Given an encouraging literature on the prognostic potential of leucoglycemic index (LGI) [serum glucose (mg/dl) × total leucocytes count (cells/mm^3)/1000], we aimed to evaluate whether intensive care unit (ICU)-admission LGI can predict post-operative vasopressor-inotropic requirements following cardiac surgery on cardio-pulmonary bypass (CPB).

Material and Methods: The data of patients undergoing cardiac surgery at our tertiary care center between January 2015 and December 2020 was retrospectively reviewed. The vasopressor-inotropic requirement was estimated using the VIS (vasoactive-inotropic score) values over the first post-operative 72 hrs. Subsequently, VIS_i (indexed VIS) was computed as $maxVIS_{[0\text{-}24hrs]} + maxVIS_{[24\text{-}48hrs]} + 2 \times maxVIS_{[48\text{-}72hrs]}/10$), and the study participants were divided into h-VIS_i ($VIS_i \geq 3$) and l-VIS_i ($VIS_i < 3$).

Results: Out of 2138 patients, 479 (22.40%) patients categorized as h-VIS_i. On univariate analysis: LGI, age, European System for Cardiac Operative Risk Evaluation score (EuroSCORE II), left-ventricle ejection fraction, prior congestive heart failure (CHF), chronic renal failure, angiotensin-converting enzyme inhibitors, combined surgeries, CPB and aortic cross-clamp (ACC) duration, blood transfusion, and immediate post-operative glucose were significant h-VIS_i predictors. Subsequent to multi-variate analysis, the predictive performance of LGI (OR: 1.09; 95% CI: 1.03–1.14; $P = 0.002$) prior CHF (OR: 2.35; 95% CI: 1.44–3.82; $P = 0.001$), CPB time (OR: 1.08; 95% CI: 1.02–1.14; $P = 0.019$), ACC time (OR: 1.03; 95% CI: 1.02–1.04; $P = 0.008$), and EuroSCORE II (OR: 1.14; 95% CI: 1.06–1.21; $P < 0.001$) remained significant. With 1484.75 emerging as the h-VIS_i predictive cut-off, patients with LGI ≥ 1484.75 also had a higher incidence of vasoplegia, low-cardiac output syndrome, new-onset atrial fibrillation, acute kidney injury, and mortality. LGI additionally exhibited a significant positive correlation with duration of mechanical ventilation and ICU stay (R = 0.495 and 0.564, P value < 0.001).

Conclusion: An elevated LGI of greater than 1484.75 independently predicted a VISindex ≥3 following adult cardiac surgery on CPB.

Keywords: Cardiac surgery, cardio-pulmonary bypass, critical care, glycemic index, leucocytes, low cardiac output, post-operative period, vasopressor agents

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Introduction

Vasopressor-inotropic support forms the mainstay of hemodynamic management in critically ill and post-operative patients following high-risk surgery.[1,2] With this said, a topical French and EuRopean Outcome Registry in Intensive Care Unit (FROG-ICU)-based study suggests an elevated morbidity–mortality in a critically ill patient subset with an escalated vasopressor-inotropic requirement.[3] The latter assumes an enhanced importance in cardiac surgical patients, often necessitating a considerable peri-operative vasoactive-inotropic support.

Specific to post-cardiac surgical outcomes, the product of immediate post-operative total leucocyte count (TLC) and serum glucose level or the leucoglycemic index (LGI) has recently been associated with an accentuated risk of post-operative mortality by Seoane *et al.*[4] Albeit noteworthy from a prognostic perspective, the Seoane *et al.* analysis was limited by the lack of account for the concurrent post-operative vasopressor-inotropic requirements.[4] This becomes more relevant amid their proposition of an elevated LGI as a harbinger of peri-operative inflammation alongside the comprehension that inflammation in turn predisposes post-operative patients to heightened vasopressor-inotropic requirements (owing to inflammatory myocardial depression and/or vascular hypo-responsiveness).[5,6]

