Sex-related differences in systemic inflammatory response and outcomes after cardiac surgery and cardiopulmonary bypass

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ABSTRACT

Objectives: Differences in inflammatory responses between men and women may contribute to sex disparities in cardiac surgery outcomes. We investigated how sex differences influence systemic inflammatory response syndrome (SIRS) and adverse outcomes after cardiac surgery.

Methods: A single-center retrospective cohort study of patients undergoing cardiac surgery from 2018 to 2020 was performed. SIRS was defined as per the American College of Chest Physicians/Society of Critical Care Medicine. Predictors of SIRS and a composite adverse outcome (death, transient ischemic attack/stroke, renal therapy, bleeding, postcardiotomy mechanical circulatory support, prolonged ICU stay) were evaluated using multivariable logistic regression. Mediation effects of SIRS were assessed using structural equation modeling.

Results: The cohort included 1,005 patients, of whom 299 (29.8%) were women. SIRS occurred in 28.1% of patients, and 12.7% experienced the composite endpoint. Female sex was significantly associated with SIRS (OR 1.56; 95% CI 1.12-2.18, p=0.009) and the composite outcome (OR 1.72; 95% CI 1.10-2.69, p=0.017). Baseline left ventricular dysfunction and intraoperative hyperlactatemia were additional common predictors. SIRS mediated 50.8% of the effect of female sex, 17.0% of left ventricular dysfunction, and 30.9% of intraoperative hyperlactatemia on the composite outcome.

Conclusions: Female sex is independently associated with postoperative SIRS and poorer outcome. Systemic inflammation, preoperative anemia and procedural hyperlactatemia are potentially modifiable factors in the mechanisms through which female sex appears to worsen outcome after cardiac surgery.

Keywords: Cardiac Surgery; Systemic Inflammatory Response Syndrome; Inflammation; Sex Differences; Postoperative Complications

BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
ECMO	Extracorporeal Membrane Oxygenation
IABP	Intra-Aortic Balloon Pump
ICU	Intensive Care Unit
OR	Odds Ratio
POD1	Postoperative Day 1
SAGER	Sex And Gender Equity In Research
SEM	Structural Equation Modelling
SIRS	Systemic Inflammatory Response Syndrome

INTRODUCTION

Despite cardiac surgery's remarkable advancements, the mortality/morbidity rates have been depicting a plateau-like trend in recent years [1]. It is reasonable to assert that the gap to be bridged is narrower in modern cardiac surgery. The systemic inflammatory response syndrome (SIRS) consequent to surgery and cardiopulmonary bypass (CPB) is often superficially considered a nuanced epiphenomenon. Yet, this reaction entails molecular mediators, immunity, and the vascular system to combat damage-related signals [2-3], and can exacerbate adverse patient outcomes [4]. Recent evidence highlights sex differences in inflammation, with distinctive patterns influenced by hormonal and genetic factors concordant with the observation of more robust inflammatory responses in women [5-8]. The sex differences in cardiac surgery outcomes is based on observations of sex as modulator of pathogenesis, clinical presentation, morbidity and mortality, but lacks obvious explanation [9-10]. We aimed to ascertain the effect of sex on the occurrence and impact of postoperative SIRS in cardiac surgery patients.

MATERIAL AND METHODS

We retrospectively reviewed data from consecutive patients undergoing CPB-assisted surgery at the Santa Maria Hospital, GVM Care & Research, Bari, Italy, from 2018 to 2020. Preoperative, intraoperative, and postoperative data were anonymously recorded in our institutional database. Approval for the study was granted by the IRCCS Istituto Tumori Giovanni Paolo II – Bari, Review Board (1431/CEL – 03/11/2023), with informed consent being waived. The resort to "Centricity" (General Electric, Boston, USA), an Intensive Care Unit (ICU) data collection system that provides automated data logging, ensured the reliability of our data. Patient age <18 years, chronic inflammatory/autoimmune diseases, emergency, endocarditis, and

