Inadequate Oxygen Delivery During Cardiopulmonary Bypass Drives Inflammatory Reaction After Cardiac Surgery

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An Abstract of this manuscript was selected for presentation at the 39th EACTS annual meeting

Word count: 4,499

ABSTRACT

Objectives: Systemic inflammatory response syndrome (SIRS) is a common complication following cardiopulmonary bypass (CPB), associated with increased mortality. We assessed the relationship between indexed oxygen delivery (DO_2i) during CPB and SIRS.

Methods: We conducted a prospective observational study at two institutions. The primary endpoint was clinically-defined SIRS 12 hours after surgery. The secondary endpoint was a composite outcome comprising death, TIA/stroke, renal replacement therapy, bleeding, mechanical circulatory support, or ICU stay >96 hours. The primary analysis modeled DO_2i in multivariable logistic regression. Linearity was assessed with restricted cubic splines, knot-sensitivity, quintiles, and piecewise fits. The optimal ROC-derived threshold was explored. Patients above and below the threshold were matched 1:1 by propensity score. Structural equation modeling (SEM) assessed mediation between DO_2i, SIRS, and outcomes.

Results: Of 1,154 patients screened, 908 were analyzed; 221 (24.3%) developed SIRS. Median DO_2i was lower in the SIRS group (274 vs 302 mL/min/m^2, p<0.001). DO_2i was inversely associated with SIRS (aOR 0.798; 95% CI 0.750-0.850, p<0.001, per +10 mL/min/m^2). In the secondary analysis, DO_2i ≤293 mL/min/m^2 was identified as threshold (sensitivity 62%, specificity 74%). Propensity score matched 390 patient pairs, with higher SIRS incidence in the low-DO_2i group (33.3% vs 14.4%; p<0.001). The composite outcome occurred more frequently in the low-DO_2i cohort (17.7% vs 8.2%; p<0.001). SEM showed mediation by SIRS, accounting for 46.2% of the DO_2i effect on outcomes (OR 1.052; 95%CI 1.036-1.067; p<0.001).

Conclusion: Low DO_2i during CPB predicts SIRS and adverse outcomes. Goal-directed perfusion to reduce inflammation warrants evaluation in randomized trials.

Keywords: Oxygen Delivery; Systemic Inflammatory Reaction Syndrome; Cardiopulmonary Bypass

ACME	Average Causal Mediation Effect
ADE	Average Direct Effect
AKI	Acute Kidney Injury
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
CRP	C-reactive protein
GDP	Goal-Directed Perfusion
ICU	Intensive Care Unit
OR	Odds Ratio
ROC AUC	Area Under The Receiver Operating Characteristic Curve
SEM	Structural Equation Modeling
SIRS	Systemic Inflammatory Reaction Syndrome

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INTRODUCTION

Cardiac surgery and cardiopulmonary bypass (CPB) trigger a systemic inflammatory reaction syndrome (SIRS) often self-terminating, but seldomly leading to hemodynamic instability, organ damage, and mortality [1-2]. This host-response is convoluted to an extent that it is difficult to recognize the specific triggers of life-threatening reactions as opposed to trivial ones. Genomics, age, peculiar preoperative conditions, and complex operations are associated to a clinically relevant response [3-4]. Genome-wide transcriptional analyses pointed out hypoxia and ischemia-reperfusion injury as hub-nodes of the immune response to cardiac surgery [5]. Targeting adequate indexed oxygen delivery (DO_2i) during CPB – the Goal-Directed Perfusion (GDP) – has been associated with reduced risk of postoperative acute kidney injury (AKI) and other morbidities as compared to the conventional CPB management that provides for the empirical calculation of the pump flow based on patients' estimated body surface, and the theoretical cardiac index adjusted by temperature [6-7]. We aimed to test the hypothesis of inadequate DO_2i during CPB as inflammatory trigger.

MATERIALS AND METHODS

We performed a prospective observational multicenter evaluation of patients who underwent cardiac surgery on CPB at two tertiary cardiac surgical centers in Italy (Santa Maria and Anthea Hospitals, GVM Care & Research, Bari), from October 2023 to December 2024. The study was approved by the IRCCS Istituto Tumori Giovanni Paolo II – Bari Review Board (1432/CEL), and written informed consent was obtained for all patients.

The primary endpoint was postoperative SIRS and its relationship with DO_2i. Emergency procedures, hypothermia (<34°C), and endocarditis were exclusion criteria. The surgical, anesthesiologic, and perfusion set-up were previously described [1-2]. Briefly, surgical access included sternotomy or minimally-invasive approaches, and cannulation was central or peripheral, depending on the surgical access. Heparin administration targeted ACT 420s. Blood cardioplegia was used in most cases, with Custodiol® reserved for reoperations or complex/combined procedures. The criteria for blood

transfusion were hemoglobin <7.5 g/dL, SvO_2 <65%. Postoperative SIRS 12 hours after surgery was defined as per the American College of Chest Physicians/Society of Critical Care Medicine parameters [8]: (1) temperature <36°C or >38°C, (2) heart rate >90 beats per minute, (3) respiratory rate >20 breaths per minute or $PaCO_2$ <32 mmHg, and (4) leukocytes <4,000/μL or >12,000/μL.

DO_2i data were collected by a researcher while the perfusionist was blinded. DO_2i was continuously monitored during CPB using the Landing® monitoring system (Eurosets, Medolla, Italy), with automated acquisition of values every 5 seconds. For the analysis, only the time interval corresponding to aortic cross-clamping was considered, avoiding bias from an inadequate estimation of DO_2i due to patients' cardiac output. The secondary outcome was a composite endpoint including death, transient ischemic attack/stroke, renal replacement therapy, bleeding requiring surgical re-exploration, mechanical circulatory support, and an Intensive Care Unit (ICU) stay >96 hours. The preparation of the manuscript followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Statistical analysis

Continuous data were reported as median with interquartile range. Groups were compared via independent samples Student's t-test or Mann-Whitney statistic. Categorical variables were reported as frequency and percentage; associations were evaluated by chi-squared or Fisher exact test as appropriate. Regression analyses were conducted with backward elimination based on the Akaike Information Criterion. A p-value <0.05 was considered significant. Missingness was negligible (~0.15%) and confined to preoperative C-reactive protein (CRP) (6.4%). We performed a single chained-equations imputation using predictive mean matching, including all analysis covariates and the outcome indicator.

Pilot phase

Sample size determination was done using G*Power software (Universität Düsseldorf, Germany) based on the Z test, with 0.2 effect size and 80% power (**Suppl. Figure S1**). The expected incidence of SIRS was based on a pilot phase of the study including 100 patients. DO_2i was analyzed for each patient as mean, standard deviation, minimum, maximum, median, first and third quartile, and both the percentage of time during which values remained below the thresholds of 280 and 300 mL/min/m^2, and the maximum number of consecutive minutes recorded below these thresholds. The median DO_2i showed the highest area under the receiver operating characteristic curve (ROC AUC 0.71; 95% Confidence Interval [CI] 0.59-0.82) for postoperative SIRS and was therefore selected as the benchmark metric. A cut-off value (300 mL/min/m^2) was derived by identifying the threshold that maximized Youden's index in the pilot population. This threshold was used to classify patients into "low" and "high" DO_2i groups for the purpose of estimating SIRS incidence and informing the sample size calculation. In the pilot cohort, the incidence of SIRS was 40.9% in the low DO_2i group and 9.1% in the high DO_2i group. To account for potential variability and ensure a conservative estimate, we adjusted the expected incidence rates by increasing the incidence of SIRS in the high DO_2i group by 50% and decreasing it by 50% in the low DO_2i group. We calculated that a sample size of 882 patients for the study. Considering potential dropouts (2%), the final adjusted sample size was 900.

Final analysis

Within the final cohort, a multivariable logistic regression model for SIRS including all significant preoperative and intraoperative variables at univariate analysis was devised. Multicollinearity was assessed using variance inflation factors (VIF), accepting VIF <5; accordingly, preoperative neutrophils were excluded from the model. A variable identifying the center was included to adjust for potential inter-center variability. The SIRS model was also re-estimated as a mixed-effects logistic regression with a random intercept for center. As sensitivity, we added center as a fixed factor and compared models by likelihood-ratio test (LRT) (**Suppl. Table S1**).

The functional form of the DO_2i-SIRS association was evaluated using restricted cubic splines (RCS) with knots placed at empirical quantiles (i.e., 4 knots and – as sensitivity specification – 5 knots) (**Suppl. Tables S2**). For each specification, overall and non-linear Wald tests were computed. Adjusted odds-ratio (OR) curves were derived across the observed DO_2i range, using 300 mL/min/m^2 as reference (**Suppl. Figure S2**). A "local slope" plot was devised to assess the log-odds change per +10 mL/min/m^2 across the DO_2i range (**Suppl. Figure S3**).

As additional shape probes, DO_2i was categorized into quintiles and modeled in the same adjusted logistic framework (**Suppl. Table S3**), and a piecewise-linear model with a single hinge at the Q3-Q4 boundary was fitted to estimate slopes below and above the hinge and to test for a slope change (**Suppl. Table S4**). The maximum value of Youden's index (sensitivity+specificity-1) was extracted for DO_2i within ROC analysis for SIRS occurrence. As sensitivity analysis we also fitted a linear spline (lsp) with a single knot placed a priori at 300 mL/min/m^2 and at the ROC-derived threshold (293 mL/min/m^2) (**Suppl. Figures S4-S5**). Model fit was compared by AIC (**Suppl. Table S5**). Model performance was assessed through 10-fold cross-validation and bootstrap resampling (1,000 iterations) with optimism correction. Discrimination was evaluated using AUC and Somers' Dxy, calibration through intercept, slope, Emax, and bias-corrected plots, and overall performance via Brier score and accuracy (**Suppl. Figures S6-S8, Suppl. Table S6**).

In addition, the exploratory 293 mL/min/m^2 cut-off identified was retained as a pragmatic target. A propensity score-matched cohort was created by using an automated procedure to select similar patients stratified by DO_2i. The propensity score was based on multivariable logistic regression model for median DO_2i ≤293 mL/min/m^2 including all preoperative predictors, type of surgery, and duration of CPB and cross-clamp. Model discrimination was based on the ROC AUC. Matching was performed in a 1:1 ratio on the basis of the lowest absolute difference in propensity scores within a maximum caliper width of 0.20 of the standard deviation of the linear predictor of the propensity score [9]. Data of paired patients were compared with dependent samples t-test (continuous variables) and McNemar's test (dichotomous information). A multivariable logistic regression was utilized to identify the independent

predictors of the composite outcome. The predictors entered into the multivariable models were selected based on their statistical significance in univariate analyses. The interplay between inadequate DO_2i, SIRS, and the composite endpoint was assessed using structural equation modeling (SEM). This analytical approach differentiates direct associations of predictors from those mediated by SIRS, which acts here as an intermediary mechanism partially explaining the link between inadequate DO_2i and the composite clinical outcome. SEM quantitatively estimates these associations by calculating the Average Causal Mediation Effect (ACME) – the portion of the effect transmitted through SIRS – and the Average Direct Effect (ADE) – the direct impact of low DO_2i on the outcome, independent from SIRS mediation. Indirect effects were estimated through a non-parametric bootstrapping approach with 1,000 simulation iterations. Specifically, we computed the Total Effects, Average Causal Mediation Effects, and Average Direct Effects. Additionally, a moderation analysis was performed to evaluate possible interactions between inadequate DO_2i and SIRS. All analyses were conducted using RStudio (Boston, MA, USA).

RESULTS

A total of 1,154 patients were screened for eligibility and 908 patients were ultimately included in this analysis (**Figure 1**). **Table 1** describes the characteristics of the overall population. Median age was 68 [61-75] years, and 270 (29.7%) were female. Median EuroSCORE II was 1.8% [1.2-3.0]. Two hundred twenty-six patients (30.4%) underwent isolated coronary artery bypass grafting (CABG), 242 (26.6%) underwent single non-CABG procedure, 223 (24.6%) and 168 (18.5%) respectively underwent 2 and 3 procedures. Postoperative SIRS occurred in 221 (24.3%) cases. Thirty-day mortality was 1.2% (11 patients), and the incidence of the composite endpoint was 13.2% (120 cases). **Suppl. Table S7** describes the characteristics of the SIRS-positive patients as compared to SIRS-negative ones. The median DO_2i was significantly lower in the SIRS cohort (274 [252-295] vs 302 [278-325] mL/min/m^2, $p<0.001$). Thirty-day mortality occurred in 4.1% of cases in the SIRS-positive group as opposed to 0.3% of the controls while the composite endpoint occurred in 78 (35.3%) and 42 (6.1%) cases, respectively ($p<0.001$).