Simultaneously, there is a growing emphasis on the need of an objective quantification of post-operative hemodynamic support. In this context, the vasoactive-inotropic score (VIS) was introduced by Gaies *et al.*,[7] VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) +100 × epinephrine dose (μg/kg/min) +100 × norepinephrine dose (μg/kg/min) +10,000 × vasopressin dose (U/kg/min) +10 × milrinone dose (μg/kg/min). However, considering that VIS provides only a snapshot assessment for a relatively dynamic parameter, Crow *et al.* added a component of duration to account for the variability of vasopressor-inotropic requirement across the post-operative course.[8] They formulated an indexed VIS as follows: VISindex = $VIS_{0\text{-}24h}$ (maximum) + $VIS_{24\text{-}48h}$ (maximum) +2 × $VIS_{48\text{-}72h}$ (maximum). The value obtained was hence depicted as an integer after being divided by 10. A VISindex ≥ 3 was subsequently recognized to have a higher predictive value for the risk of poor composite outcomes after infant cardiac surgery than the maximum VIS alone.[8]

We sought to retrospectively evaluate if an elevated LGI could predict a high post-operative VISindex ≥3 or h-VIS_i after elective cardiac surgery on cardio-pulmonary bypass (CPB) as our primary objective. As secondary objectives, we aimed to study the association of LGI with post-operative outcomes such as acute kidney injury (AKI), new-onset atrial fibrillation (NOAF), cerebro-vascular accident (CVA), sepsis, mediastinitis and mortality, and correlation with duration of mechanical ventilation (DO-MV) and length of stay in ICU and the hospital (LOS-ICU and LOS-H).

Material and Methods

A retrospective review of patients aged above 18 years who underwent elective cardiac surgery on cardiopulmonary bypass (CPB) at our tertiary cardiac care center from 2015 to 2020 was performed after getting a formal approval from the institutional ethics committee (IEC/ABVIMS/RMLH/686) with a waiver of informed consent requirements. The presence of an infectious, systemic inflammatory or hematological disease that could alter the leucocyte count, chronic steroid therapy, pre-operative use of inotropes or mechanical circulatory assistance, and emergency cardiac surgical procedures or heart transplantation constituted the exclusion criteria of the study. The patients who required peri-operative use of an intra-aortic balloon pump (IABP), extra-corporeal membrane oxygenation (ECMO), or deep hypothermic circulatory arrest (DHCA) during the procedure were also excluded from the analysis.

The demographic data such as age, sex, body mass index (BMI in kg/m^2), smoking history, pre-existing co-morbidities, hypertension, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, history of prior myocardial infarction (MI), chronic renal failure (CRF) or CVA, congestive heart failure (CHF) and drug intake history of diuretics, and angiotensin-converting enzyme inhibitors (ACEIs) or β-blockers were collected from the medical record archives. Using the electronic patient database, pre-operative laboratory parameters such as hemoglobin (Hb), TLC, differential leucocyte count (DLC), blood urea nitrogen, serum creatinine, aspartate transaminase, and alanine aminotransferase values were noted. Furthermore, the pre-operative left-ventricle ejection fraction (LVEF) was recorded.

A standard peri-operative anesthetic and hemodynamic management was followed for all the patients in accordance with the institutional protocol. All patients were ventilated intra-operatively using volume-controlled ventilation tailored to result in an end-tidal carbon dioxide level of 30–35 mmHg with a conventional mixture of oxygen and air (a fractional inspired oxygen concentration of 0.6) and a peak end expiratory pressure of 5 cm of H_2O. With a heparin dose of 4mg/kg, the patient was heparinized targeting an activated

clotting time >420 seconds. Subsequently, aortic and venous cannulation was performed to allow placement of the aortic cross clamp (ACC) and infusion of cardioplegia (del Nido cardioplegia at 20 mL/kg) to induce cardioplegic arrest. The flow on CPB was managed with a goal of 65 mmHg perfusion pressure and a core body temperature of 28 to 32°C, that is, mild to moderate hypothermia.

