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Original Article

Impact of Inflammation After Cardiac Surgery on 30-Day Mortality and Machine Learning Risk Prediction

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Objectives: To investigate the impact of systemic inflammatory response syndrome (SIRS) on 30-day mortality following cardiac surgery and develop a machine learning model to predict SIRS.

Design: Retrospective cohort study.

Setting: Single tertiary care hospital.

Participants: Patients who underwent elective or urgent cardiac surgery with cardiopulmonary bypass (CPB) from 2016 to 2020 (N = 1,908).

Interventions: Mixed cardiac surgery operations were performed on CPB. Data analysis was made of preoperative, intraoperative, and postoperative variables without direct interventions.

Measurements and Main Results: SIRS, defined using American College of Chest Physicians/Society of Critical Care Medicine parameters, was assessed on the first postoperative day. The primary outcome was 30-day mortality. SIRS incidence was 28.7%, with SIRS-positive patients showing higher 30-day mortality (12.2% *v* 1.5%, $p < 0.001$). A multivariate logistic model identified predictors of SIRS. Propensity score matching balanced 483 patient pairs. SIRS was associated with increased mortality (OR 2.77; 95% CI 1.40-5.47, $p = 0.003$). Machine learning models to predict SIRS were developed. The baseline risk model achieved an area under the curve of 0.77 ± 0.04 in cross-validation and 0.73 (95% CI 0.70-0.85) on the test set, while the procedure-adjusted risk model showed improved performance with an area under the curve of 0.81 ± 0.02 in cross-validation and 0.82 (95% CI 0.76-0.85) on the test set.

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Conclusions: SIRS is significantly associated with increased 30-day mortality following cardiac surgery. Machine learning models effectively predict SIRS, paving the way for future investigations on potential targeted interventions that may mitigate adverse outcomes.

Key Words: systemic inflammatory reaction syndrome; cardiac surgery; machine learning; risk prediction

INTRODUCTION

Contemporary cardiac surgery strives to correct structural heart diseases with the least impact on patient homeostasis. However, the primary challenges are traumatic surgical access and cardiopulmonary bypass (CPB). Human biology's response to these stimuli often results in a systemic inflammatory reaction (SIRS), especially after prolonged CPB. This response, part of innate immunity, involves molecular mediators, immune cells, and blood vessels to protect against pathogens and damage.[1] However, an excessive response is associated with worse outcomes.[2] No randomized controlled trials (RCTs) have shown a clear benefit in preventing surgically-induced inflammation with pharmacologic agents.[3-5] A key step in addressing SIRS is identifying patients likely to develop it postoperatively. We aimed to assess the impact of postoperative SIRS on 30-day mortality and develop a predictive model for SIRS using machine learning.

METHODS

Ethical Statement

The study was approved by the IRCCS Istituto Tumori Giovanni Paolo II–Bari Review Board (1431/CEL) with a waiver of informed consent.

We retrospectively evaluated patients who underwent elective or urgent cardiac surgery with CPB from June 2016 to June 2020 at a single hospital. Preoperative, intraoperative, and postoperative parameters were collected anonymously in the institutional database for quality control. Data reliability was ensured by the Centricity ICU information system (General Electric, Boston, MA), enabling continuous, real-time data collection. The primary endpoint was 30-day mortality. Additionally, we aimed to develop a predictive model for SIRS assessed 12 hours postsurgery (POD1). Routinely measured inflammatory biomarkers were investigated on POD1. Surgical, anesthesiologic, and perfusion setups were previously described.[2] Blood transfusion criteria were hemoglobin 7.5 mg/dL and SvO_2 <65%. Postoperative SIRS was defined using the American College of Chest Physicians/Society of Critical Care Medicine parameters[6]: (1) body temperature <36 °C or >38 °C, (2) heart rate >90 bpm, (3) respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg, and (4) white blood cell count <4,000/μL or >12,000/μL or >10% immature forms (bands). The preparation of the manuscript followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Statistical Analysis

Continuous data were reported as mean with standard deviation or median with interquartile range and compared using the t-test or Mann-Whitney statistic. Normality was checked with the Shapiro-Wilk test. Categorical variables were reported as frequency and percentage and evaluated with the χ^2 test. Regression analyses were conducted with backward elimination based on the Akaike information criterion. Regression results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs), with $p < 0.05$ considered significant. A multivariable logistic regression identified SIRS predictors. Participants were matched by propensity score within a caliper of the standard deviation of the linear predictor multiplied by 0.2,[7] omitting SIRS predictors. To better understand the relationship between SIRS and 30-day mortality, we used structural equation modeling (SEM), a technique that separates the direct effect of each predictor from the effect mediated through SIRS. In this context, SIRS acts as a mediator, meaning it partly explains how certain intraoperative factors influence mortality. SEM enables us to quantify these effects by calculating the average causal mediation effect, which represents the portion of the effect that passes through SIRS, and the average direct effect, which represents the direct impact of the predictor on mortality, independent of SIRS. Specifically, SEM included the following variables: intraoperative hemoglobin nadir, peak lactate, vasopressor support as predictors; SIRS on POD1 as mediator; 30-day mortality as the outcome. Despite SEM is meant as exploratory analysis and confounders are likely to exist, causal relationships were assumed between intraoperative factors, SIRS, and mortality. To enhance robustness, we used non-parametric bootstrapping with 1,000 simulations to estimate these effects.[8,9] A sensitivity analysis was conducted to assess the robustness of the mediation results to unmeasured confounding. Analyses were performed with RStudio and Python.