Table 2 reports the multivariable regression model for SIRS. Younger age, female gender, higher EuroSCORE II and left ventricular ejection fraction, preoperative anemia, leukocytosis, thrombocytosis, and increased CRP were independent predictors of SIRS. Intraoperative hemoglobin nadir, blood transfusion, and the need for pharmacological support were also significantly associated with postoperative SIRS (**Figure 2**). Center was not associated with postoperative SIRS. Low median DO_2i was an independent predictor of SIRS (OR 0.798; 95% CI 0.750-0.850, p<0.001, per +10 mL/min/m^2). RCS models showed no statistically significant non-linear component (non-linear Wald p was 0.099 with 4 knots, and 0.155 with 5 knots), and yielded curves that were monotonic over most of the observed range (**Suppl. Figure S2**). The derivative ("local slope") plot confirmed an approximately constant log-odds change per +10 mL/min/m^2 between ~250-330 mL/min/m^2, with wider uncertainty only at the distribution tails (**Suppl. Figure S3**). In quintile analyses (reference Q5), adjusted ORs were elevated in lower DO_2i quintiles indicating a graded monotonic trend (**Suppl. Table S3**). The piecewise-linear model with a hinge at the Q3-Q4 boundary corroborated a stronger risk decrease at higher DO_2i values (**Suppl. Table S4**). As sensitivity, we repeated the primary continuous model excluding preoperative CRP from the adjustment; the DO_2i estimate was unchanged (aOR per +10 mL/min/m^2 was 0.797; 95% CI 0.749-0.848, AIC 663.6).

In a secondary analysis, the cut-off value for median DO_2i as possible predictor of SIRS was explored. ROC curves were analyzed, and the best value according to the Youden's index was set at a median DO_2i 293 mL/min/m^2 (sensitivity 62%, specificity 74%) (**Suppl. Figure S9**). Propensity scoring successfully matched 390 patients who had a median DO_2i ≤293 mL/min/m^2 to 390 for which median DO_2i exceeded the cut-off value. The score performed well in balancing measured confounders (**Suppl. Figure S10**). **Table 1** shows the propensity matched comparison of groups based on the median DO_2i critical value. The median DO_2i in the high-delivery group was 318 [305-338] mL/min/m^2 as opposed to 270 [252-282] mL/min/m^2 in the low-delivery group. The low-DO_2i cohort showed a lower intraoperative hemoglobin nadir, higher transfusion rates (19.7% vs 12.6%, p=0.009), and increased need for intraoperative pharmacological support. The incidence of SIRS was significantly higher in the low-

delivery group (33.3% vs 14.4%, p<0.001), that also demonstrated excessive 30-day mortality as opposed to matched controls (2.3% vs 0.3%, p=0.026). The composite outcome occurred in 69 (17.7%) cases in the low-DO_2i cohort and 32 (8.2%) in the matched controls (<0.001). The postoperative course of low-delivery patients was characterized by prolonged mechanical ventilation, higher need for pharmacological hemodynamic support (31.0% vs 23.3%, p=0.020) and blood transfusions (23.3% vs 14.9%, p=0.004). Surgical revision for bleeding was also more frequent in the low-delivery cohort. Postoperative laboratory results showed increased leukocyte, neutrophil, lymphocyte, and platelet counts in the low-delivery group, with CRP being also significantly higher (53.3 [18.9-78.1] vs 28.6 [16.3-44.4] mg/dL, p<0.001) (**Figure 3**).

Table 2 reports the multivariable model for the composite outcome. Both SIRS (OR 3.873; 95% CI 2.350-6.383, p<0.001) and the median DO_2i below the critical value (OR 1.697; 95% CI 1.051-2.742, p=0.031) were associated to the composite endpoint. Other factors such as female sex, EuroSCORE II, CPB time, and the intraoperative hemoglobin nadir were associated to the composite outcome.

SEM offered an in-depth characterization of the mediating role played by SIRS in linking inadequate DO_2i to the composite clinical outcome, as detailed in **Table 3**. Specifically, SIRS accounted for 46.2% of the total effect that low median DO_2i exerted on the composite endpoint (**Figure 4**). Additionally, we assessed whether DO_2i moderated the relationship between SIRS and the composite outcome. However, the interaction term "SIRS+DO_2i" was not statistically significant, indicating that the effect of SIRS on the composite endpoint did not differ across varying levels of DO_2i (**Suppl. Figure S11**).

DISCUSSION

Postoperative SIRS is a prevalent and clinically significant complication of cardiac surgery, potentially leading to organ dysfunction and poorer clinical outcomes [1-2]. Based on clinical and translational evidence [4], this prospective investigation identified low median DO_2i during CPB as a strong independent predictor of postoperative SIRS (OR 0.798; 95% CI 0.750-0.850, p<0.001, per +10 mL/min/m^2), along with younger age, female sex, elevated EuroSCORE II, increased preoperative CRP and leukocytosis, and intraoperative vasopressor use. Notably, these variables are consistent with the

top predictors of postoperative SIRS identified by machine learning models derived from the a recent retrospective cohort study [2]. Notwithstanding, median DO_2i outperformed other SIRS predictors (**Figure 2**), such as preoperative CRP, leukocytes, hemoglobin, platelets, and intraoperative hemoglobin nadir and lactates' peak showing a clear, graded, inverse association with postoperative SIRS when modeled as a continuous exposure. Across the observed range, each 10 mL/min/m^2 increase in DO_2i reduced SIRS odds by ≈20%, after comprehensive adjustment for preoperative status and intraoperative factors. This may be due to the frame of DO_2i itself which has other major predictors embedded (hemoglobin) but also relies on additional instances like CPB flow. The notion of younger age, female sex, and elevated CRP is also consistent with previous observational studies [10-12]. However, in the quantile analysis, Q4 was not significantly different from Q5; the piecewise model and the local-slope plot indicated a persistently negative log-odds slope beyond the Q3-Q4 hinge. The apparent Q4-Q5 similarity reflects reduced slope and wider uncertainty at higher DO_2i rather than a true plateau, aligning with the continuous and piecewise estimates.

Hence, despite the undisputed evidence of linearity between DO_2i and SIRS, it must be recognized that threshold-based targets (e.g., 280-300 mL/min/m^2) are the cornerstone of GDP, facilitating real-time decision-making at the pump [6]. Therefore, while our continuous models quantify the risk gradient adequately, the secondary – explorative – threshold analyses yield an implementable target consistent with AKI-oriented practice. Indeed, ROC analysis identified an optimal DO_2i cutoff of 293 mL/min/m^2 for predicting SIRS, demonstrating acceptable sensitivity and specificity. Following propensity score matching, patients with median DO_2i ≤293 mL/min/m^2 experienced significantly higher SIRS incidence (33.3% vs. 14.4%), elevated postoperative CRP, increased 30-day mortality (2.3% vs. 0.3%), and greater reliance on transfusions and vasopressor support. Postoperative laboratory results further corroborated the clinical findings, with significantly increased leukocyte, neutrophil, lymphocyte, platelet counts, and CRP levels observed in patients with lower DO_2i.

Our findings extend previous observations by associating reduced intraoperative DO_2i with increased postoperative inflammation, identifying tissue hypoxia as a plausible and modifiable stimulus for SIRS development post-CPB. Inadequate DO_2i during CPB may "prime" the immune system, precipitating

systemic inflammation upon reperfusion. Consequently, interventions aimed at maintaining adequate oxygenation, such as GDP, may potentially attenuate postoperative SIRS.

This concept is further supported by our outcome analysis, in which postoperative SIRS significantly mediated the impact of inadequate DO_2 on a composite outcome, with the effect of SIRS being almost half mediated by SIRS. Decades of research have demonstrated that when DO_2 falls below a “dysoxia threshold”, tissues experience anaerobic metabolism, lactate accumulation, and organ injury [13-14]. Extensive evidence supports the correlation between insufficient intraoperative DO_2 during CPB and adverse clinical outcomes [6-7]. Notably, the GIFT trial by Ranucci et al. provided causal evidence for adequate DO_2i as an effective strategy to prevent AKI in CPB-assisted surgery (relative risk 0.45; 95% CI 0.25–0.83; p=0.01) [6], underpinning GDP as a Class 1A recommendation in the latest European guidelines on adult cardiac surgery [15]. Speculatively, part of this effect may be due to the amelioration of the inflammatory-driven portion of kidney damage throughout the perioperative phase of CBP-assisted heart surgery. However, while AKI has been associated with short-lasting reductions in DO_2i (~15 min) [16], SIRS is more likely the result of a cumulative, time-integrated imbalance between oxygen supply and metabolic demand.

Considering the detrimental effects of SIRS post-cardiac surgery, various randomized controlled trials have evaluated interventions targeting innate immune responses, yielding inconsistent efficacy [17-18]. From a mechanistic viewpoint, maintaining adequate intraoperative DO_2 likely mitigates inflammation triggered by tissue hypoxia, reducing damage-associated molecular patterns and subsequent inflammatory cascade activation. Thus, GDP may serve not only as an organ-protective strategy but also as an "anti-inflammatory" approach.

This study has limitations. Full blinding of perfusionists was not technically feasible; however, continuous DO_2i data access was effectively prevented throughout surgery. The assessment of SIRS was restricted to postoperative day 1, potentially missing late-onset cases. While our study included two centers, clinical and perfusion protocols were consistent across both institutions, thus limiting inter-center variability, as showed by our mixed effect model. Although the sepsis-oriented criteria for SIRS are widely used following cardiac surgery, our findings, including robust biomarker evidence of

inflammation (e.g., significantly higher postoperative leukocyte and CRP levels in low-DO_2i patients), support their clinical relevance. Nonetheless, future studies should explore more precise, biomarker-based definitions tailored specifically to cardiac surgery contexts. Importantly, threshold analyses were considered secondary and were not meant to replace the continuous effect as the main inference – the exploratory 293 mL/min/m^2 was retained for translational relevance but do not supersede the continuous-effect inference given the risks of information loss and potential misclassification near the cut-point. Despite careful propensity score matching, residual confounding from post-exposure (DO_2i during cross-clamp) factors (i.e., transfusions, vasoactive support, or re-exploration for bleeding) remains possible. Patients who developed SIRS may differ in unmeasured factors. Thus, causality cannot be inferred, and findings should be interpreted within this observational context. Surgical urgency and access were not explicitly collected; however, we mitigated this limitation by balancing procedural type, operative times, and preoperative risk factors, which are closely related to these variables. Detailed data on individual vasoactive drug dosages were also not assessed. Although we applied both 10-fold cross-validation and bootstrap resampling with optimism correction to evaluate model performance, these internal validation strategies cannot replace external validation. Besides, while intraoperative oxygenation parameters were monitored rigorously, explicit GDP strategies were not applied, which constitutes a clear objective for future randomized investigations. A differential attribution of findings to low DO_2 during versus after CPB is not feasible, as our analysis was deliberately limited to the cross-clamp period. Furthermore, it is prudent to acknowledge possible unmeasured confounding factors that could have impacted our mediation analysis. Specifically, although the SIRS criteria effectively represent the clinical manifestations of systemic inflammation, they do not directly measure the underlying inflammatory mechanisms. SEM inherently depends on defined assumptions about causal relationships between variables, assumptions that might not fully encompass the complexity of inflammatory responses following cardiac surgery. Consequently, the robustness and interpretation of our findings hinge upon the validity of these assumptions, and any violation could substantially affect the conclusions drawn. Thus, our SEM-based mediation analysis should be interpreted as exploratory, providing preliminary insights into potential mediating effects rather than

establishing definitive causal relationships. Missingness was negligible (~0.15%) and limited to preoperative CRP; we used single chained-equations imputation to complete these values, noting the minimal information loss. Finally, our findings are not directly corroborated by prior randomized trials, highlighting the need for external validation and future trials.

CONCLUSION

Our study identifies low DO_2i during CPB as an independent predictor of postoperative SIRS and worsened outcome. Beyond AKI, intraoperative ischemia emerges as a significant immuno-inflammatory mediator, underscoring the necessity of adequate oxygenation. Future studies should evaluate GDP's effectiveness as an anti-inflammatory strategy in cardiac surgery.