hypothermia (<34°C) were exclusion criteria. Patients underwent coronary artery bypass grafting (CABG), single non-CABG procedure, or combined surgery. The single non-CABG procedures included valve repairs or replacements, aortic surgery, and other procedures such as atrial septal defect closure, removal of intracardiac mass with or without concomitant left atrial appendage closure and/or ablation of atrial fibrillation. The primary endpoint was (postoperative day 1 – POD1). SIRS was defined as per the 1991 American College of Chest Physicians/Society of Critical Care Medicine parameters [11]: temperature >38°C or <36°C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or $PaCO_2$ <32 mmHg, leukocyte count >12.000/mL or <4,000/mL. The secondary outcome measures included the individual components of a composite endpoint: death, transient ischemic attack/stroke, renal replacement therapy, bleeding requiring surgical re-exploration, extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pump (IABP), and an ICU stay >96 hours. The study was performed in accordance with the Sex and Gender Equity in Research (SAGER) guidelines [12]. Detailed accounts of the surgical, anesthesiologic, and perfusion approaches have been provided in a prior document [3]. Briefly, patients underwent surgery via sternotomy or minimally invasive approaches. Anticoagulation was achieved with heparin (target ACT 420 s). Cannulation was central or peripheral, depending on the surgical access, and CPB was initiated. Blood cardioplegia was the standard myocardial protection strategy, with Custodiol® reserved for selected cases, primarily reoperations or complex combined procedures. Transfusion was triggered by hemoglobin levels <7 g/dL.

Statistical analysis

We reported continuous data as means with standard deviations or medians with interquartile ranges. Group differences were evaluated using the Student's t-test or the Mann-Whitney test,

depending on data distribution. The normality of continuous variables was investigated via Shapiro-Wilk tests. For categorical variables, we reported frequencies and percentages and assessed associations using the chi-squared test. In our dataset, no variable had more than 5% missing data. The missing data mechanism was investigated using Little's Missing Completely at Random test. Multiple Imputation by Chained Equations was applied to handle the missing data. The imputation process was iterated 10 times to ensure convergence and accuracy. Multicollinearity was ascertained via Variance Inflation Factor, considering values <5 acceptable. To achieve parsimonious models, we employed backward elimination guided by the Akaike Information Criterion. Regression findings were presented as odds ratios (OR) and 95% confidence intervals (CI), and we considered p-value <0.05 as statistically significant. In the overall population, a multivariable logistic regression was utilized to identify independent SIRS predictors. The relationship between SIRS and the composite outcome was examined through a multivariable logistic regression. The predictors entered into the multivariable models were selected based on their statistical significance in univariate analyses (conducted using logistic regression). To explore the relationship between SIRS and the composite endpoint, we applied structural equation modeling (SEM), a technique that distinguishes the direct effects of predictors from those mediated through SIRS. Here, SIRS serves as a mediator, partly explaining how certain intraoperative factors influence mortality. SEM quantifies these effects by calculating the Average Causal Mediation Effect (ACME), representing the effect mediated through SIRS, and the Average Direct Effect (ADE), reflecting the direct impact of predictors on the composite endpoint, independent of SIRS. The SEM model included female sex, baseline left ventricular function, and intraoperative hyperlactatemia as predictors; SIRS on POD1 as the mediator; and the composite endpoint as the outcome. While exploratory and acknowledging potential confounders, SEM assumes causal links between

preoperative/intraoperative factors, SIRS, and the composite endpoint. This approach involved estimating indirect effects through non-parametric bootstrapping (1,000 simulations). Our analysis focused on the computation of Total Effects, Average Causal Mediation Effects, and Average Direct Effects. We conducted a moderation analysis to investigate the potential interactions between sex and SIRS. Preoperative and operative factors significantly associated with the composite outcome were included as covariates adjusting for preoperative SIRS variables. The analysis was conducted in RStudio (Boston, MA, USA).

RESULTS

One-thousand-five patients were included in the analysis. **Table 1** describes the population. Median age was 68 [61-74] years, and 299 (29.8%) were female. The median EuroSCORE II was 1.9% [1.2-3.2]. Four-hundred-nineteen patients (41.7%) underwent isolated CABG, 333 (33.1%) single non-CABG surgery, 196 (19.5%) and 57 (5.7%) underwent 2 and 3 procedures, respectively. SIRS occurred in 282 (28.1%) patients. Thirty-day mortality was 2.5%, while 128 patients (12.7%) experienced the composite outcome.