Predictive Models for SIRS

An exploratory analysis evaluated various predictive models for SIRS on POD1, showing random forest outperforming other models (Supplementary Table S1). The baseline risk model (BRM) development involved: (1) feature selection: identifying the top 10 preoperative variables predicting postoperative SIRS; (2) dataset division: training (70%), validation (15%), and test sets (15%); (3) addressing class imbalance with the synthetic minority over-sampling technique

(SMOTE); (4) min-max scaling; and (5) random forest hyperparameter optimization.

A procedure-adjusted risk model (PARM) was developed, incorporating 5 additional intraoperative variables to refine predictions. Model discrimination was evaluated using cross-validation (CV) and the area under the curve (AUC) with 95% CI, along with Recall and Precision. The DeLong method assessed differences in receiver operating characteristic curves. Calibration was performed via Platt scaling, with calibration curves plotted and quality assessed using the Hosmer-Lemeshow test with a chi-square statistic (10 groups, 8 degrees of freedom). SHapley Additive exPlanations analysis elucidated individual features' contributions to the best-performing model. Detailed information is available in the Supplementary Appendix. Development followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis Statement.[10]

RESULTS

A total of 1,908 patients were included in this analysis. Table 1 describes the population characteristics. Median age was 69 [62-75] years, and 1,311 (68.7%) were male. The median EuroSCORE II was 2.1% [1.2-4.1]. Seven hundred sixteen patients (37.5%) underwent isolated coronary artery bypass grafting (CABG)—673 (35.3%) had a single non-CABG procedure, 400 (21.0%) underwent 2 procedures, and 119 (6.2%) had 3 procedures. SIRS was present in 548 patients (28.7%) on POD1. Eighty-seven patients died within 30 days postoperatively, resulting in a 4.6% mortality rate.

Table 1 also compares preoperative characteristics of SIRS-positive and SIRS-negative patients. SIRS-positive patients were less frequently male (62.0% *v* 71.4%, $p < 0.001$) and had a higher EuroSCORE II (2.7% [1.5%-5.9%] *v* 2.0% [1.2%-3.4%], $p < 0.001$), and higher diabetes (25.5% *v* 19.1%, $p = 0.002$) and reintervention (10.8% *v* 6.5%, $p = 0.002$) rates. They had lower preoperative hemoglobin (12.9 [11.4-14.2] *v* 13.7 [12.4-14.6] g/dL, $p < 0.001$), higher leukocytosis (8.3 [6.8-10.0] *v* 6.9 [5.9-8.2] $\times 10^3/\mu L$, $p < 0.001$), neutrophils (5.6 [4.3-7.2] *v* 4.4 [3.5-5.3] $\times 10^3/\mu L$, $p < 0.001$), platelets (216 [166-260] *v* 191 [158-228] $\times 10^3/\mu L$, $p < 0.001$), and elevated C-reactive protein (CRP; 3.7 [0.7-13.2] *v* 1.8 [0.4-6.6] mg/dL, $p < 0.001$). They underwent more complex procedures with longer CPB and cross-clamp times: 91 [67-129] *v* 84 [64-113] min ($p < 0.001$) and 61 [42-88] *v* 57 [40-80] min ($p = 0.014$), respectively. Serum lactate peak was higher (1.7 [1.3-2.7] *v* 1.4 [1.2-1.9] mmol/L, $p < 0.001$) and hemoglobin nadir was lower (8.7 [7.5-10.0] *v* 9.5 [8.4-10.5] g/dL, $p < 0.001$). SIRS-positive patients more often required intraoperative blood transfusions, vasopressor support, and pre–intensive care unit (ICU) mechanical circulatory support (intraaortic balloon pump or extracorporeal membrane oxygenation, or both).

The postoperative course for SIRS-positive patients showed higher 30-day mortality (12.2% *v* 1.5%, $p < 0.001$), longer mechanical ventilation and ICU stay, increased transfusion rate (30.5% *v* 18.9%, $p < 0.001$), higher need for vasoactive drugs (59.3% *v* 26.3%, $p < 0.001$), dialysis (7.8% *v* 1.8%, $p < 0.001$), bleeding requiring surgical revision (7.3% *v* 4.4%, $p = 0.014$), and mechanical circulatory support (6.9% *v* 1.3%, $p < 0.001$). POD1 lab data showed pronounced leukocytosis (15.3 [13.4-18.2] *v* 11.5 [9.6-13.9] $\times 10^3/\mu L$, $p < 0.001$), with higher levels of neutrophils, lymphocytes, platelets, and CRP.

Multivariable Regression for Postoperative SIRS

Table 2 shows the multivariable regression model for postoperative SIRS. Female sex, preoperative anemia, leukocytosis, lymphopenia, and thrombocytosis were positively associated with SIRS at POD1. Higher preoperative glomerular filtration rate values were also unexpectedly predictive of SIRS. Additionally, intraoperative hemoglobin nadir, peak serum lactates, and the need for vasopressor support were significantly associated with SIRS at POD1.