Funding Statement: no funding

Conflict of Interest Statement: nothing to disclose

IRB/ERB/EC Approval: the study was approved by the IRCCS Istituto Tumori Giovanni Paolo II – Bari, Review Board (1431/CEL – 03/11/2023) and written informed consent was obtained from all patients

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author

Author Contributions: E.S. contributed to the conception and design of the study, data acquisition, analysis, and interpretation, and drafted the manuscript. G.B., D.B., M.R., P.V., G.S., and G.P. were involved in data acquisition, analysis, and interpretation, and critically revised the manuscript. D.P., R.L., and R.W. provided substantial contributions to the study's conception, supervised the analysis/interpretation of the data, and critically revised the manuscript. All authors have read and approved the final manuscript

FIGURE LEGEND

Central Image. Low DO_2i during cardiopulmonary bypass is associated with increased risk of postoperative SIRS and adverse outcomes. Goal-directed perfusion may mitigate inflammation-related complications. DO_2i: indexed oxygen delivery; SIRS: systemic inflammatory response syndrome

Figure 1. Flowchart of the study cohort

Figure 2. Receiver Operating Characteristic Curves of the Main Predictors of SIRS. DO_2i: indexed oxygen delivery; SIRS: systemic inflammatory reaction syndrome

Figure 3. Inflammatory Markers within the Propensity Score Matched Subpopulation. DO_2i: indexed oxygen delivery

Figure 4. Mediation Effect Plot. DO_2i: indexed oxygen delivery; SIRS: systemic inflammatory reaction syndrome

342 **Table 1. Characteristics of Patients by DO_2i Threshold after Propensity Score Matching**

Variables	Unit	Overall	Low DO_2i	High DO_2i	p-value	SMD before PSM	SMD after PSM
Cohort	n	908 (100)	390	390			
Preoperative Data							
Age	years	68 [61-75]	68 [60-75]	68 [60-74]	0.932	-0.092	-0.005
Female sex	n, %	270 (29.7)	126 (32.3)	112 (28.7)	0.312	0.244	0.075
Body Mass Index	kg/m^2	26.7 [24.2-29.8]	26.4 [24.2-29.7]	26.8 [24.2-29.7]	0.568	-0.110	-0.051
EuroSCORE II	%	1.8 [1.2-3.0]	1.9 [1.2-3.1]	1.8 [1.1-2.9]	0.208	0.129	0.052
Left ventricular ejection fraction	%	55 [50-60]	55 [50-60]	55 [53-60]	0.491	0.105	0.020
Risk factors	n, %						
Obesity		225 (24.8)	94 (24.1)	96 (24.6)	0.934	-0.042	-0.012
Diabetes		177 (19.5)	71 (18.2)	69 (17.7)	0.926	-0.036	0.013
Previous cardiac surgery		62 (6.8)	25 (6.4)	26 (6.7)	1.000	0.042	-0.010
Laboratory data							
Hemoglobin	g/dL	13.6 [12.3-14.6]	13.6 [12.4-14.6]	13.5 [12.3-14.4]	0.879	-0.199	0.011
Leukocytes	x10^3/µL	7.2 [6.0-8.7]	7.1 [6.0-8.5]	7.1 [5.9-8.7]	0.875	0.166	0.010
Neutrophils	x10^3/µL	4.5 [3.6-5.8]	4.4 [3.7-5.6]	4.5 [3.6-5.8]	0.787	0.150	-0.007
Lymphocytes	x10^3/µL	1.8 [1.5-2.2]	1.8 [1.5-2.2]	1.8 [1.5-2.1]	0.871	0.016	0.008
Thrombocytes	x10^3/µL	195 [161-241]	196 [159-244]	195 [163-241]	0.876	0.134	0.037

CRP	mg/dL	1.3 [0.3-5.1]	1.3 [0.2-5.0]	1.1 [0.3-4.6]	0.937	0.025	-0.036
Glomerular filtration rate	mL/min	83 [64-100]	84 [64-100]	84 [65-103]	0.576	-0.140	-0.043
Intraoperative Data							
Procedure	n, %				0.877	0.139	0.014
Isolated CABG		276 (30.4)	153 (39.2)	157 (40.3)			
Single non-CABG		242 (26.6)	134 (34.4)	131 (33.6)			
Two procedures		223 (24.6)	82 (21.0)	80 (20.5)			
Three procedures		168 (18.5)	21 (5.4)	22 (5.6)			
Surgical times	Minutes						
CPB		88 [66-116]	89 [64-119]	88 [67-115]	0.860	0.110	0.031
Cross-clamp		60 [42-84]	61 [43-85]	60 [42-81]	0.693	0.079	0.023
Median DO_2i	$mL/min/m^2$	295 [270-320]	270 [252-282]	318 [305-338]	<0.001		
Median DO_2i < critical value	n, %	432 (47.6)	-	-	-		
Hemoglobin (nadir)	g/dL	9.2 [8.1-10.2]	9.1 [7.8-10.1]	9.3 [8.2-10.2]	0.018		
Lactates (peak)	mmol/L	1.5 [1.2-2.0]	1.5 [1.2-1.9]	1.5 [1.2-2.0]	0.851		
Blood transfusion	n, %	147 (16.2)	77 (19.7)	49 (12.6)	0.009		
Pharmacological support	n, %	287 (31.6)	138 (35.4)	105 (26.9)	0.013		
Postoperative Results							
SIRS	n, %	221 (24.3)	130 (33.3)	56 (14.4)	<0.001		

Mortality (30-day)	n, %	11 (1.2)	9 (2.3)	1 (0.3)	0.026		
Composite outcome	n, %	120 (13.2)	69 (17.7)	32 (8.2)	<0.001		
Duration							
Mechanical ventilation	Hours	3 [1-11]	4 [2-12]	3 [1-10]	0.002		
ICU stay	Days	1 [1-2]	1 [1-3]	1 [1-1]	<0.001		
Complications	n, %						
Vasoactive support (>24h)		246 (27.1)	121 (31.0)	91 (23.3)	0.020		
Revision for bleeding		22 (2.4)	16 (4.1)	3 (0.8)	0.005		
Renal replacement therapy		13 (1.4)	8 (2.1)	3 (0.8)	0.225		
TIA/stroke		2 (0.2)	1 (0.3)	1 (0.3)	1.000		
Blood transfusion	n, %	172 (18.9)	91 (23.3)	58 (14.9)	0.004		
Mechanical circulatory support	n, %	5 (0.6)	1 (0.3)	1 (0.3)	1.000		
Laboratory data							
Leukocytes	x10^3/µL	12.3 [10.0-15.0]	12.9 [10.4-15.4]	11.7 [9.8-14.5]	0.001		
Neutrophils	x10^3/µL	10.5 [8.3-12.9]	11.0 [8.9-13.4]	9.9 [8.2-12.3]	<0.001		
Lymphocytes	x10^3/µL	1.1 [0.8-1.5]	1.1 [0.8-1.7]	1.0 [0.7-1.4]	0.001		
Thrombocytes	x10^3/µL	152 [118-189]	154 [115-194]	152 [122-185]	0.788		
CRP	mg/dL	36.4 [18.4-65.7]	53.3 [18.9-78.1]	28.6 [16.3-44.4]	<0.001		

CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; CRP: C-reactive protein; ICU: intensive care unit; SIRS: systemic inflammatory reaction syndrome

345 **Table 2. Multivariable Logistic Regression Models**

Variable	Estimate	Odds Ratio [95% CI]	p-value
SIRS			
Constant	1.75	5.752 [0.761-43.479]	0.090
Age (x10 years)	-5.81	0.461 [0.375-0.566]	<0.001
Female gender	0.59	1.795 [1.157-2.786]	0.009
EuroSCORE II (x1%)	4.09	1.282 [1.135-1.447]	<0.001
Left Ventricular Ejection Fraction (x5%)	3.16	1.280 [1.111-1.475]	<0.001
Preoperative Hemoglobin (x1 g/dL)	-3.14	0.742 [0.637-0.863]	<0.001
Preoperative C-Reactive Protein (x1 mg/dL)	6.04	1.257 [1.152-1.371]	<0.001
Preoperative Leukocytes (x1 x10^3/µL)	6.25	1.167 [1.002-1.359]	<0.001
Preoperative thrombocytes (x50 x10^3/µL)	1.82	0.461 [0.375-0.566]	0.047
Median DO_2i (x10 mL/min/m^2)	-4.76	0.798 [0.750-0.850]	<0.001
Intraoperative hemoglobin nadir (x1 g/dL)	-1.62	0.779 [0.649-0.934]	0.007
Intraoperative lactates peak (x1 mmol/L)	4.31	1.247 [0.986-1.577]	0.065
Intraoperative blood transfusion	-0.46	0.629 [0.350-1.130]	0.121
Intraoperative pharmacological support	0.86	2.356 [1.495-3.713]	<0.001
Composite Outcome			
Constant	-4.01	0.018 [0.008-0.042]	<0.001
Female gender	0.49	1.624 [1.012-2.605]	0.044
EuroSCORE II (%)	3.59	1.480 [1.234-1.776]	<0.001
Preoperative C-Reactive Protein (mg/dL)	1.97	1.054 [0.990-1.123]	0.102
Preoperative Leukocytes (x10^3/µL)	1.57	1.168 [0.986-1.384]	0.072
CPB time (min)	3.59	1.319 [1.063-1.638]	0.012
Median DO_2i < critical value	0.53	1.697 [1.051-2.742]	0.031
Intraoperative hemoglobin nadir (g/dL)	-1.25	0.668 [0.456-0.977]	0.038
SIRS	1.35	3.873 [2.350-6.383]	<0.001
Interaction term			

Median DO_2i < critical value + SIRS	-0.20	0.820 [0.331- 2.037]	0.670

Notes: Continuous predictors were min–max scaled prior to fitting for numerical stability; odds ratios are back-transformed and expressed per clinically meaningful increments. DO_2i: indexed oxygen delivery; SIRS: systemic inflammatory reaction syndrome

Table 3. Mediation Analysis for SIRS as Mediator of Median DO_2i < Critical Value for Composite Outcome

	Estimate	Odds Ratio [95%CI]	p-value
Total Effect	0.11	1.117 [1.065-1.164]	<0.001
Average Causal Mediation Effect	0.06	1.052 [1.036-1.067]	<0.001
Average Direct Effect	0.07	1.061 [1.014-1.106]	0.004
Proportion Mediated (Average Causal Mediation Effect/Total Effect): 46.2%			<0.001

DO_2i: indexed oxygen delivery; SIRS: systemic inflammatory reaction syndrome

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Figure 1

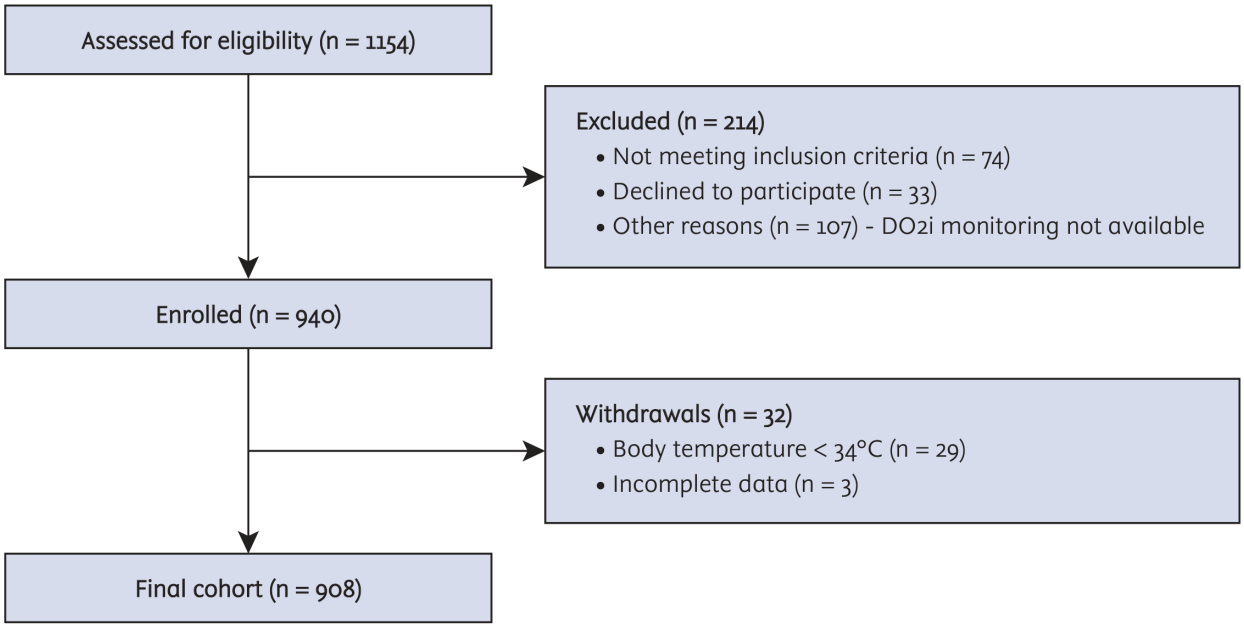

Assessed for eligibility (n = 1154)
Excluded (n = 214)
• Not meeting inclusion criteria (n = 74)
• Declined to participate (n = 33)
• Other reasons (n = 107) - DO2i monitoring not available
Enrolled (n = 940)
Withdrawals (n = 32)
• Body temperature < 34°C (n = 29)
• Incomplete data (n = 3)
Final cohort (n = 908)