The peri-operative glucose homeostasis was assessed and managed using an intravenous insulin regimen in order to maintain a blood glucose between 140 and 180 mg/dL. Packed red blood cells (PRBCs) were transfused as needed to preserve the hematocrit above 24%. The inotrope in the form of 5 μg/kg/min dobutamine was routinely initiated at the time of re-warming for all the patients. ACC was removed after de-airing alongside re-warming to a temperature ≥35°C. Consequently, ventilation was re-instituted, and patients were gradually weaned off CPB using inotropic and vasoactive support. Temporary epicardial pacing was employed if required. With regard to the hemodynamic support titration, an inotropic infusion of 0.05 μg/kg/min epinephrine was added to 5 μg/kg/min dobutamine in order to assist in maintaining a cardiac index (CI) >2 L/min/m^2. Vasopressors, such as norepinephrine/vasopressin, were resorted in case of a difficulty in achieving a mean arterial pressure (MAP) above 65mmHg despite CI augmentation.[9] Milrinone was employed in settings of echo-cardiographic diagnosis of significant right ventricular dysfunction and coexistent pulmonary artery hypertension. Inotropic-vasopressor management was aided by trans-esophageal echocardiograhy and/or minimally invasive CI evaluation (FloTrac™, Edwards Lifesciences, Irvine, CA, USA) with the aim of maintenance of biventricular performance and hemodynamic stability. Once hemodynamic stability was ascertained, heparin was reversed using intravenous infusion of protamine (dose equivalent to administered heparin). Hb was maintained above 10 g/dL using transfusion of blood products. Steel wires were used for sternal closure followed by layered skin sutures. Intra-operative parameters such as the number of PRBCs transfused and durations of surgery, CPB, and ACC were recorded.

The patients were shifted to the ICU, and blood samples were sent for hematological indices and post-operative serum glucose values. On ICU admission, LGI was computed by dividing the product of serum glucose and TLC by 1000 and expressed in mg/dL.mm^3.[4] The maximum serum lactate values within the 72-hour post-operative period was recorded from the arterial blood gas analysis. Low cardiac output syndrome (LCOS) was defined as CI <2.0 L/min/m^2 with systolic blood pressure <90 mmHg, in conjunction with signs of tissue hypo-perfusion in the absence of hypovolemia.[9] Vasoplegia was defined as a combination of MAP <65 mmHg and CI ≥2.5 L/min/m^2, requiring vasopressor support.[10] AKI was defined based on the acute kidney injury network (AKIN) criteria as an elevation of serum creatinine ≥1.5 times the baseline level within 48 hours.[11] At the same time, other post-operative outcomes such as incidence of NOAF, CVA, sepsis, mediastinitis, and mortality were noted. With all the study participants being extubated and discharged from ICU or the hospital in accordance with the standard institutional protocol, the DO-MV, LOS-ICU, and LOS-H were also recorded.

VIS_i computation and group categorization: The post-operative vasopressor-inotropic requirement of the study participants was retrospectively obtained from the post-operative ICU charts (with hourly documentation of vasopressor-inotropic doses). The former was used to calculate the corresponding VIS values. The VISindex for the first 3 post-operative days was hence estimated employing the maximum VIS values of the consecutive 24 h post-operative epochs, as outlined in the formula described above, and the study patients were divided into two groups: h-VIS_i (VISindex ≥3) and l-VIS_i (VISindex <3).

Statistical analysis

The categorical variables of the h-VIS_i and l-VIS_i groups were translated as numerical values and percentages and compared using the Chi-square test. The continuous variables were denoted as mean ± standard deviation and evaluated using the unpaired *t*-test. For estimating the correlation among variables, the Spearman correlation analysis was employed. The multi-variate analysis was performed with binary logistic regression. The non-parametric receiver operating characteristic (ROC) curve analysis was used to elaborate the accuracy of all variables in predicting an elevated VISindex, as demonstrated by their respective area under the curve (AUC). The optimal cut-off value of LGI associated with VISindex was determined using the Youden index (J = sensitivity + specificity − 1) of the ROC curve. The sensitivity, specificity, and predictive values were then reported employing the derived cut-off. The statistical software SPSS version 20 (IBM Corp, Armonk, NY, USA) was applied for the analysis. A confidence interval of 95% with 80% power of study, with a P value < 0.05 was considered significant.