Propensity Score Matching Analysis and SIRS Association With 30-Day Mortality

Propensity scoring matched 483 SIRS patients to 483 non-SIRS patients, balancing preoperative and intraoperative confounders, though significant predictors of SIRS remained unbalanced (Table 1). SIRS-positive patients were less frequently male (61.7% *v* 68.4%, $p = 0.026$) and had lower preoperative hemoglobin (13.0 [11.6-14.2] *v* 13.7 [12.3-14.8] g/dL, $p < 0.001$), higher preoperative CRP (3.1 [0.7-10.8] *v* 1.9 [0.4-9.4] mg/dL, $p = 0.004$), and higher platelet (214 [167-256] *v* 197 [161-239] $\times 10^3/\mu L$, $p < 0.001$) levels. Intraoperatively, SIRS patients had lower hemoglobin nadir (8.7 [7.6-10.0] *v* 9.3 [8.1-10.5] g/dL, $p < 0.001$), higher peak serum lactate (1.6 [1.3-2.4] *v* 1.5 [1.2-2.0] mmol/L, $p = 0.003$), and more frequent vasopressor use (52.6% *v* 33.1%, $p < 0.001$). SIRS-positive patients had higher 30-day mortality (9.7% *v* 2.9%, $p < 0.001$), longer ICU stays (2 [2-4] *v* 2 [1-3] days, $p < 0.001$), more vasopressor use (58.0% *v* 34.6%, $p < 0.001$), and higher dialysis rates (5.8% *v* 1.9%, $p = 0.015$). Laboratory data showed increased leukocytes, neutrophils, lymphocytes, and platelets, but CRP levels did not differ significantly.

Multivariable logistic regression in the matched subgroups (Table 3) identified age, preoperative CRP, and intraoperative factors (cross-clamp duration, hemoglobin nadir, peak lactates, and need for vasopressors or mechanical circulatory support) as independent predictors of 30-day mortality. SIRS was significantly associated with 30-day mortality (OR 2.77; 95% CI 1.40-5.47, $p = 0.003$). Structural equation modeling showed SIRS as a mediator of the effect of its predictors on 30-day mortality (Table 4), mediating 24.3% of the effect of intraoperative anemia, 9.9% of the effect of vasopressors, and 4.0% of the effect of peak lactate concentration, all significant ($p < 0.001$) (Fig 4). Logistic regression with interaction terms of SIRS and its predictors found no significant interactions, suggesting the impact of SIRS on mortality was consistent across varying levels of these mediators. Interaction plots are shown in Supplementary Fig S2. A sensitivity analysis was conducted to assess the robustness of the mediation results to unmeasured

Table 1
Characteristics of Patients by SIRS in the Overall Population and the Matched Subgroups