Figure 2

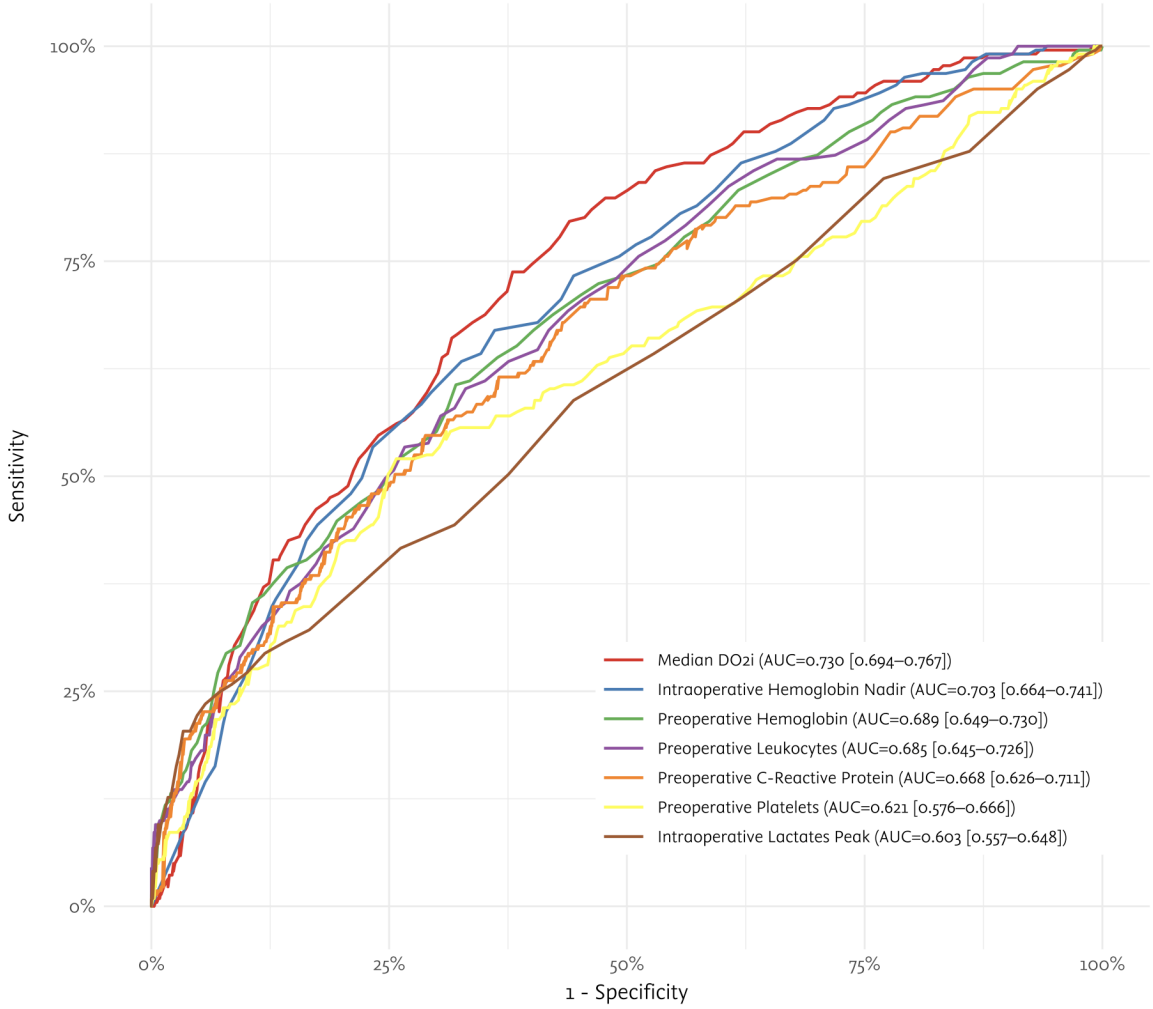

100%
75%
50%
25%
0%
Sensitivity
0%
25%
50%
75%
100%
1 - Specificity
Median DO2i (AUC=0.730 [0.694–0.767])
Intraoperative Hemoglobin Nadir (AUC=0.703 [0.664–0.741])
Preoperative Hemoglobin (AUC=0.689 [0.649–0.730])
Preoperative Leukocytes (AUC=0.685 [0.645–0.726])
Preoperative C-Reactive Protein (AUC=0.668 [0.626–0.711])
Preoperative Platelets (AUC=0.621 [0.576–0.666])
Intraoperative Lactates Peak (AUC=0.603 [0.557–0.648])

Figure 3

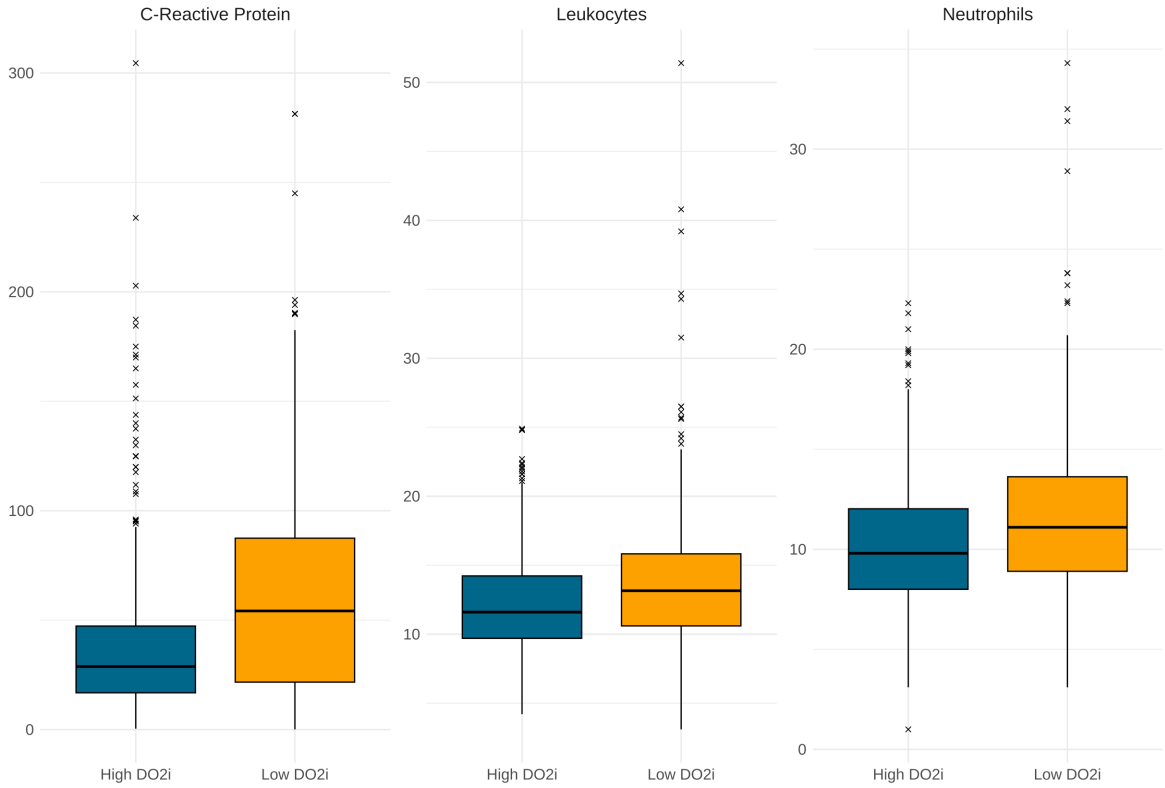
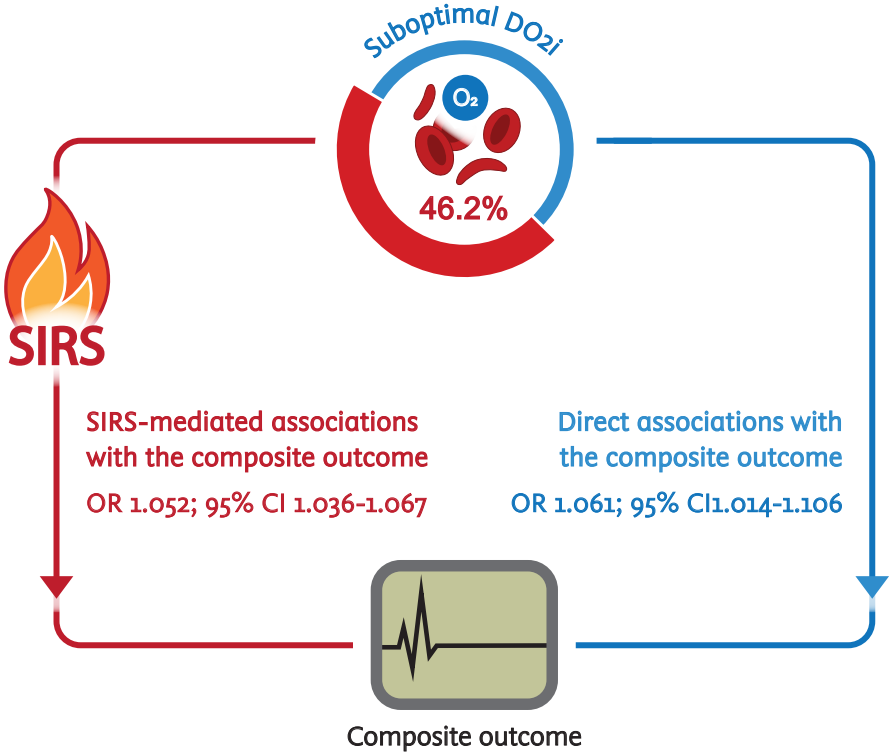

C-Reactive Protein
300
200
100
0
High DO2i
Low DO2i
Leukocytes
50
40
30
20
10
High DO2i
Low DO2i
Neutrophils
30
20
10
0
High DO2i
Low DO2i

Figure 4

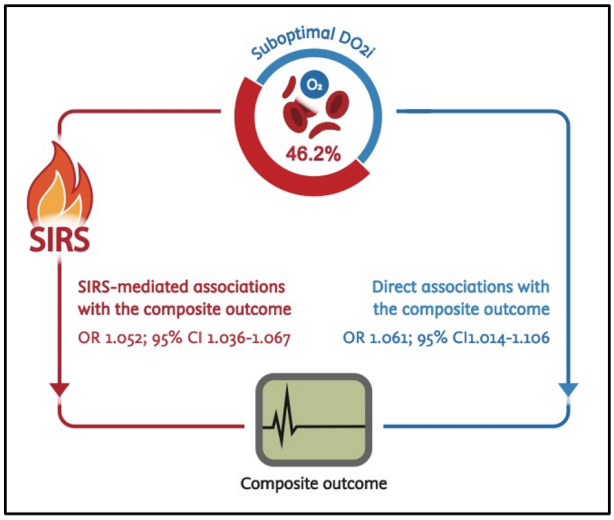

Suboptimal DO2i
O2
46.2%
SIRS
SIRS-mediated associations with the composite outcome
OR 1.052; 95% CI 1.036-1.067
Direct associations with the composite outcome
OR 1.061; 95% CI1.014-1.106
Composite outcome

Graphical abstract

Inadequate Oxygen Delivery During Cardiopulmonary Bypass Drives Inflammatory Reaction After Cardiac Surgery