Table 1 describes the sex-specific preoperative characteristics. Females displayed lower Body Mass Index (BMI) (26.6 [23.4-30.0] vs 27.0 [24.5-30.1] kg/m^2, p=0.04), lower preoperative hemoglobin (12.8 [11.7-13.8] vs 14.0 [12.6-14.9] g/dL, p<.001), higher platelets (208 [180-247] vs 191 [154-235] x10^3/µL, p<.001), and lower glomerular filtration rate (GFR) (78 [62-96] vs 83 [64-103] mL/min, p=0.05). Females underwent less frequently CABG, with a higher prevalence of single non-CABG operations and combined procedures. The intraoperative hemoglobin nadir was lower (8.6 [7.8-9.5] vs 9.8 [8.7-10.7] g/dL, p<.001) in the female cohort, further characterized by higher rates of intraoperative transfusions (22.1% vs 9.9%, p<.001). Females showed a higher SIRS occurrence (41.8% vs 22.8%, p<.001).

The composite outcome occurred more frequently in females (18.7% vs 10.2%, p<.001), who were more likely to receive vasoactive support (42.5% vs 26.6%, p<.001) and ECMO or IABP (1.7% vs 0.3%, p=0.04). Mortality did not differ between groups. Laboratory data of female patients at POD1 showed pronounced leukocytosis (13.3 [11.2-16.3] vs 12.4 [10.2-15.1] x10^3/µL, p=0.001), with higher neutrophils (11.0 [9.0-13.6] vs 10.3 [8.2-12.7] $x10^3$/µL, p=0.001), and platelets (161 [128-198] vs 152 [118-190] $x10^3$/µL, p=0.04).

Table 2 shows the multivariable regression SIRS occurrence. Among covariates, female sex (OR 1.56; 95%CI 1.12-2.18, p=0.009), worse left ventricular function (OR 0.73; 95%CI 0.61-0.88, p<.001), preoperative anemia (OR 0.73; 95%CI 0.56-0.94, p=0.02), and thrombocytosis (OR 1.54; 95%CI 1.29-1.85, p<.001) were positively associated with SIRS. Intraoperative hemoglobin nadir (OR 0.42; 95%CI 0.31-0.57, p<.001) and lactates peak (OR 1.20; 95%CI 1.09-1.31, p<.001) were also significantly associated with SIRS. **Table 3** reports the multivariable model for the composite outcome. Both SIRS (OR 4.81; 95%CI 3.11-7.49, p<.001) and female sex (OR 1.72; 95%CI 1.10-2.69, p=0.017) were associated to the composite endpoint. Other factors such as BMI, baseline left ventricular function, complex surgery, and intraoperative lactates were associated to the composite outcome.

SEM provided a complex understanding of the mediating function of SIRS in the effects of its predictors on the composite outcome, as indicated in **Table 4**. SIRS mediated 50.8% of the effect attributable to female sex, 17.0% of that due to left ventricular dysfunction, and 30.9% of the effect caused by intraoperative hyperlactatemia on the composite outcome (**Figure 1**).

A logistic regression scrutinized the SIRS-outcome relationship across sexes, as potential moderator. The “SIRS+female” interaction term was significantly associated to the composite endpoint (OR 4.70; 95%CI 1.69-13.06, p=0.003), suggesting that the impact of SIRS on the

composite outcome was different across varying levels of the moderator (**Figure 2**). The composite endpoint captures the cumulative burden of postoperative complications, as we showed that female sex was not associated with any component of the composite but rather with a broader response that prolonged ICU stay (**Suppl. Table S2, Figures S1-S2**).

DISCUSSION

SIRS is a typical response following cardiac surgery, yet an excessive reaction may lead to organ damage. In our cohort of 1,005 patients, we explored the association between SIRS and negative outcomes. We report that being female independently predicted SIRS. Additionally, preoperative anemia, left ventricular dysfunction, thrombocytosis, as well as intraoperative factors like hemoglobin nadir and lactates peak, were associated with SIRS. These insights bring to the forefront the pivotal role of sex in steering the immune-inflammatory axis. This regulatory effect, when observed together with hyperlactatemia, can determine clinically consequential SIRS.

Despite no difference in mortality, the composite outcome occurred more frequently in females. In the multivariable analysis, several factors contributing to a worsened postoperative path were identified. Notably, SIRS emerged as leading predictor of the composite endpoint, with the female sex being also significantly associated with a compromised postoperative course. The prolonged ICU stay observed in female patients may be driven by the extended need for vasopressor support, which is a natural consequence of a strong SIRS response. This finding highlights the importance of optimizing therapies to reduce the need for prolonged support. To address the identified risk factors, perioperative interventions such as optimizing preoperative hemoglobin levels, improving intraoperative perfusion, and considering anti-inflammatory strategies could be valuable, particularly for female patients. Such strategies