Variables	Unit	All	SIRS Positive	SIRS Negative	p Value	Matched SIRS Positive	Matched SIRS Negative	p Value
Cohort	n	1,908	548	1,360		483	483	
Age	y	69 [62-75]	70 [62-76]	69 [61-75]	0.213	70 [62-76]	69 [62-75]	0.113
Males	n, %	1,311 (68.7)	340 (62.0)	971 (71.4)	<0.001	298 (61.7)	332 (68.4)	0.026
Body mass index	kg/m^2	26.8 [24.2-29.8]	26.7 [24.2-29.6]	26.8 [24.2-30.0]	0.563	26.7 [24.2-29.8]	26.9 [24.1-29.7]	0.889
EuroSCORE II	%	2.1 [1.2-4.1]	2.7 [1.5-5.9]	2.0 [1.2-3.4]	<0.001	2.6 [1.4-5.1]	2.2 [1.2-4.6]	0.097
Left ventricular ejection fraction	%	55 [50-60]	55 [45-60]	55 [50-60]	<0.001	55 [47-60]	55 [50-60]	0.144
Risk factors	n, %							
Obesity		468 (24.5)	129 (23.5)	339 (24.9)	0.563	118 (24.4)	118 (24.4)	1.000
Diabetes		400 (21.0)	140 (25.5)	260 (19.1)	0.002	115 (23.8)	114 (23.6)	1.000
Previous cardiac surgery		147 (7.7)	59 (10.8)	88 (6.5)	0.002	50 (10.4)	34 (7.0)	0.087
Laboratory data								
Hemoglobin	g/dL	13.5 [12.1-14.5]	12.9 [11.4-14.2]	13.7 [12.4-14.6]	<0.001	13.0 [11.6-14.2]	13.7 [12.3-14.8]	<0.001
Leukocytes	$\times 10^3/\mu L$	7.2 [6.1-8.7]	8.3 [6.8-10.0]	6.9 [5.9-8.2]	<0.001	8.0 [6.6-9.5]	7.8 [6.7-9.5]	0.814
Neutrophils	$\times 10^3/\mu L$	4.6 [3.7-5.9]	5.6 [4.3-7.2]	4.4 [3.5-5.4]	<0.001	5.1 [4.2-6.6]	5.2 [4.3-6.6]	0.659
Lymphocytes	$\times 10^3/\mu L$	1.8 [1.5-2.1]	1.8 [1.5-2.1]	1.8 [1.5-2.1]	0.195	1.8 [1.5-2.1]	1.9 [1.6-2.2]	0.217
Thrombocytes	$\times 10^3/\mu L$	195 [160-238]	216 [166-260]	191 [158-228]	<0.001	214 [167-256]	197 [161-236]	<0.001
C-reactive protein	mg/dL	2.2 [0.5-8.3]	3.7 [0.7-13.2]	1.8 [0.4-6.6]	<0.001	3.1 [0.7-10.8]	1.9 [0.4-9.4]	0.004
Creatinine	mg/dL	0.9 [0.8-1.1]	1.0 [0.8-1.2]	0.9 [0.8-1.1]	0.127	1.0 [0.8-1.2]	0.9 [0.8-1.2]	0.586
Glomerular filtration rate	mL/min	77 [58-98]	73 [52-96]	78 [60-100]	<0.001	74 [53-96]	77 [57-98]	0.248
Procedure	n, %				0.003			0.744
Isolated CABG		716 (37.5)	186 (33.9)	530 (39.0)		165 (34.2)	173 (35.8)	
Single non-CABG		673 (35.3)	181 (33.0)	492 (36.2)		161 (33.3)	151 (31.3)	
Two procedures		400 (21.0)	137 (25.0)	263 (19.3)		121 (25.1)	116 (24.0)	
Three procedures		119 (6.2)	44 (8.0)	75 (5.5)		36 (7.5)	43 (8.9)	
Surgical times	min							
CPB		86 [65-117]	91 [67-129]	84 [64-113]	<0.001	90 [67-125]	94 [68-127]	0.455
Cross-clamp		58 [41-83]	61 [42-88]	57 [40-80]	0.014	61 [42-86]	64 [42-92]	0.337
Lactates (peak)	mmol/L	1.5 [1.2-2.0]	1.7 [1.3-2.7]	1.4 [1.2-1.9]	<0.001	1.6 [1.3-2.4]	1.5 [1.2-2.0]	<0.001
Hemoglobin (nadir)	g/dL	9.3 [8.1-10.4]	8.7 [7.5-10.0]	9.5 [8.4-10.5]	<0.001	8.7 [7.6-10.0]	9.3 [8.1-10.5]	<0.001
Blood transfusion	n, %	314 (16.5)	151 (27.6)	163 (12.0)	<0.001	113 (23.4)	109 (22.6)	0.819
Vasopressor support	n, %	632 (33.1)	296 (54.0)	336 (24.7)	<0.001	254 (52.6)	160 (33.1)	<0.001
Mechanical circulatory support	n, %	66 (3.5)	44 (8.0)	22 (1.6)	<0.001	23 (4.8)	20 (4.1)	0.755
SIRS	n, %	548 (28.7)	548 (100)	0 (0.0)	-	483 (100)	0 (0.0)	-
Mortality (30-day)	n, %	87 (4.6)	67 (12.2)	20 (1.5)	<0.001	47 (9.7)	14 (2.9)	<0.001
Duration								
Mechanical ventilation	h	4 [2-11]	5 [3-18]	4 [2-7]	<0.001	5 [3-17]	5 [3-12]	0.050
ICU stay	d	2 [1-3]	2 [2-5]	2 [1-2]	<0.001	2 [2-4]	2 [1-3]	<0.001
Complications	n, %							
Vasopressors (>24 h)		682 (35.7)	325 (59.3)	357 (26.3)	<0.001	280 (58.0)	167 (34.6)	<0.001
Revision for bleeding		100 (5.2)	40 (7.3)	60 (4.4)	0.014	30 (6.2)	28 (5.8)	1.000
Renal replacement therapy		59 (3.1)	43 (7.8)	16 (1.8)	<0.001	28 (5.8)	9 (1.9)	0.015
Blood transfusion	n, %	429 (22.3)	170 (30.5)	259 (18.9)	<0.001	139 (28.8)	118 (24.4)	0.145
Mechanical circulatory support	n, %	56 (2.9)	38 (6.9)	18 (1.3)	<0.001	19 (3.9)	16 (3.3)	0.731
Intraaortic balloon pump		42 (2.2)	28 (5.1)	14 (1.0)	<0.001	14 (2.9)	13 (2.7)	1.000
Extracorporeal membrane oxygenation		19 (1.0)	14 (2.6)	5 (0.4)	<0.001	7 (1.5)	4 (0.8)	0.544
Laboratory data								
Leukocytes	$\times 10^3/\mu L$	12.7 [10.3-15.5]	15.3 [13.4-18.2]	11.5 [9.6-13.9]	<0.001	15.2 [13.4-17.9]	11.6 [10.0-14.1]	<0.001
Neutrophils	$\times 10^3/\mu L$	10.6 [8.4-12.9]	12.8 [11.1-15.2]	9.4 [7.8-11.6]	<0.001	12.7 [11.1-15.1]	9.5 [8.0-11.7]	<0.001
Lymphocytes	$\times 10^3/\mu L$	1.0 [0.7-1.3]	1.1 [0.8-1.5]	0.9 [0.7-1.2]	<0.001	1.1 [0.8-1.4]	1.0 [0.7-1.3]	0.001
Thrombocytes	$\times 10^3/\mu L$	154 [119-191]	162 [119-212]	151 [119-184]	<0.001	162 [123-210]	150 [116-185]	<0.001
C-reactive protein	mg/dL	72.2 [59.0-90.0]	75.3 [62.0-95.8]	71.5 [58.0-88.0]	<0.001	74.1 [62.4-95.0]	72.8 [60.8-90.4]	0.209

Abbreviations: CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ICU, intensive care unit; SIRS, systemic inflammatory reaction syndrome.