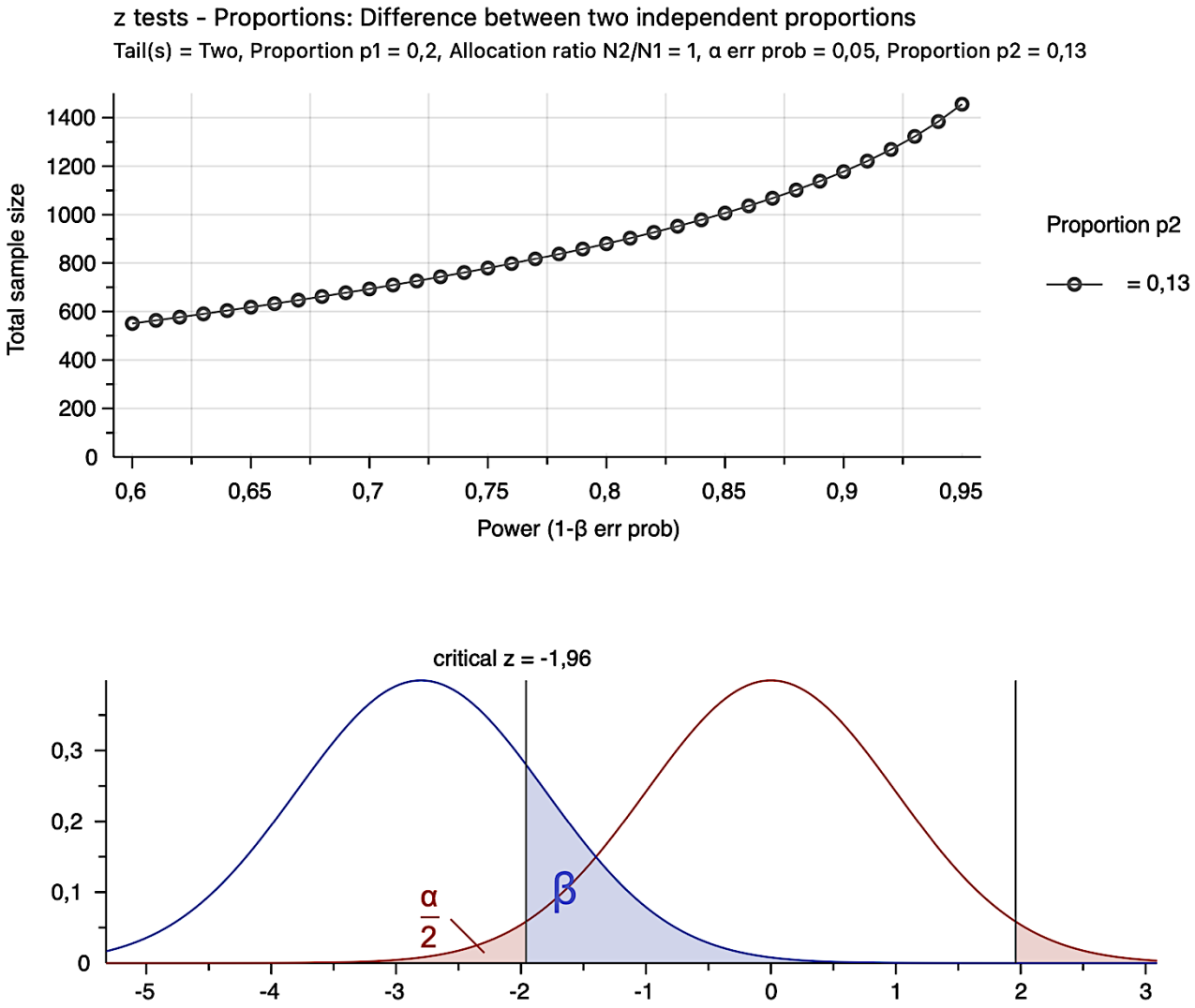
Summary

In 908 adult patients undergoing cardiac surgery with cardiopulmonary bypass, low indexed oxygen delivery (**DO_2i ≤293 mL/min/m²**) was associated with a higher risk of **systemic inflammation** and **adverse outcomes**. Goal-directed perfusion strategies may reduce inflammation-related complications



Legend: DO_2i: indexed oxygen delivery; SIRS: systemic inflammatory reaction syndrome

Suppl. Figure S1. Sample Size Determination



Suppl. Table S1. Center Effect Diagnostics and DO_2i Estimates (SIRS Model)

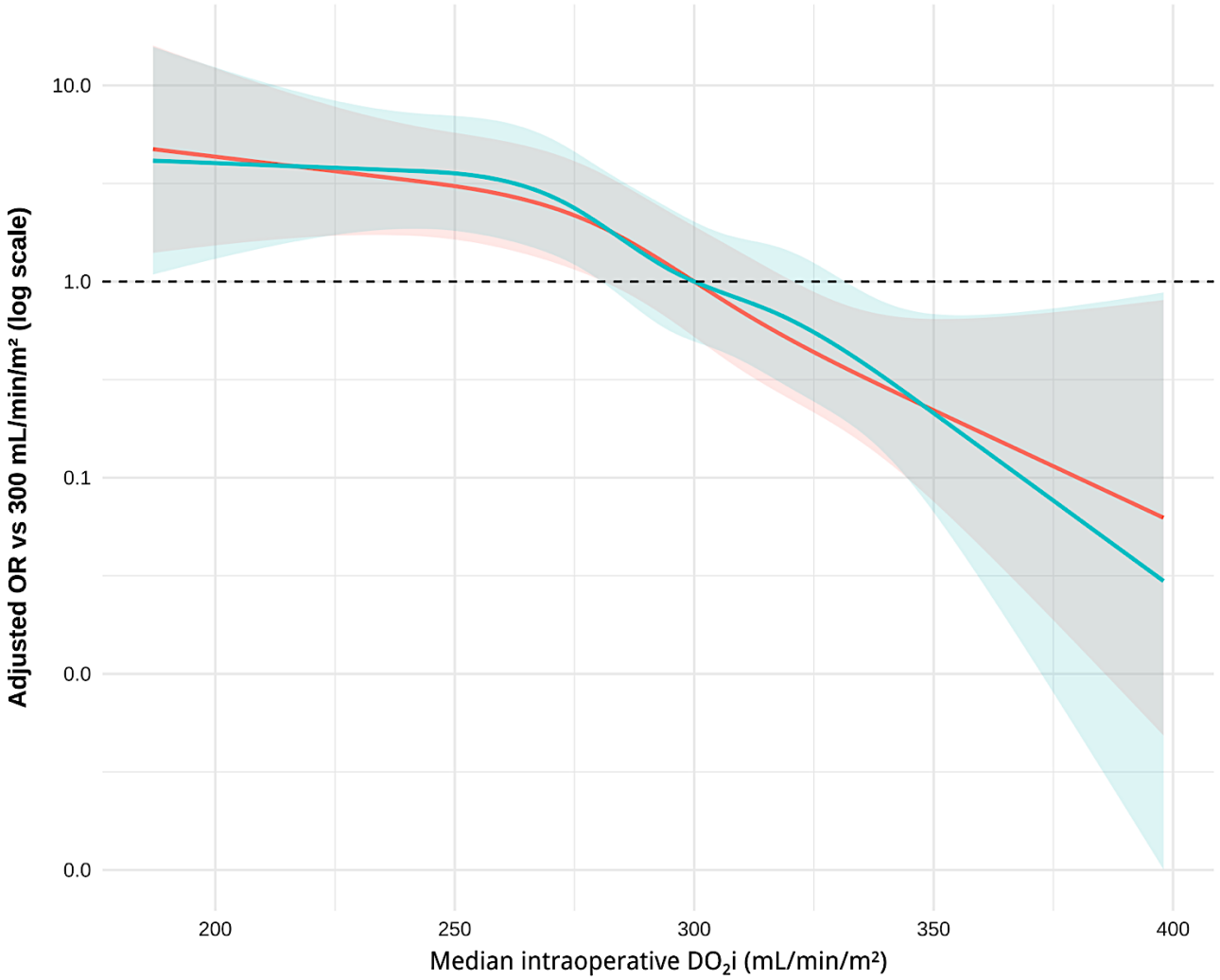
Metric	Value
Mixed-effects diagnostics	
Centers, n	2
Observations, n	908
Random intercept variance (center)	0.000
Random intercept SD (center)	0.000
Intraclass Correlation Coefficient (ICC) (latent scale)	0
Model singularity (lme4::isSingular)	TRUE
R^2 marginal (fixed effects only)	0.607
R^2 conditional (fixed + random effects)	0.607
DO_2i (median): GLM vs GLMM	
GLM - OR [95% CI]; p-value	0.0089 [0.00235-0.0335]; 3.24×10^{-12}
GLMM - OR [95% CI]; p-value	0.0089 [0.00235-0.0335]; 3.24×10^{-12}
Sensitivity: center fixed (GLM)	
Model fit (no center): Residual DF / Dev / AIC	893 / 602.88 / 632.88
Model fit (+ center): Residual DF / Dev / AIC	892 / 602.49 / 634.49
LRT p-value	0.5319
center1 - [95% CI]; p-value	0.855 [0.525-1.393]; 0.5303

Note. Mixed-effects logistic regression with a random intercept for center. Random variance estimated at the boundary (singular fit), implying ICC ≈0 and identical marginal/conditional R^2.

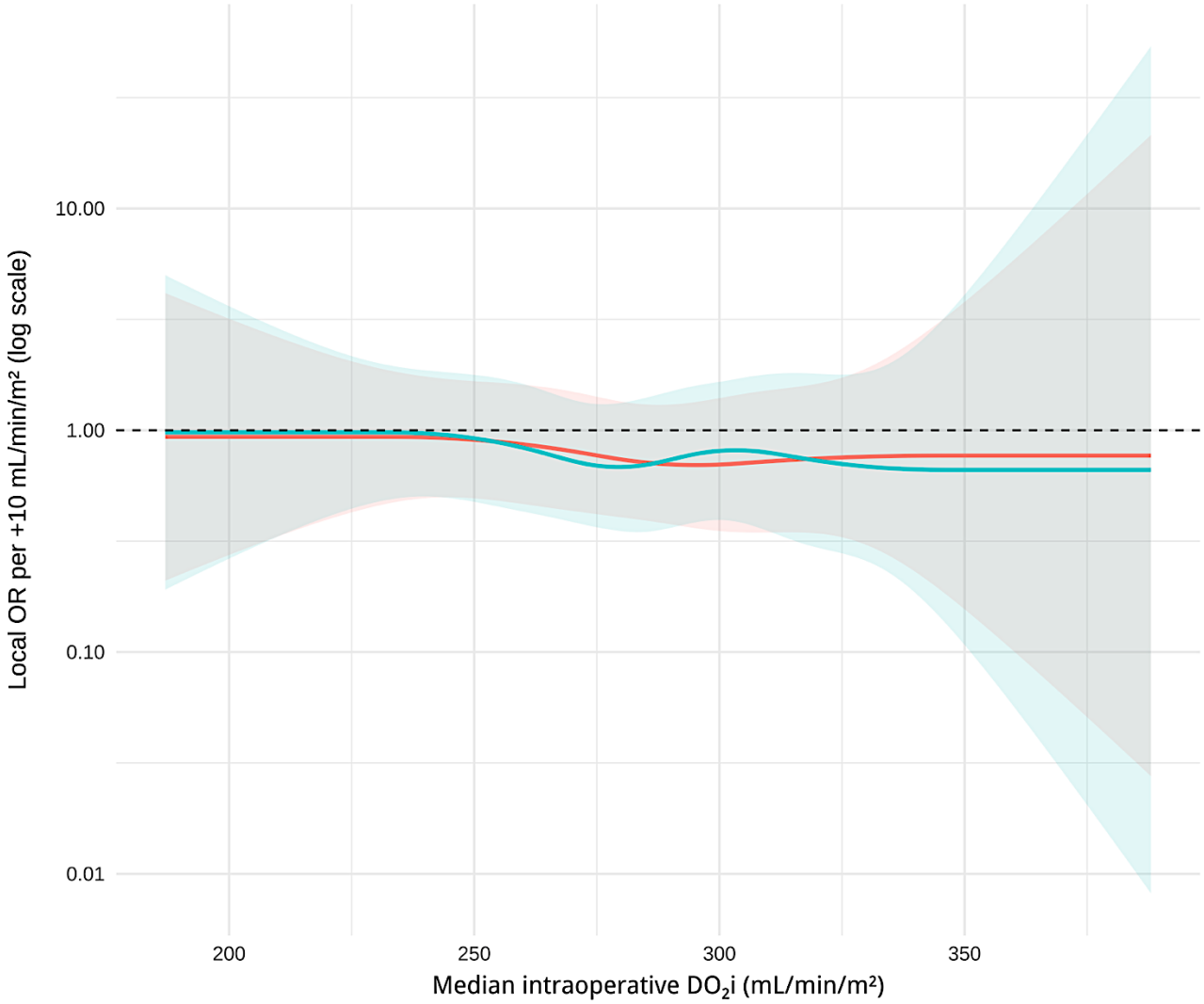
Suppl. Table S2. Adjusted Restricted Cubic Spline Models Coefficients