Results

During the period from January 2015 to December 2020, a total of 2659 adult patients underwent elective cardiac surgery on CPB including single-valve replacements, double-valve replacements, isolated coronary artery bypass graft (CABG),

or combined CABG and valve replacement surgery. The patient enrolment methodology is depicted as a flowchart in Figure 1 wherein 2138 were patients finally enrolled in the study. Of these, 763 were females (35.68%) and 1375 were males (64.31%). A total of 479 patients (22.40%) had high post-operative vasopressor-inotropic requirements (VISindex ≥3), classifying as the h-VIS_i group. The demographic and peri-operative variables of the h-VIS_i and l-VIS_i (VISindex <3) group patients are illustrated in Table 1. The patients in the h-VIS_i group experienced a longer DO-MV, LOS-ICU, and LOS-H, as compared to those in the l-VIS_i group [Table 1].

The following parameters emerged as significant predictors of an elevated VISindex ≥3 on univariate analysis: advanced age, lower pre-operative LVEF, pre-operative use of ACEIs, EuroSCORE II, and CPB and ACC duration. Patients with pre-existing co-morbidities such as CRF and CHF and patients who underwent combined surgeries rather than isolated procedures were also associated with VISindex ≥3. The number of PRBC units transfused intra-operatively and ICU admission LGI were the additional risk predictors on the univariate analysis. Remarkably, LGI was found to be independently associated with post-operative VISindex ≥3 (multi-variate logistic analysis; OR: 1.09; 95% CI: 1.03–1.14; *P* value = 0.002). Other significant variables discovered following multi-variate analysis include pre-existing CHF (OR: 2.35; 95%CI: 1.44–3.82; *P* value = 0.001), EuroSCORE II (OR: 1.14; 95% CI: 1.06–1.21; *P* value < 0.001), duration of CPB (OR: 1.08; 95% CI: 1.02–1.14; *P* value = 0.019), and duration of ACC (OR: 1.03; 95%CI: 1.02–1.04; *P* value = 0.008), as outlined in Table 2.

Based on the ROC-curve analysis, the cut-off LGI value of 1484.75 was found to best differentiate the h-VIS_i patients from the l-VIS_i patients with an AUC = 0.781, 77.81% sensitivity, and 78.30% specificity [Figure 2]. Post-operative AKI, LCOS, vasoplegia, NOAF, and mortality also transpired with an increased frequency in the patients who had an on-ICU admission LGI greater than the above-mentioned threshold [Table 3]. Although the LGI values positively correlated with DO-MV and LOS-ICU (Spearman correlation coefficient R = 0.495 and 0.564, *P* < 0.001) [Figure 3], the parameter did not correlate with LOS-H (R = 0.007, *P* = 0.758).

Discussion

An ICU-admission LGI ≥1484.75 emerging as an independent predictor of elevated post-operative vasopressor-inotropic requirement constitutes the principal finding of our study. The basis of this elevated vasopressor-inotropic requirement with enhanced LGI is nested in the observation of an accentuated incidence of LCOS and vasoplegia in patients with LGI ≥1484.75. The other risk factors associated with VISindex ≥3 were in congruence with those entailing a higher eventual risk of LCOS or vasoplegia in general.[12,13]

Vasopressors and inotropes, although integral to hemodynamic management, have been linked to unfavorable outcomes