Table 2
Multivariable Logistic Regression With Backward Elimination for SIRS at Postoperative Day 1

Variable	Estimate	Odds Ratio	95% CI Lower	95% CI Upper	p-value
Constant	−1.98	0.14	0.05	0.35	<0.001
Male gender	−0.30	0.74	0.57	0.95	0.021
Left ventricular ejection fraction (%)	−0.71	0.90	0.77	1.03	0.127
Preoperative hemoglobin (g/dL)	−1.07	0.82	0.68	0.99	0.044
Preoperative CRP (mg/dL)	1.74	1.03	0.99	1.08	0.135
Preoperative leukocytes ($\times 10^3/\mu L$)	6.63	1.87	1.23	2.84	0.003
Preoperative neutrophils ($\times 10^3/\mu L$)	4.63	1.23	0.85	1.77	0.271
Preoperative lymphocytes ($\times 10^3/\mu L$)	−3.28	0.75	0.63	0.88	<0.001
Preoperative thrombocytes ($\times 10^3/\mu L$)	3.07	1.38	1.20	1.59	<0.001
Preoperative glomerular filtration rate (mL/min)	1.59	1.21	1.04	1.41	0.015
Intraoperative hemoglobin nadir (g/dL)	−10.65	0.76	0.60	0.95	0.015
Intraoperative lactates peak (mmol/L)	3.74	1.16	1.07	1.26	<0.001
Intraoperative vasopressors	1.02	2.77	2.15	3.58	<0.001
Intraoperative mechanical circulatory support	0.51	1.66	0.88	3.12	0.115

Abbreviations: CRP, C-reactive protein; SIRS, systemic inflammatory reaction syndrome.

confounding. The partial R^2 of SIRS with 30-day mortality was 0.0064, indicating that SIRS explained 0.64% of the variance in 30-day mortality. The robustness value (q = 1) showed that an unmeasured confounder would need to explain at least 7.73% of the residual variance in both SIRS and 30-day mortality to fully account for the observed effect (Supplementary Tables S5, S6, and S7; Supplementary Fig S3).

Predictive Models

The exploratory analysis is detailed in the Supplementary Appendix. Various predictive models using preoperative and intraoperative variables were trained, with the random forest model standing out (AUC 0.74; 95% CI 0.69-0.80). Supplementary Table S2 shows the results of the feature importance analysis. The BRM achieved an AUC of 0.77 ± 0.04 in 5-fold CV and 0.73 (95% CI 0.70-0.85) on the test set (Fig 1). To enhance predictive performance and account for procedural effects on SIRS, the PARM was developed. The increased feature set improved model efficacy, resulting in an AUC of 0.81 ± 0.02 in CV and 0.82 (95% CI 0.76-0.85) on the test set (Fig 1). Supplementary Table S3 presents a thorough evaluation of both BRM and PARM. The AUC difference between BRM and PARM, assessed via the DeLong method, showed a value of $p < 0.001$ and a 95% CI of 0.05 to 0.12, indicating significant improvement in predictive capability by including intraoperative variables.

Shapley additive explanations values for each PARM feature were computed, with waterfall plots illustrating the contribution and direction (positive or negative) of each feature for individual predictions (Fig 2). Fig 3 shows calibration plots for each model. The Hosmer-Lemeshow statistic for BRM was 12.13 (p = 0.15) before calibration and 3.37 (p = 0.91) after calibration, indicating improved calibration and alignment between predicted and observed outcomes. For PARM, the statistic was 13.37 (p = 0.10) before calibration and 9.66 (p = 0.29) after calibration.

DISCUSSION

Inflammation following cardiac surgery is a common response, but SIRS is associated with poorer outcomes even in otherwise successful operations. Our retrospective analysis of nearly 2,000 patients undergoing CPB-assisted cardiac

Table 3
Multivariable Logistic Regression With Backward Elimination for 30-day Mortality in the Matched Subgroups

Variable	Estimate	Odds Ratio	95% CI Lower	95% CI Upper	P Value
Constant	−5.92	0.00	0.00	0.05	<0.001
Age	4.28	2.24	1.36	3.71	0.002
Left ventricular ejection fraction (%)	−1.85	0.75	0.54	1.03	0.079
Preoperative CRP (mg/dL)	3.82	1.09	1.01	1.17	0.026
Preoperative thrombocytes (x10^3/μL)	−2.25	0.80	0.56	1.10	0.151
Duration of cross-clamp (min)	6.98	1.43	1.05	1.94	0.024
Intraoperative hemoglobin nadir (g/dL)	−4.60	0.58	0.36	0.96	0.033
Intraoperative lactates peak (mmol/L)	3.94	1.20	1.06	1.35	0.004
Intraoperative vasopressors	1.25	3.48	1.49	8.13	0.004
Intraoperative mechanical circulatory support	1.28	3.61	1.41	9.26	0.007
SIRS	1.02	2.77	1.40	5.47	0.003

Abbreviations: CRP, C-reactive protein; SIRS, systemic inflammatory reaction syndrome.