Term	Estimate	SE	z	p-value	Estimate	SE	z	p-value
	4 knots				5 knots			
Intercept	7.741	2.933	2.640	0.008	6.777	3.225	2.101	0.036
DO_2i (linear)	-0.007	0.009	-0.807	0.420	-0.003	0.010	-0.272	0.786
DO_2i (spline 1)	-0.045	0.029	-1.550	0.121	-0.088	0.062	-1.410	0.159
DO_2i (spline 2)	0.138	0.131	1.054	0.292	0.345	0.352	0.979	0.327
DO_2i (spline 3)	-	-	-	-	-0.453	0.639	-0.708	0.479
Age	-0.094	0.013	-7.228	<0.001	-0.094	0.013	-7.197	<0.001
Female (vs male)	0.509	0.231	2.199	0.028	0.507	0.232	2.188	0.029
EuroSCORE II	0.197	0.067	2.924	0.003	0.194	0.068	2.873	0.004
LVEF	0.055	0.015	3.706	<0.001	0.056	0.015	3.726	<0.001
Preop Hb	-0.306	0.080	-3.815	<0.001	-0.304	0.080	-3.785	<0.001
Preop WBC	0.225	0.046	4.921	<0.001	0.224	0.046	4.905	<0.001
Preop CRP	0.032	0.009	3.421	<0.001	0.032	0.009	3.404	<0.001
Preop Platelets	0.003	0.002	1.905	0.057	0.003	0.002	1.886	0.059
Preop eGFR	-0.011	0.005	-2.335	0.020	-0.011	0.005	-2.327	0.020
Surgery (2)	-0.325	0.267	-1.219	0.223	-0.330	0.267	-1.237	0.216
Surgery (3)	0.085	0.343	0.246	0.806	0.083	0.344	0.243	0.808
Surgery (4)	0.193	0.570	0.338	0.735	0.176	0.572	0.309	0.758
Bypass time	0.003	0.005	0.546	0.585	0.002	0.005	0.527	0.598
Clamp time	-0.006	0.006	-0.919	0.358	-0.006	0.006	-0.873	0.383
Intraop Hb nadir	-0.224	0.096	-2.341	0.019	-0.231	0.096	-2.399	0.016
Intraop lactate peak	0.275	0.136	2.025	0.043	0.285	0.138	2.066	0.039
Intraop RBC transfusion	-0.473	0.303	-1.559	0.119	-0.480	0.304	-1.578	0.115
Pharmacologic support	0.806	0.242	3.333	<0.001	0.803	0.242	3.320	<0.001

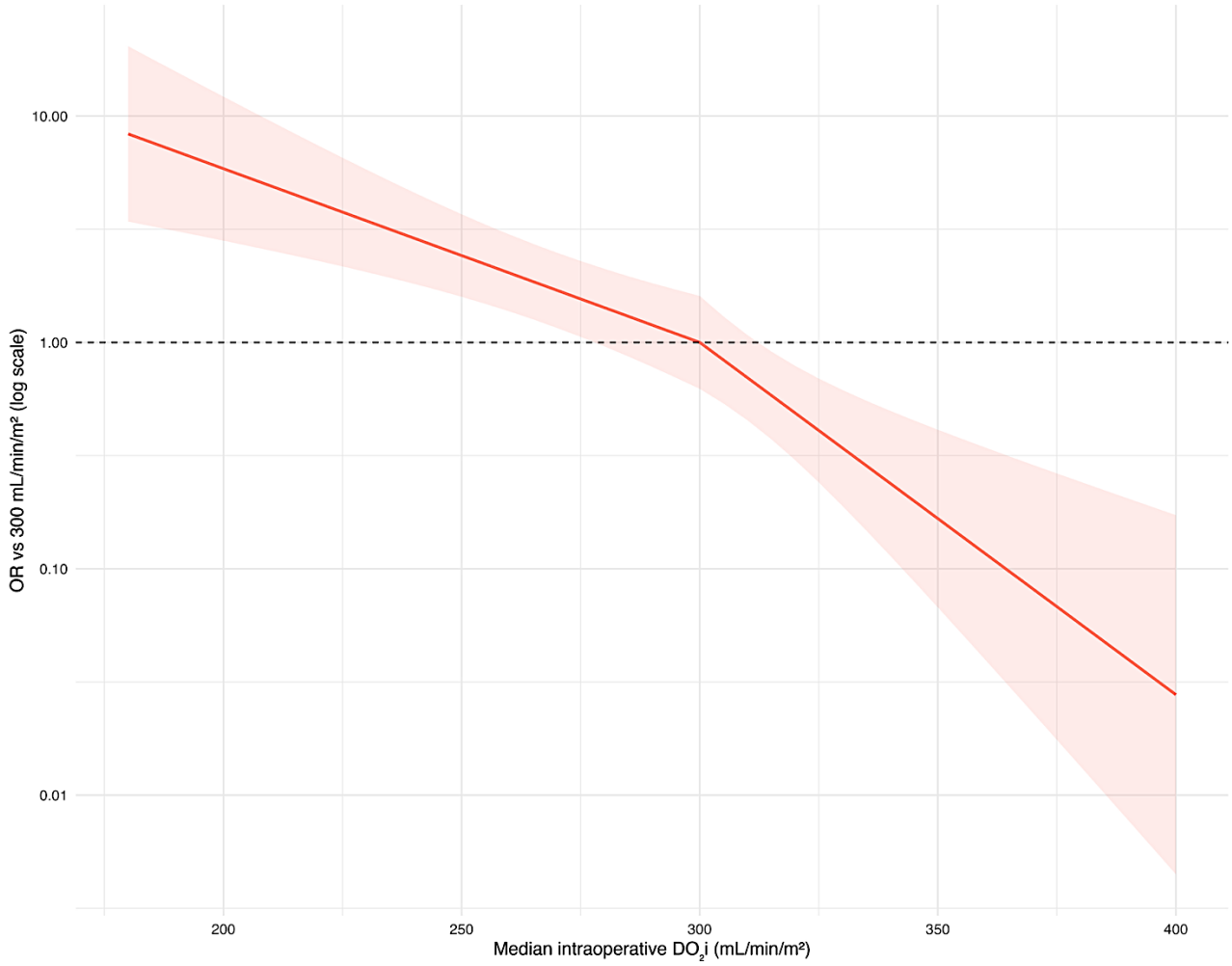
Suppl. Figure S2. Adjusted Restricted Cubic Spline Regression Showing the Adjusted effect-scale association between DO_2i and SIRS. Odds ratio (y-axis, log scale) across the observed DO_2i range with reference set at 300 mL/min/m^2. Red Line: 4 Knots; Blue Line: 5 Knots. Non-linear Wald p was 0.099 (4 knots) and 0.155 (5 knots)



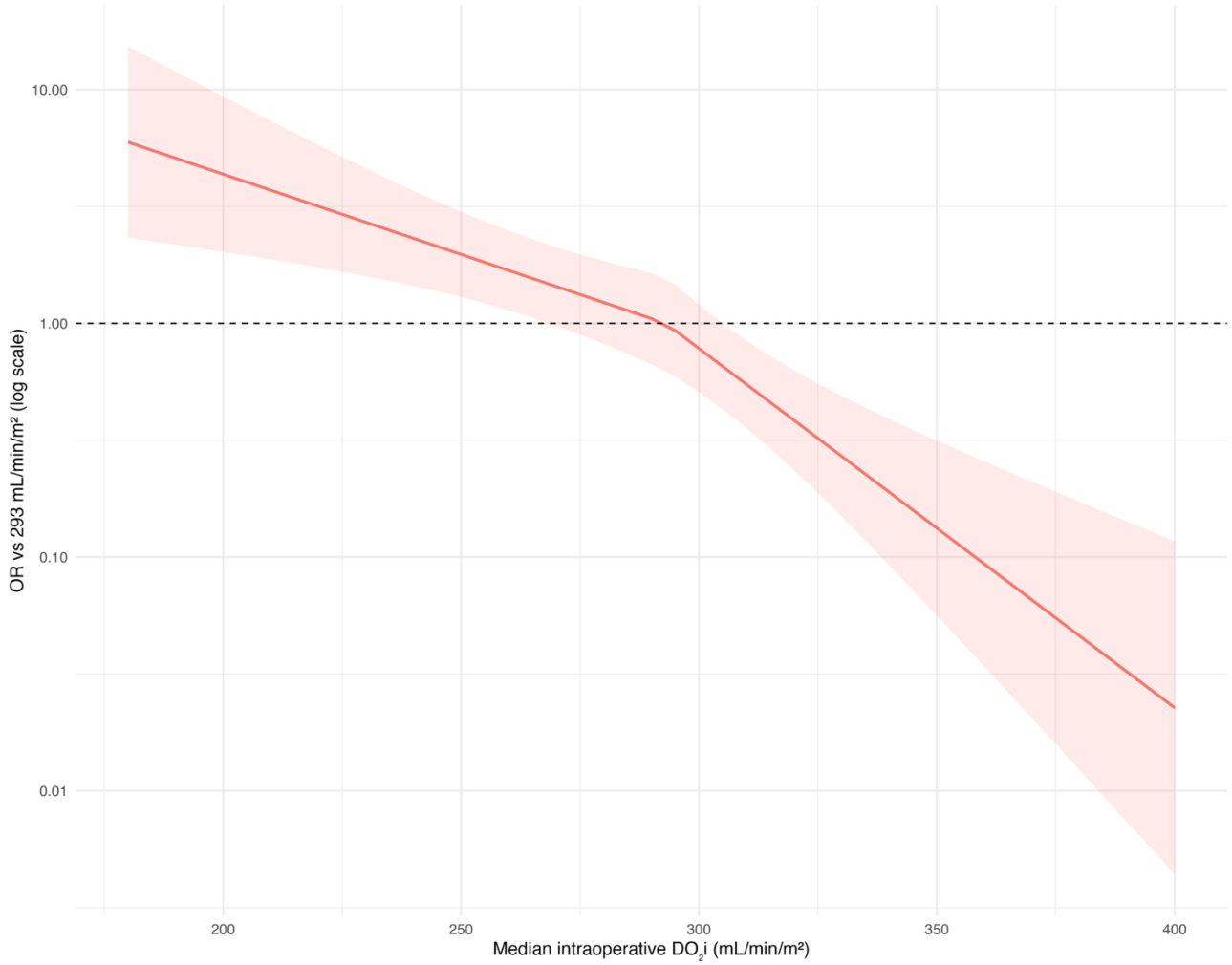
Suppl. Figure S3. Local Slope Plot (d log-odds / d DO_2i). Red Line: 4 Knots; Blue Line: 5 Knots



Suppl. Figure S4. Sensitivity Analysis – Linear spline (lsp) with a Single Knot Placed a Priori at 300 mL/min/m^2. Odds ratio (y-axis, log scale) across the observed DO_2i range with reference set at 300 mL/min/m^2



Suppl. Figure S5. Sensitivity Analysis – Linear spline (lsp) with a Single Knot Placed a Priori at 293 mL/min/m^2. Odds ratio (y-axis, log scale) across the observed DO_2i range with reference set at 300 mL/min/m^2



Suppl. Table S3. Logistic Regression Using DO_2i Quintiles for Postoperative SIRS (reference Q5: 327-398 mL/min/m2)

DO_2i Quintiles	**Odds Ratio [95% CI]**	**p-value**
Q1 [186-275 mL/min/m^2]	10.012 [4.658-23.351]	<0.001
Q2 [266-286 mL/min/m^2]	5.864 [2.678-13.857]	<0.001
Q3 [287-305 mL/min/m^2]	3.487 [1.568-8.300]	0.003
Q4 [306-326 mL/min/m^2]	1.405 [0.587-3.497]	0.452