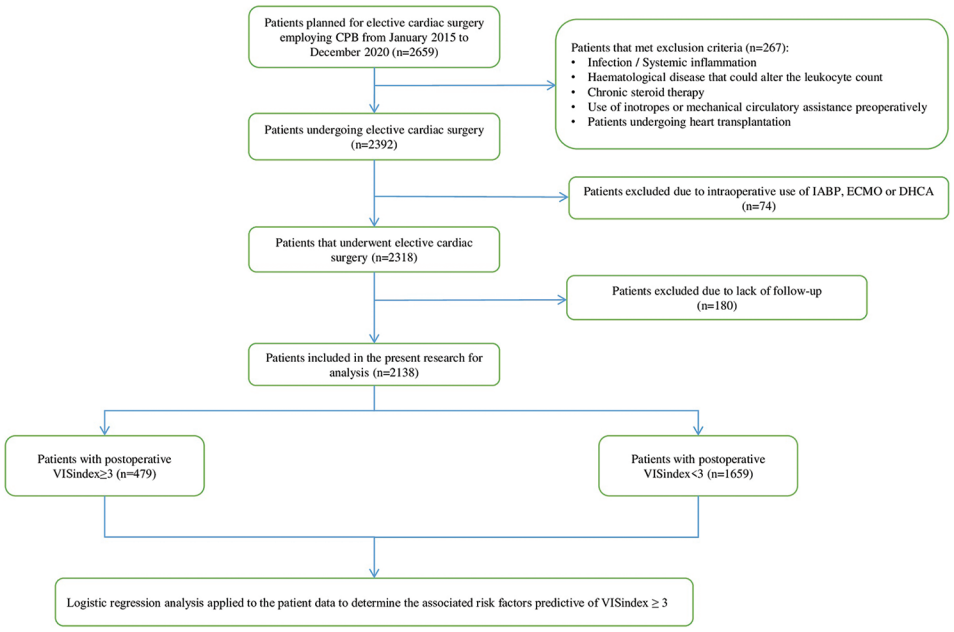

Figure 1: Patient enrolment methodology depicted as a flowchart model

at higher doses.[14] Koponen *et al.*[15] conducted a large single-center retrospective analysis outlining the merit of VIS in predicting composite poor outcomes and 1-year mortality post-cardiac surgery. These findings align with the results from a prospective cohort study conducted by Baysal *et al.*[16] highlighting the importance of VIS to predict combined morbidity–mortality following elective on-pump CABG. However, regarding the comprehensive quantification of post-operative vasopressor-inotropic requirement, VISindex has been shown to have improved sensitivity over VIS for prognosticating poor outcomes, as highlighted by Crow *et al.*[8] Thus, drawing on our research finding of the VISindex predictive potential of LGI, it can assist in stratification of the degree of hemodynamic support requirement in the cardiac surgical subset.

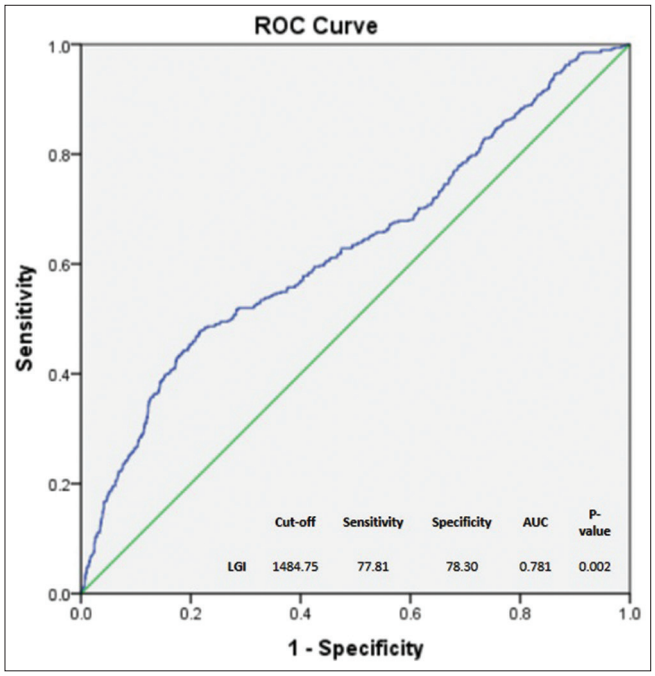

Figure 2: VISindex ≥3 predictive potential of LGI assessed in context of AUC under the ROC curve delineating the highest AUC of 0.781. The VISindex-predictive cut-off value of LGI has been presented in the lower part of the figure. AUC, area under the curve; LGI, leucoglycemic index; ROC, receiver operating characteristic

Beyond vasopressor-inotropic requirements, an elevated LGI was additionally found to be associated with a higher incidence of AKI, LCOS, vasoplegia, new onset AF, and mortality in our study. This is corroborated by the findings of Seoane *et al.*[4] that demonstrate such a prognostic value of LGI in patients undergoing CABG surgery. However, Seoane *et al.* project association of LGI and heightened incidence of LCOS without presenting the contextual account of the vasopressor-inotropic support or more importantly the component of vascular hypo-responsiveness.[4] At the same time, LGI correlated with DO-MV and LOS-ICU in our analysis.