Table 4
Mediation Analysis for SIRS as Mediator for 30-day Mortality in the Matched Subgroups

	Estimate	Odds Ratio	95% CI Lower	95% CI Upper	p Value
SIRS as mediator of intraoperative hemoglobin nadir (g/dL)					
Total effect	−0.322	0.72	0.59	0.87	<0.001
Average causal Mediation effect	−0.078	0.92	0.88	0.97	<0.001
Average direct effect	−0.244	0.78	0.63	0.91	0.002
Proportion mediated (average causal mediation effect/total effect): 24.3%					<0.001
SIRS as mediator of intraoperative lactates peak (mmol/L)					
Total effect	0.945	2.58	2.13	2.67	<0.001
Average causal Mediation effect	0.038	1.04	1.01	1.14	<0.001
Average direct effect	0.910	2.48	1.90	2.63	<0.001
Proportion mediated (average causal mediation effect/total effect): 4.0%					<0.001
SIRS as mediator of intraoperative vasopressors					
Total effect	0.115	1.12	1.09	1.16	<0.001
Average causal Mediation effect	0.011	1.01	1.00	1.02	<0.001
Average direct effect	0.103	1.11	1.07	1.14	<0.001
Proportion mediated (average causal mediation effect/total effect): 9.9%					<0.001

procedures aimed to elucidate the relationship between SIRS and 30-day mortality. We found a 28.7% incidence of SIRS, independently associated with specific preoperative and intraoperative factors. Baseline leukocytosis, lymphopenia, and thrombocytosis were predictive of postoperative SIRS. Preoperative anemia and female gender were also independent predictors. Intraoperative factors, such as minimum hemoglobin levels, peak serum lactate, and the need for vasopressor support, were significantly linked to SIRS on POD1. Unexpectedly, better baseline renal function was also predictive of SIRS, possibly due to its correlation with younger age, which is associated with more intense inflammation in cardiac surgery.[2,11]

In assessing the impact of SIRS on 30-day mortality in a matched subpopulation, we found the mortality rate three times higher in SIRS-positive patients compared to non-SIRS patients. Multivariable regression identified several independent mortality factors, with SIRS-positive patients showing a 177% higher 30-day mortality risk than controls. Notably, hemoglobin nadir, peak lactate levels, and vasopressor support were predictors of both mortality and SIRS. Our analysis showed that positivity to SIRS significantly mediated the influence of these factors on 30-day mortality, with nearly 25% of hemoglobin nadir's impact, 4.0% of lactate peak's effect, and 9.9% of vasopressor support necessity channeled through SIRS.

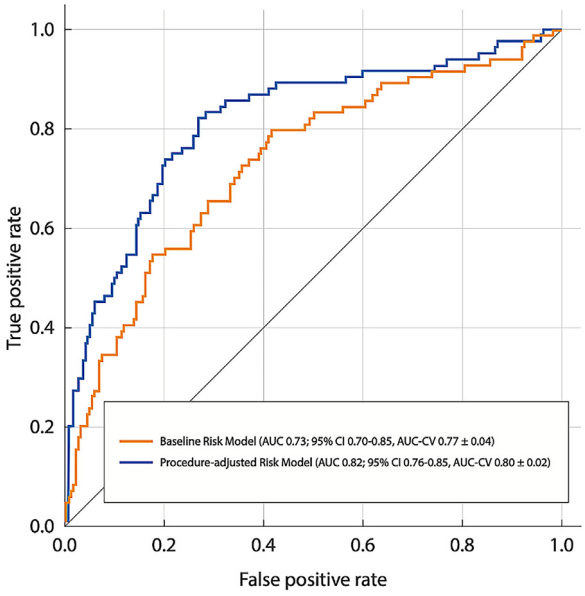

Fig 1. Receiver operating characteristic curve of the baseline risk model and of the procedure-adjusted predictive model.

The association between postoperative SIRS and increased mortality risk is supported by sporadic evidence in the literature. A study from our group involving 502 patients undergoing cardiac surgery with CPB indicated higher incidence of poor outcomes, including in-hospital mortality, in SIRS-positive patients compared to matched controls.[2] McCallum et al. reported an association between postoperative SIRS and in-hospital mortality in a retrospective sample of over 2,700 patients.[12] Viikinkoski et al. identified a link between SIRS and 90-day mortality in a prospective study of over 250 patients, although in univariate analysis.[13] Studies have also shown an independent association between SIRS following transcatheter aortic valve implantation and increased mortality at various intervals,[14,15] though contested by other evidence.[16] A prospective study of about 400 patients undergoing transcatheter edge-to-edge mitral valve repair found a statistically significant relationship between SIRS and 3-year mortality.[17] Our investigation adds contemporary and robust evidence of a significant correlation between SIRS and short-term mortality following cardiac surgery in a large, propensity-matched cohort and provides a perspective on how intraoperative factors like hemoglobin nadir, peak lactate levels, and vasopressor support affect outcomes.