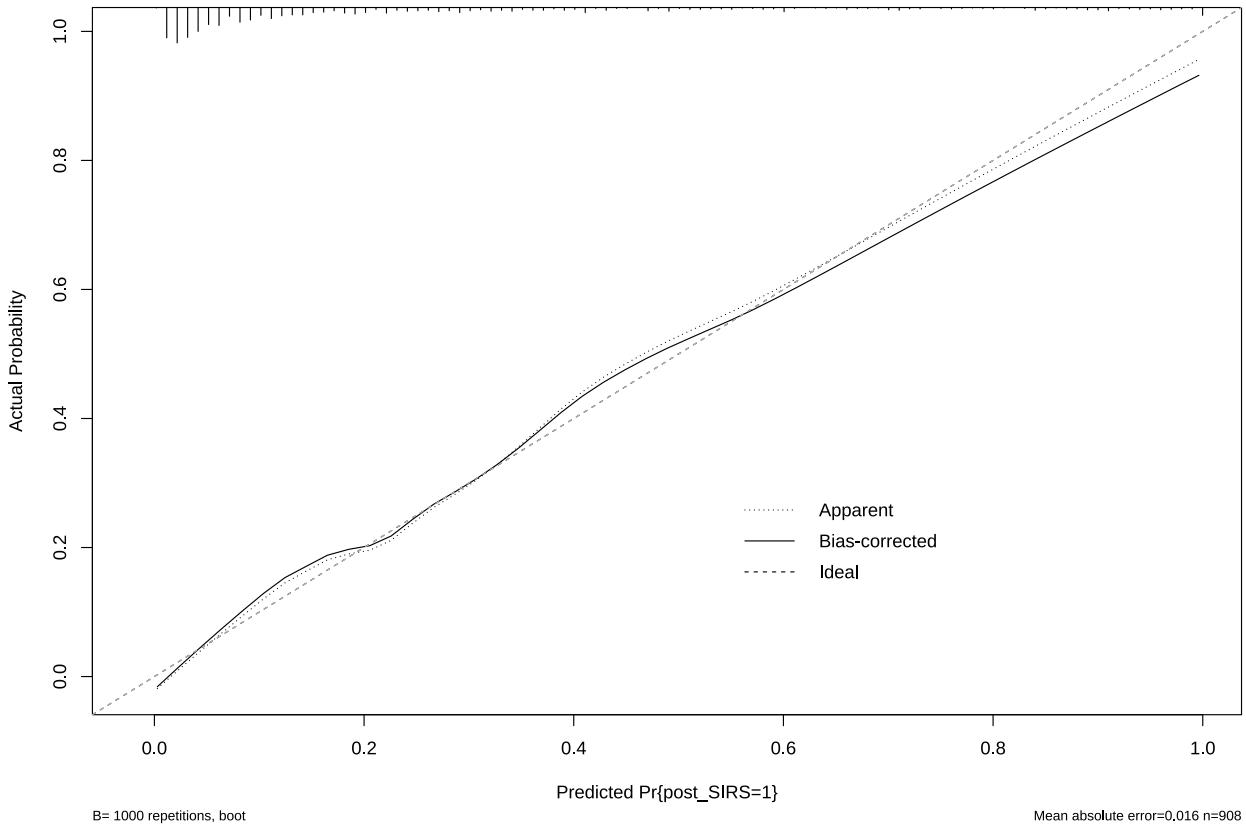
Suppl. Table S4. Piecewise Linear Model at the Q3-Q4 Boundary

Segment	Beta	SE	p-value
Slope ≤ 305 mL/min/m^2	-0.019	0.004	<0.001
Slope > 305 mL/min/m^2	-0.037	0.012	0.001

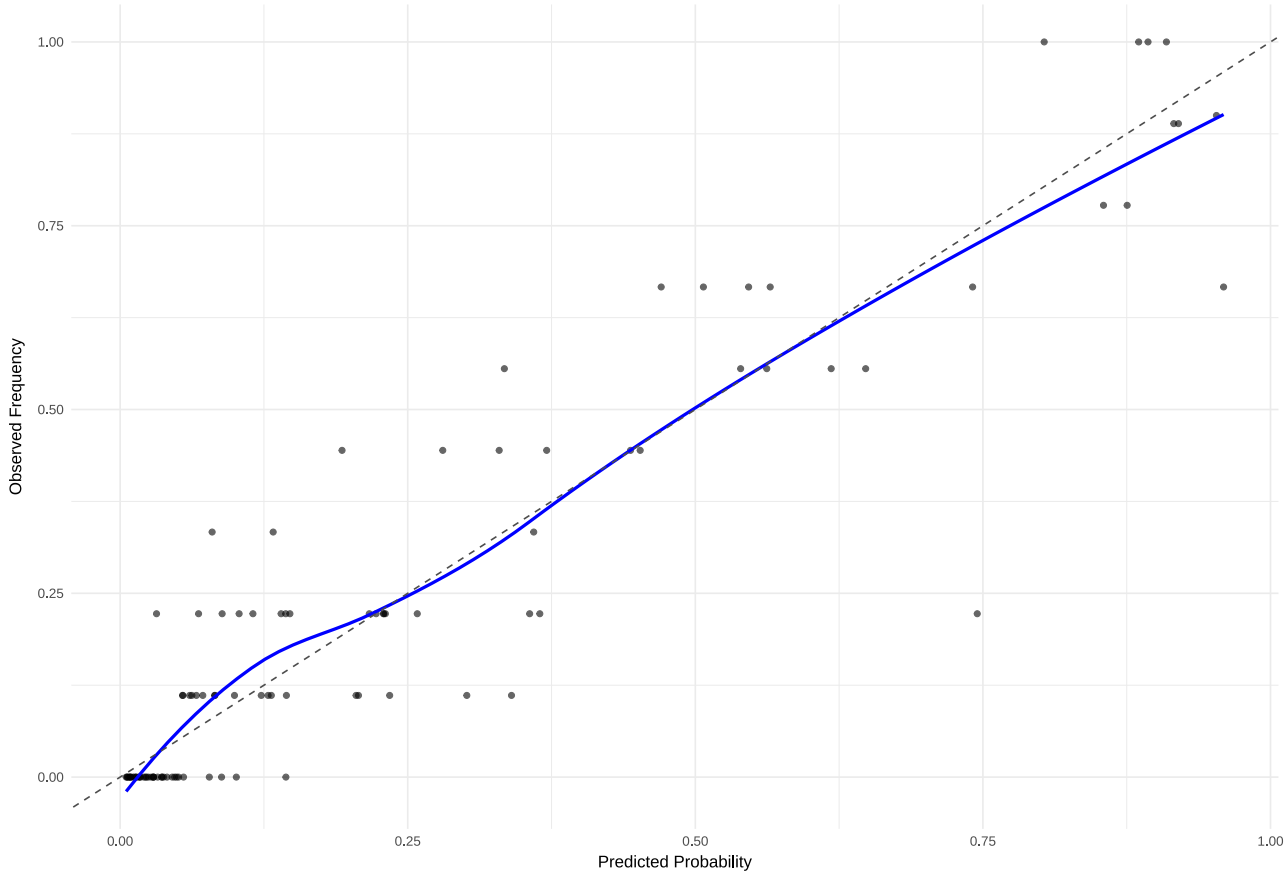
Suppl. Table S5. Model Fit Comparison (AIC) and Nonlinearity Tests

Model	Specification	AIC	p-value
Linear	-	635.92	NA
Restricted cubic spline	4 knots	635.21	0.099
Restricted cubic spline	5 knots	636.02	0.155
Broken-stick (linear spline)	Knot at 300	635.75	0.151
Broken-stick (linear spline)	Knot at 293	634.96	0.092

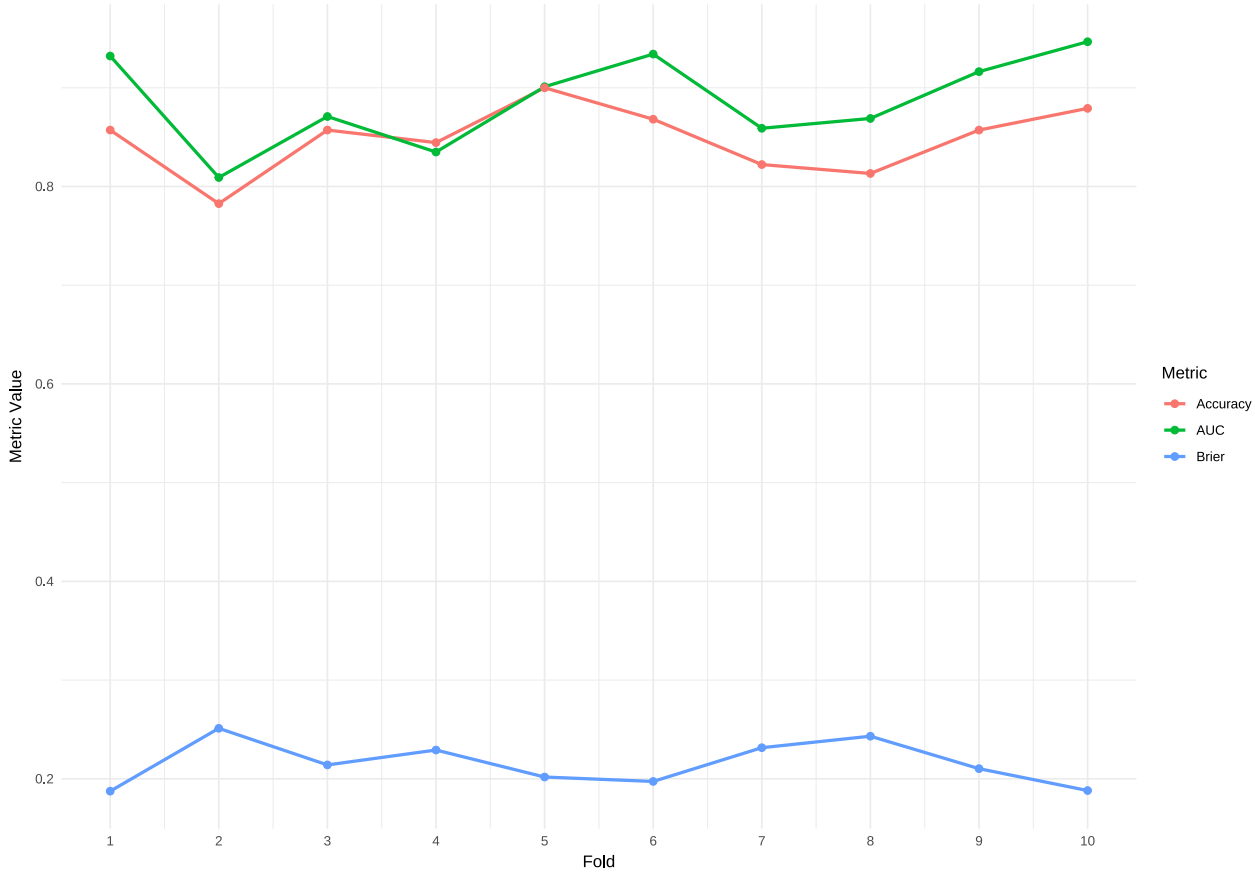
Suppl. Figure S6. Bias-corrected Calibration Curve of the Logistic Regression Model for Predicting SIRS. Internal Validation Was Performed Using 1,000 Bootstrap Resamples



Suppl. Figure S7. 10-fold Cross-Validated Calibration Curve of the Logistic Regression Model for Predicting SIRS



Suppl. Figure S8. Internal model performance across the 10-fold cross-validation



Suppl. Table S6. Internal performance of the logistic regression model evaluated through 10-fold cross-validation and via bootstrap resampling (1,000 iterations)

10-fold cross-validation		
Metric	**Mean**	**Standard Deviation**
AUC	0.887	0.046
Brier Score	0.215	0.023
Accuracy	0.848	0.034
Calibration Intercept	0.097	0.582
Calibration Slope	1.070	0.443

Bootstrap resampling (1,000 iterations)			
Metric	**Original**	**Corrected**	**Optimism**
AUC (from Somers' Dxy)	0.898	0.889	0.009
Somers' Dxy	0.796	0.777	0.018
Calibration Intercept	0.000	-0.061	0.061
Calibration Slope	1.000	0.932	0.068
E_max	0.000	0.026	0.026
Brier Score	0.105	0.111	-0.005