may help mitigate the worse outcomes observed in female patients and should be the focus of future research. Other preoperative variables like left ventricular dysfunction, increased BMI, and renal impairment, were independent predictors of the composite outcome, along with intraoperative factors like complex surgical operations and sustained lactate production. The nexus between SIRS, the composite endpoint, and their common predictors was ascertained via SEM. Our findings suggest that SIRS significantly mediates the impact of the common predictors on the composite outcome, with the effect of female sex being half mediated by SIRS, along with one third (30.9%) of the peak lactate's effect, and 17.0% of the impact from left ventricular dysfunction. Additionally, the analysis revealed that sex significantly moderated the SIRS impact on the composite endpoint, underscoring that the sex differences observed in cardiac surgery outcomes may be to some extent a consequence of differential inflammatory responses.

Female sex is considered an aggravating condition within the major risk scores [13-14]. Indeed, females appear burdened with more comorbid conditions and delayed diagnosis and treatments [15-17]. Females have been consistently reported as experiencing worse outcomes following diverse operations, among which valve [10, 18-20], aortic [21-23], and assist device procedures [24]. A series of non-randomized studies documented higher mortality rates in females undergoing CABG [25-27]. An analysis by the Society of Thoracic Surgeons revealed that intraoperative anemia accounts for 38% of the increased risk of perioperative mortality in females [28]. Intraoperative anemia may be caused by procedural occurrences like hemodilution, though the determinant of transfusion necessity and suboptimal outcomes remains the low baseline hemoglobin [29]. Cavalli et al. recently examined the appropriateness of WHO thresholds (hemoglobin <130 g/L for males and <120 g/L for females)

in a retrospective analysis of >6000 patients receiving cardiac surgery and CPB, concluding that the currently adopted thresholds disproportionately disadvantage female patients, and advocating for a unified hemoglobin target of 130 g/L for both sexes to ensure a 15% risk threshold for intraoperative transfusions [30]. Our study emphasizes that inflammation may represent a missing link between anemia and outcome. Our group already reported an improved discrimination performance of the EuroSCORE II, if preoperative hemoglobin is added as covariate [31]. Inflammation has been consistently shown as detrimental in cardiac surgery patients. We reported data from a 502 consecutive patients showing a poorer outcome (a composite endpoint identical to that hereby analyzed) in SIRS positive patients as compared to propensity matched negative controls [4]. However, female sex did not emerge as contributing factor neither to SIRS nor to worsened outcome until data from a larger population were gathered. Other studies highlighting the negative prognostic value of inflammation exist, but none examined the role of sex [32-36]. Against this backdrop, we provide evidence of SIRS as significant predictor of poor in-hospital outcome, but also show the "inflammatory variation" of the gender gap in cardiac surgery. Indeed, female sex exerted the majority of its effect on the outcome through SIRS, that acted as mediator. Moreover, sex significantly moderated the impact of SIRS on the composite endpoint, with a doubled risk in females as compared to males. In addition, we explored the complex mechanisms through which SIRS affects outcomes, entailing other factors like the baseline cardiac function and intraoperative hyperlactatemia. Future prospective investigations might provide more comprehensive insights into the relationship between sex, inflammation, and postoperative outcomes, potentially guiding targeted interventions to reduce sex differences in cardiac surgery outcomes.

Limitations

Our study's limitations warrant consideration. First, our study relies on historical single-site data. We only have data available up to the immediate postoperative period. As such, our analysis is constrained to POD1, preventing the inclusion of subsequent time points. The use of SIRS criteria in cardiac surgery could face criticism given that the definition was conceptualized for sepsis. Unfortunately, there is currently no alternative definition for SIRS nor a consensus on using biomarkers or clinical/biomarkers combinations. While biomarkers might offer insights, their use without an established consensus would compromise the comparability of our results with the existing research. Indeed, employing SIRS criteria after cardiac surgery is a widely accepted practice. Furthermore, we lacked specific data on the types and doses of vasoactive drugs, which could impact lactate levels. Despite baseline differences and the heterogeneity of procedures, with varying techniques and durations, likely contributed to differences in inflammatory responses, our multivariable analyses included adjustments for procedure type and intraoperative factors, minimizing the confounding effects on SIRS outcomes. However, residual confounding cannot be excluded and further studies are needed to confirm these findings. We did not apply propensity score matching based on gender to preserve cohort heterogeneity and examine real-world interactions between predictors. While this may limit direct comparability, our multivariable models and structural equation modeling address confounding and highlight the independent and mediated effects of gender on SIRS and outcomes. Lastly, future prospective studies may ascertain the relationship of sex and inflammation with mortality rather than with a composite outcome. While our approach complicates interpretation, limiting the analysis to 'hard endpoints' would result in too few events. Future studies will explore more focused endpoints.