Moreover, we implemented artificial intelligence to predict SIRS in these patients. Our machine learning models demonstrated satisfactory risk-assessment capabilities. The BRM stratifies patients by baseline SIRS risk, informing surgical, anesthesiologic, and perfusion planning, and guiding

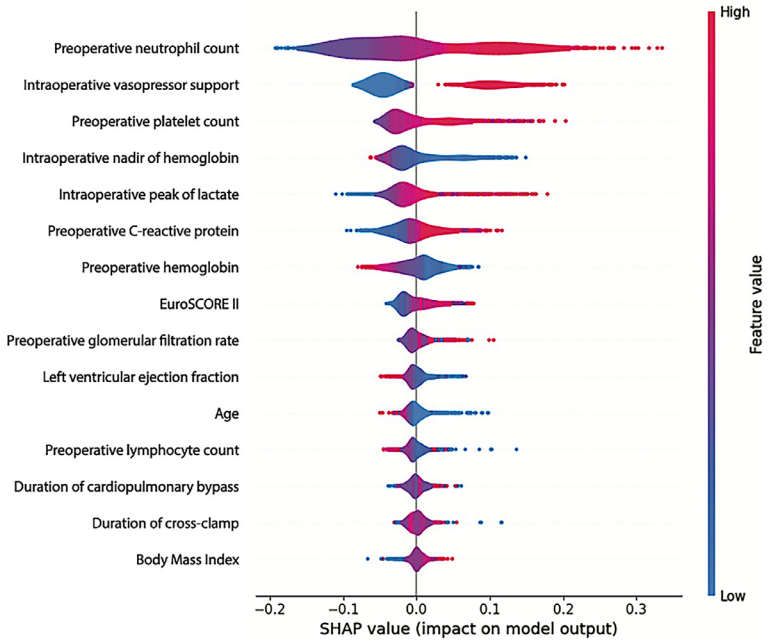

Fig 2. Shapley additive explanations analysis of the procedure-adjusted risk model.

interventions to manage excessive inflammation. Postoperative refinement through the PARM allows for tailored care strategies, potentially optimizing resource allocation and enhancing outcomes. Machine learning is ideal for consolidating comprehensive risk assessments and identifying influential SIRS predictors. Some variables affecting SIRS risk are modifiable, opening avenues for future research to manage post-cardiac surgery inflammation. Considering intraoperative anemia's influence on SIRS and mortality, approaches like goal-directed perfusion pioneered by De Somer and Ranucci may warrant further investigation.[18,19] Our risk prediction models could also address the limitations of prior RCTs, which often included many patients unlikely to develop significant postoperative inflammation, thereby reducing the apparent efficacy of treatments.[3-5] We advocate for future RCTs to incorporate high inflammatory burden as a selection criterion.

Our study has limitations: SIRS observation was limited to POD1, and yet unmeasured factors, such as pacemaker use, may have influenced the postoperative observation of SIRS. Applying SIRS criteria, originally defined for early sepsis,[6] to post–cardiac surgery inflammation is common[12-18] but may require future biomarker-based definitions to prove clinical relevance. The propensity score matching deliberately left unbalanced the predictors of SIRS to preserve the validity of

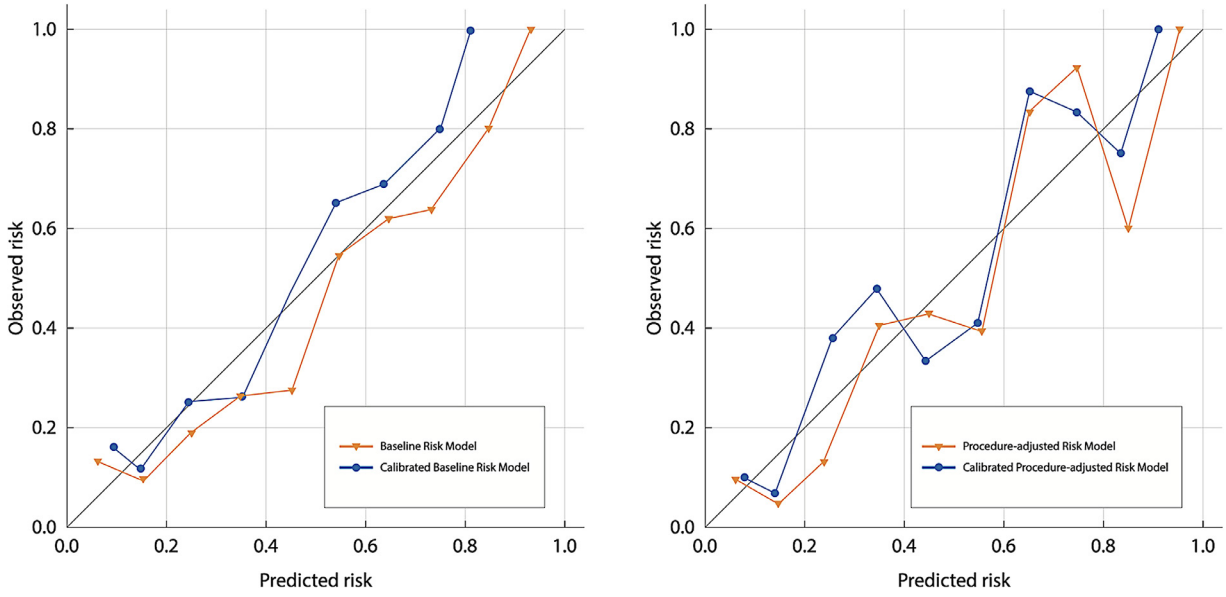

Fig 3. Calibration curves for the baseline risk model and procedure-adjusted risk model.