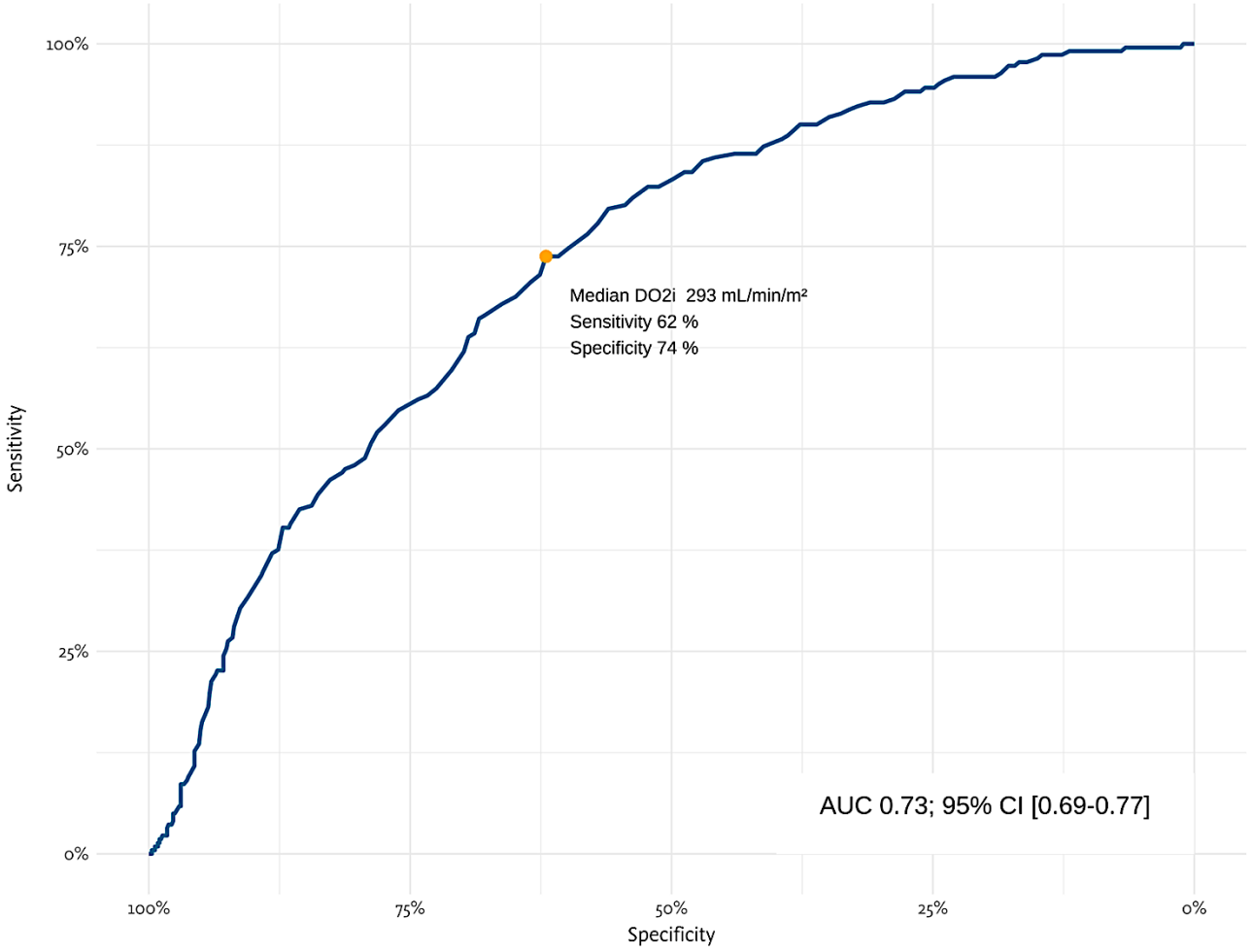
Suppl. Table S7. Characteristics of Patients by SIRS

Variables	Unit	SIRS	NoSIRS	p-value
Cohort	n	221 (24.3)	687 (75.7)	
Preoperative Data				
Age	years	65 [57-70]	70 [62-76]	<0.001
Female sex	n, %	97 (43.9)	173 (25.2)	<0.001
Body Mass Index	kg/m^2	26.7 [23.9-30.1]	26.6 [24.2-29.7]	0.838
EuroSCORE II	%	2.3 [1.4-4.3]	1.7 [1.1-2.7]	<0.001
Left ventricular ejection fraction	%	60 [50-64]	55 [50-60]	<0.001
Risk factors	n, %			
Obesity		60 (27.1)	165 (24.0)	0.371
Diabetes		50 (22.6)	127 (18.5)	0.204
Previous cardiac surgery		27 (12.2)	35 (5.1)	<0.001
Laboratory data				
Hemoglobin	g/dL	12.6 [11.3-14.0]	13.9 [12.6-14.7]	<0.001
Leukocytes	x10^3/µL	8.2 [6.8-10.2]	6.8 [5.9-8.2]	<0.001
Neutrophils	x10^3/µL	5.4 [4.3-7.0]	4.3 [3.4-5.4]	<0.001
Lymphocytes	x10^3/µL	1.9 [1.5-2.2]	1.8 [1.5-2.2]	0.240
Thrombocytes	x10^3/µL	230 [170-270]	191 [159-229]	<0.001
CRP	mg/dL	3.7 [0.8-12.7]	0.9 [0.2-3.8]	<0.001
Glomerular filtration rate	mL/min	80 [62-101]	84 [66-100]	0.171
Intraoperative Data				
Procedure	n, %			0.002
Isolated CABG		85 (38.5)	191 (27.8)	
Single non-CABG		56 (25.3)	186 (27.1)	
Two procedures		47 (21.3)	176 (25.7)	
Three procedures		33 (14.9)	135 (19.6)	
Surgical times	Minutes			

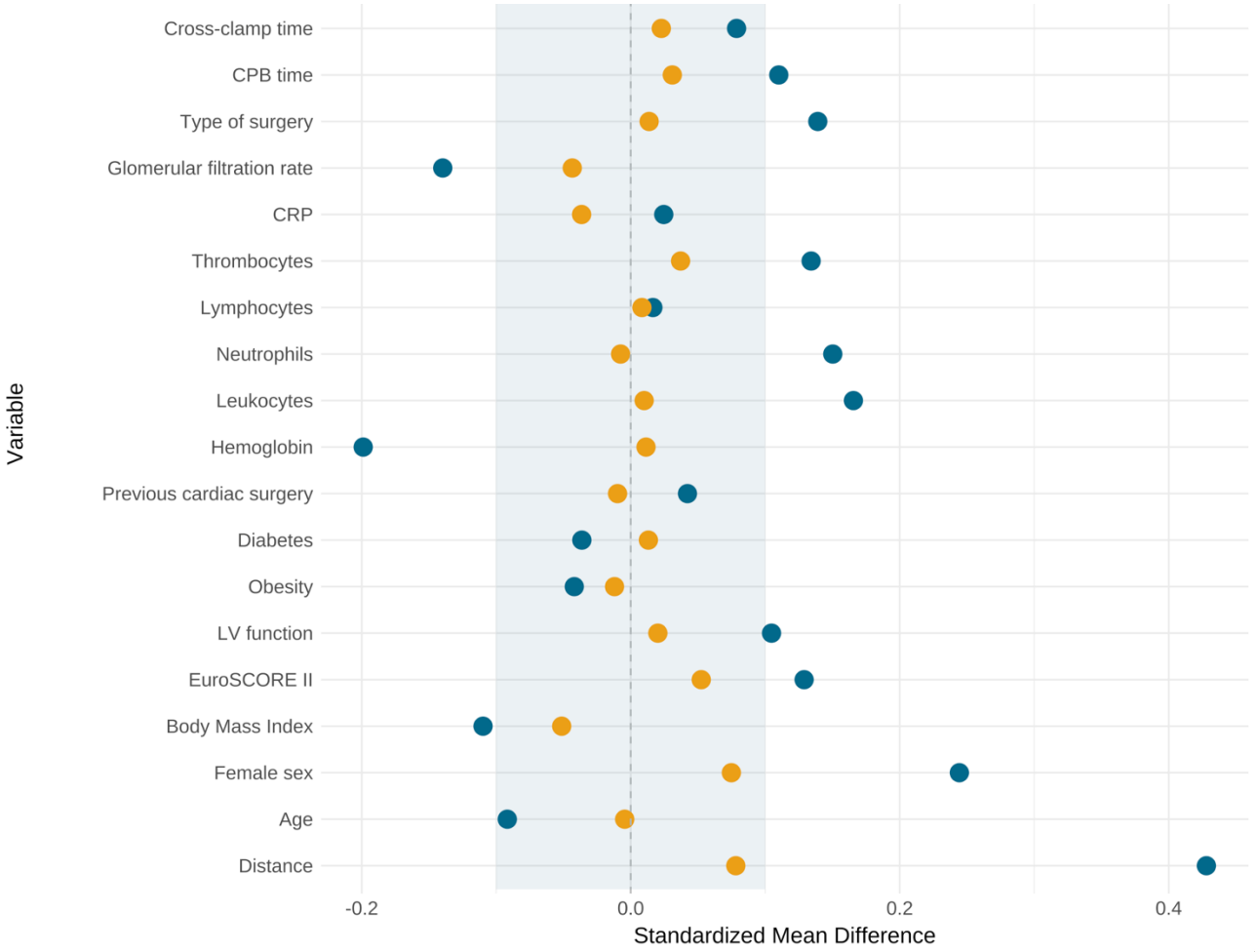
CPB		89 [67-133]	87 [65-113]	0.086
Cross-clamp		60 [40-93]	60 [43-81]	0.556
Median DO_2i	mL/min/m^2	274 [252-295]	302 [278-325]	<0.001
Median DO_2i < critical value	n, %	163 (73.8)	269 (39.2)	<0.001
Hemoglobin (nadir)	g/dL	8.3 [7.4-9.3]	9.4 [8.4-10.5]	<0.001
Lactates (peak)	mmol/L	1.7 [1.3-2.5]	1.5 [1.2-1.9]	<0.001
Blood transfusion	n, %	64 (29.0)	83 (12.1)	<0.001
Pharmacological support	n, %	115 (52.0)	172 (25.0)	<0.001
Postoperative Results				
SIRS	n, %	221 (100)	0 (0.0)	
Mortality (30-day)	n, %	9 (4.1)	2 (0.3)	<0.001
Composite outcome	n, %	78 (35.3)	42 (6.1)	<0.001
Duration				
Mechanical ventilation	Hours	6 [3-18]	2 [1-8]	<0.001
ICU stay	Days	2 [2-4]	1 [1-1]	<0.001
Complications	n, %			
Pharmacological support (>24h)		112 (50.7)	134 (19.5)	<0.001
Revision for bleeding		13 (5.9)	9 (1.3)	<0.001
Renal replacement therapy		11 (5.0)	2 (0.3)	<0.001
TIA/stroke		2 (0.9)	0 (0.0)	0.059
Blood transfusion	n, %	70 (31.7)	102 (14.8)	<0.001
Mechanical circulatory support	n, %	4 (1.8)	1 (0.1)	0.014
Laboratory data				
Leukocytes	x10^3/µL	15.0 [13.2-17.8]	11.4 [9.6-13.7]	<0.001
Neutrophils	x10^3/µL	12.9 [11.0-15.1]	9.6 [8.0-11.8]	<0.001
Lymphocytes	x10^3/µL	1.1 [0.8-1.6]	1.0 [0.7-1.5]	0.004
Thrombocytes	x10^3/µL	163 [123-213]	150 [118-182]	<0.001
CRP	mg/dL	96.3 [78.1-123.0]	29.7 [13.5-50.3]	<0.001

CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; CRP: C-reactive protein; ICU: intensive care unit; SIRS: systemic inflammatory reaction syndrome

Suppl. Figure S9. Receiver Operating Characteristic Curve of the Median of Intraoperative DO_2i; Median DO_2i ≤293 mL/min/m² Was Identified as Best Cut-Off Predictor of SIRS at POD1 (Sensitivity 62% – Specificity 74%). DO_2i: indexed oxygen delivery; POD1: postoperative day 1; SIRS: systemic inflammatory reaction syndrome



Suppl. Figure S10. Covariate Balance Plot Before and After Propensity Score Matching. CPB: cardiopulmonary bypass; CRP: C-reactive protein; LV: left ventricular



Suppl. Figure S11. Moderation Effect of SIRS on the Impact of the Median DO_2i < Critical Value on the Composite Outcome