The novel LGI has been evaluated in both operative and non-operative scenarios.[4,17] León-Aliz *et al.*,[18] in their evaluation of the prognostic significance of LGI in patients with ST-elevation MI, observed a poor composite outcome predictive LGI cut-off of 1.158 (1158 after adjusting for the difference in units by a factor of 10^3). This is in contrast to a substantially higher mortality predictive LGI cut-off value of 2000, as outlined by Seoane *et al.*[4] This difference can be attributed to the peri-operative stress serving as a pivotal impetus for pro-inflammatory milieu with CPB-associated systemic inflammation, compounding the matter furthermore.[19,20] Nevertheless, our VISindex predictive cut-off of 1484.75 stands lower than the aforementioned cut-off shown by Seoane *et al.*,[4] plausibly owing to a different primary outcome under evaluation.

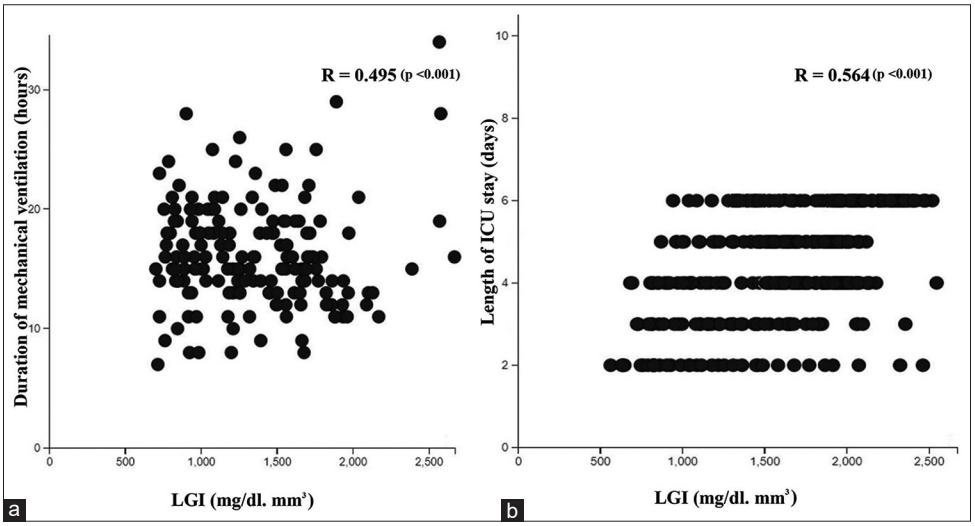

Figure 3: Scatterplot diagram demonstrating the correlation between LGI and DOMV (a) and between LGI and LOS-ICU (b)

Table 1: Demographic and peri-operative parameters illustrating the comparison between the h-VIS$_i$ and l-VIS$_i$ groups