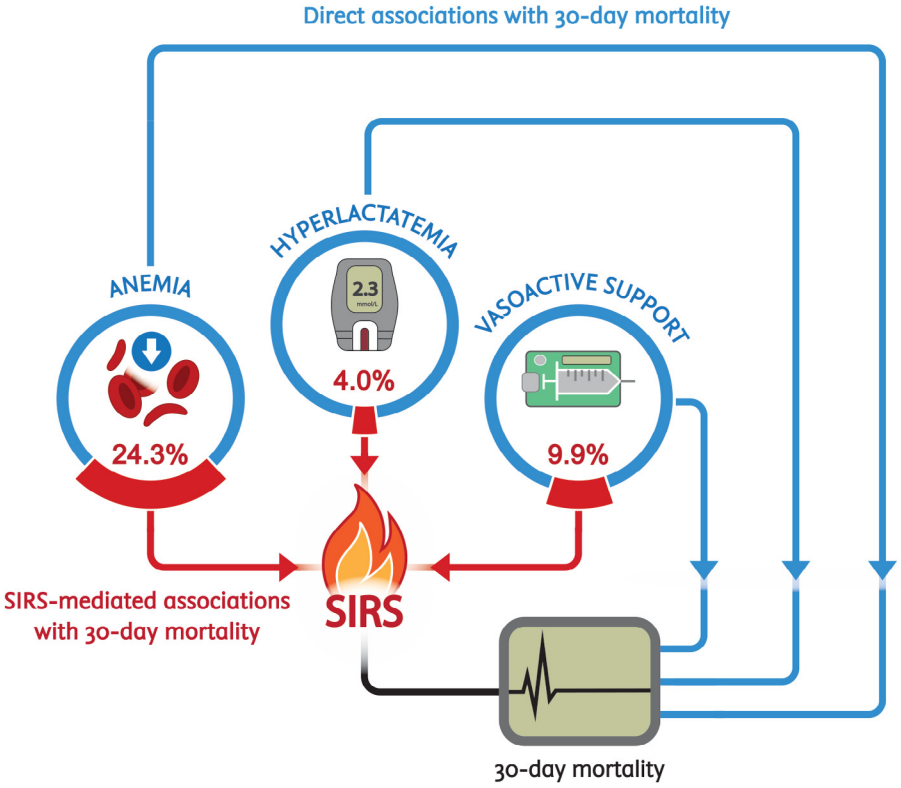

Fig 4. Structural equation modeling diagram.

the outcome analysis. Additionally, It is cautious to consider potential unmeasured confounders that may have influenced the mediation analysis. In particular, while the SIRS criteria are valuable indicators of systemic inflammation, they capture clinical manifestations of SIRS rather than the underlying process itself. The inflammatory reaction likely plays a central role in the hemodynamic instability, vasopressor requirement, and mortality, perhaps representing itself the confounder linking these factors. However, SEM relies on specific assumptions regarding causal relationships among variables, which may not fully capture the complexity of the inflammatory response in cardiac surgery. The validity of our mediation analysis depends on these assumptions, and deviations from them could alter the interpretation of the results. The sensitivity analysis demonstrated that only strong confounders explaining over 7.7% of the residual variance could fully negate the effect of SIRS on 30-day mortality. These findings suggest that the association is robust, though not immune to potential confounding. Therefore, our SEM analysis is only intended as exploratory, aiming to provide insights into potential mediating relationships rather than establish definitive causal pathways. Given the complexity of SIRS and its underlying mechanisms, the results should be interpreted with caution.

Moreover, the machine learning models were developed using retrospective data from a single center; SMOTE was used to address class imbalance; other predictive models, not tested in this study, might speculatively offer better performance, and this represents a potential limitation of our preliminary analysis. Despite using a test set, the lack of a holdout dataset for hyperparameter tuning and the absence of external validation may introduce overfitting and limit the generalizability of the results. Additionally, the absence of a risk reclassification analysis limits the study's ability to fully assess the incremental value of the SIRS predictor over established models like EuroSCORE II. Despite these limitations, our study provides valuable insights into SIRS and its impact on postoperative outcomes in cardiac surgery patients.

CONCLUSION

Our study establishes a pivotal association between SIRS and increased 30-day mortality following cardiac surgery. We found that specific preoperative and intraoperative factors, including hemoglobin nadir, peak lactate levels, and vasopressor support, are crucial in predicting SIRS and its impact on patient outcomes. Implementing machine learning models shows promise in enhancing patient stratification and guiding targeted interventions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Enrico Squiccimarro: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data

curation, Conceptualization. **Roberto Lorusso:** Writing – review & editing, Supervision, Methodology. **Antonio Consiglio:** Software, Methodology, Formal analysis, Data curation. **Cataldo Labriola:** Writing – review & editing, Methodology, Investigation, Data curation. **Renard G. Haumann:** Writing – review & editing, Methodology, Formal analysis. **Felice Piancone:** Writing – review & editing, Data curation. **Giuseppe Speziale:** Writing – review & editing, Investigation. **Richard P. Whitlock:** Writing – review & editing, Supervision, Methodology. **Domenico Paparella:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization.

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2024.12.013.

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