Parameters	h-VIS$_i$ Group (n=479)	l-VIS$_i$ Group (n=1659)	P
Demographic Parameters			
Age (years)	46.80±13.07	44.88±11.89	0.007
Male gender	301 (62.84)	1074 (64.74)	0.445
BMI (kg/m^2)	24.21±5.51	23.71±5.66	0.115
Smoking	178 (37.16)	569 (34.30)	0.247
Hypertension	174 (36.33)	585 (35.26)	0.668
Hyperlipidemia	229 (47.81)	768 (46.29)	0.558
Diabetes mellitus	205 (42.80)	658 (39.66)	0.218
COPD	25 (5.22)	72 (4.34)	0.415
Coronary artery disease	74 (15.45)	214 (12.90)	0.150
Pre-operative CHF	37 (7.72)	57 (3.44)	<0.001
Pre-operative CRF	29 (6.05)	58 (3.50)	0.013
Prior MI	26 (23.85)	167 (28.89)	0.283
Prior Stroke	30 (6.26)	83 (5.00)	0.278
LVEF (%)	48.63±8.67	51.10±10.05	0.019
EuroSCORE II	5.18±1.83	4.53±1.05	<0.001
ACE inhibitor use	97 (20.25)	272 (16.40)	0.049
Diuretic use	67 (13.99)	249 (15.01)	0.579
Beta blocker use	130 (27.14)	484 (29.17)	0.481
Laboratory Parameters			
Hb (g/dL)	12.72±1.78	11.84±1.76	0.148
Pre-operative TLC (cells/mm^3)	7359±2063	7446±2023	0.390
Pre-operative ANC (cells/mm^3)	5205±1444	5261±1421	0.412
Pre-operative ALC (cells/mm^3)	3252±887	1813±508	0.315
Serum creatinine (mg/dL)	0.66±0.35	0.64±0.34	0.368
BUN (mg/dL)	15.57±5.08	15.10±5.48	0.083
ALT (IU/L)	35.60±9.03	34.88±8.98	0.122
AST (IU/L)	70.62±17.41	69.94±17.99	0.507
Operative parameters			
Single-valve replacement surgeries	269 (56.16)	1007 (60.70)	0.062
Isolated CABG surgeries	36 (7.52)	153 (9.22)	0.246
Dual-valve replacement surgeries	81 (16.91)	341 (20.55)	0.078
Combined surgeries	86 (17.95)	165 (9.95)	<0.001
Duration of surgery (minutes)	252.13±33.37	249.18±29.48	0.274
Duration of CPB (minutes)	75.81±9.14	72.68±11.18	<0.001
Duration of ACC (minutes)	49.89±9.21	46.72±11.11	<0.001
PRBC transfused	1.58±1.03	1.24±1.08	0.002
ICU-admission parameters			
Post-operative blood glucose (mg/dL)	166.87±41.13	161.27±32.75	0.023
Post-operative TLC (cells/mm^3)	7657±2301	7460±2080	0.137
LGI (mg/dL.mm^3)	1422.50±536.72	1192.16±401.52	<0.001
Post-operative Outcomes			
Post-operative serum lactate* (mmol/L)	6.58±3.85	4.76±3.44	<0.001
DO-MV (hours)	19.95±7.36	14.04±2.63	<0.001
LOS-ICU (days)	4.51±1.13	3.01±0.84	<0.001
LOS-H (days)	8.66±1.99	6.06±1.69	<0.001
NOAF	30 (6.26)	31 (1.87)	<0.001
AKI	14 (2.92)	24 (1.45)	0.031
Mortality	33 (6.89)	58 (3.49)	0.001

*Data are presented as mean±standard deviation or number (%). P<0.05 are italicized. *Maximum serum lactate in the 72-hour post-operative period. ACC: aortic cross clamp, ACE: angiotensin-converting enzyme, AKI: acute kidney injury, ALC: absolute lymphocyte count, ALT: alanine aminotransferase, ANC: absolute neutrophil count, AST: aspartate transaminase, BMI: body mass index, BUN: blood urea nitrogen, CABG: coronary artery bypass graft, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, CPB: cardio-pulmonary bypass, CRF: chronic renal failure, DO-MV: duration of mechanical ventilation, EuroSCORE II: European system for cardiac operative risk evaluation II, Hb: hemoglobin, LGI: leucoglycemic index; LOS-H: length of stay in the hospital, LOS-ICU: length of stay in ICU, LVEF: left ventricular ejection fraction, MI: myocardial infarction, NOAF: new onset atrial fibrillation, PRBC: packed red blood cells, TLC: total leukocyte count.*

Table 2: Univariate and multi-variate regression analysis for predictive risk factors associated with VISindex ≥3

Parameter	Univariate Analysis			Multi-variate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.01	1.01-1.02	0.007	1.01	0.93-1.11	0.096
LVEF	0.96	0.95-0.97	0.019	0.97	0.92-1.04	0.085
Pre-operative CHF	2.35	1.54-3.61	<0.001	2.35	1.44-3.82	0.001
Pre-operative CRF	1.78	1.12-2.81	0.013	1.34	0.80-2.25	0.266
EuroSCORE II	1.13	1.06-1.20	<0.001	1.14	1.06-1.21	<0.001
Combined surgeries	1.98	1.49-2.63	<0.001	1.62	0.92-2.31	0.113
ACE Inhibitor use	1.30	1.00-1.68	0.049	1.48	0.68-2.29	0.364
Duration of CPB	1.03	1.02-1.04	<0.001	1.08	1.02-1.14	0.019
Duration of ACC	1.03	1.02-1.04	<0.001	1.03	1.02-1.04	0.008
PRBC transfused	1.33	1.21-1.47	0.002	1.20	0.91-1.50	0.501
Post-operative blood glucose	1.00	1.00-1.01	0.023	1.00	0.94-1.08	0.900
LGI	1.06	1.04-1.10	<0.001	1.09	1.03-1.14	0.002

P<0.05 are italicized. ACC: aortic cross clamp, ACE: angiotensin-converting enzyme, CHF: congestive heart failure, CI: confidence interval, CPB: cardio-pulmonary bypass, CRF: chronic renal failure, EuroSCORE-II: European system for cardiac operative risk evaluation II, LCOS: low cardiac output syndrome, LGI: leukoglycemic index, LVEF: left ventricular ejection fraction, OR: odds ratio, PRBC: packed red blood cell.

Table 3: Incidence of post-operative complications on stratifying patients as per the VISindex-predictive LGI cut-off

Parameter	LGI ≥1484.75 (*n*=589)	LGI <1484.75 (*n*=1549)	*P*
Vasoplegia	79 (13.41)	95 (6.13)	<0.001
NOAF	24 (4.07)	37 (2.39)	0.036
AKI	17 (2.89)	21 (1.36)	0.017
LCOS	49 (8.32)	81 (5.23)	0.008
Sepsis	19 (3.22)	60 (3.87)	0.478
Mediastinitis	23 (3.90)	77 (4.97)	0.225
Mortality	37 (6.28)	54 (3.48)	0.004
CVA	7 (1.19)	12 (0.77)	0.363

Data are presented as number (%). P<0.05 are italicized. AKI: acute kidney injury, CVA: cerebro-vascular accident, LCOS: low cardiac output syndrome, LGI: leukoglycemic index, NOAF: new onset atrial fibrillation.

The predictive value of LGI can be heralded by an augmented peri-operative inflammation following CPB.[19] Leucocytic elevation, as seen during inflammation, is exaggerated by concomitant hyperglycemia, thus underlining the merit of LGI in indicating a pro-inflammatory milieu.[20,21] Systemic inflammation, in turn, is associated with post-operative vascular hypo-responsiveness and myocardial depression, often culminating in vasoplegic syndrome and/or LCOS post-cardiotomy, respectively.[5,22] Similarly, hyperglycemia has also been associated with vasoplegia, possibly via enhanced inducible nitric oxide synthase production and subsequent nitric oxide synthesis by activation of protein kinase C-beta II.[23] Moreover, systemic inflammation and LCOS-vasoplegia-linked hypo-perfusion, in conjunction, predispose to morbid organ outcomes such as post-operative AKI.[24,25] Indeed, LGI was associated with a higher incidence of AKI in our study.

To the best of our knowledge, this is the first study investigating the potential links of LGI and vasopressor-inotropic requirements in a cohort of patients undergoing cardiac surgery employing CPB. The single-center patient cohort under evaluation was considerably large and exclusively composed of on-pump cases unlike pre-existing research studies including both on-pump and off-pump surgeries, likely to add a level of homogeneity from the peri-operative inflammatory purview.[4] Even within the context of studies concerning post-operative vasoactive support, our research endeavor remarkably employs a more reliable parameter, integral VISindex, which incorporates components of both dose and duration of hemodynamic support. This becomes all the more pertinent when there is a dearth of literature centralizing the focus on the aforementioned index of peri-operative importance.

The retrospective design forms a limitation in this study, making it inherently prone to residual confounding.[26] Being a single-center study, the research findings require external validation and prospective analysis on a larger scale in the future. Another limitation of this study is presented by the lack of generalizability owing to a plausible variability in vasopressor-inotropic support institution, anti-inflammatory strategies, and glycemic management protocols. Last, the lack of well-established pro-inflammatory markers such as the C-reactive protein and the measurements pertaining to vascular resistances in our study presents additional limitations.

Conclusion

LGI ≥1484.75 emerged as an independent predictor of a high integral VISindex following CPB and predicted poor outcomes such as AKI, NOAF, and overall mortality. Although the prospective validation of the predictive links is awaited, the index research findings endorse a potential role

of cost-effective, readily available, and novel pro-inflammatory markers such as the LGI in a peculiarly predisposed cardiac surgical setting.

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Conflicts of interest
There are no conflicts of interest.

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