CONCLUSION

The current analysis may identify a missing link between female sex, postoperative inflammation, and poor outcome following cardiac surgery. Preoperative anemia and intraoperative hyperlactatemia are potentially modifiable factors. This hypothesis generating analysis paves the way for future investigation assessing targeted interventions to reduce the inflammatory burden and ameliorate the outcome of female patients.

IRB/ERB/EC Approval: the study was approved by the IRCCS Istituto Tumori Giovanni Paolo II – Bari, Review Board (1431/CEL – 03/11/2023)

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Table 1. Characteristics of Patients by Sex

Variables	Unit	All	Females	Males	p-value
Cohort	n	1,005	299 (29.8)	706 (70.2)	
Preoperative Data					
Age	years	68 [61-74]	69 [62-75]	68 [60-74]	0.085
Body Mass Index	kg/m^2	26.8 [24.2-30.0]	26.6 [23.4-30.0]	27.0 [24.5-30.1]	0.04
EuroSCORE II	%	1.9 [1.2-3.2]	1.9 [1.6-3.0]	1.8 [1.1-3.3]	0.20
Left ventricular ejection fraction	%	55 [50-60]	55 [55-60]	55 [50-60]	0.006
Risk factors	n, %				
Obesity		253 (25.2)	75 (25.1)	178 (25.2)	>.99
Diabetes		221 (22.0)	56 (18.7)	165 (23.4)	0.12
Previous cardiac surgery		79 (7.9)	25 (8.4)	54 (7.6)	0.80
Laboratory					
Hemoglobin	g/dL	13.6 [12.3-14.6]	12.8 [11.7-13.8]	14.0 [12.6-14.9]	<.001
Leukocytes	$x10^3/\mu L$	7.3 [6.0-8.7]	7.3 [5.9-8.7]	7.3 [6.0-8.7]	0.57
Neutrophils	$x10^3/\mu L$	4.6 [3.7-5.8]	4.6 [3.7-5.9]	4.6 [3.7-5.8]	0.91
Lymphocytes	$x10^3/\mu L$	1.8 [1.5-2.2]	1.8 [1.5-2.1]	1.8 [1.5-2.2]	0.56
Thrombocytes	$x10^3/\mu L$	195 [161-240]	208 [180-247]	191 [154-235]	<.001
CRP	mg/dL	2.0 [0.4-7.5]	1.9 [0.4-8.4]	2.1 [0.4-7.5]	0.88
Glomerular filtration rate	mL/min	82 [64-102]	78 [62-96]	83 [64-103]	0.05
Intraoperative Data					
Procedure	n, %				<.001
Isolated CABG		419 (41.7)	94 (31.4)	325 (46.0)	
Single non-CABG		333 (33.1)	122 (40.8)	211 (29.9)	
Two procedures		196 (19.5)	66 (22.1)	130 (18.4)	
Three procedures		57 (5.7)	17 (5.7)	40 (5.7)	
Surgical times	Minutes				

CPB		86 [64-115]	85 [62-116]	86 [65-115]	0.75
Cross-clamp		58 [41-81]	60 [41-80]	57 [41-82]	0.76
Lactates (peak)	mmol/L	1.5 [1.2-1.9]	1.6 [1.2-2.0]	1.5 [1.2-1.9]	0.19
Hemoglobin (nadir)	g/dL	9.3 [8.3-10.5]	8.6 [7.8-9.5]	9.8 [8.7-10.7]	<.001
Whole blood transfusion	n, %	136 (13.5)	66 (22.1)	70 (9.9)	<.001
Vasoactive support	n, %	311 (30.9)	102 (34.1)	209 (29.6)	0.18
Postoperative Results					
SIRS	n, %	282 (28.1)	125 (41.8)	157 (22.2)	<.001
Composite outcome	n, %	128 (12.7)	56 (18.7)	72 (10.2)	<.001
Mortality (30-day)		25 (2.5)	11 (3.7)	14 (2.0)	0.18
TIA or stroke		6 (0.6)	4 (1.3)	2 (0.3)	0.13
Renal replacement therapy		19 (1.9)	6 (2.0)	13 (1.8)	>.99
Revision for bleeding		23 (2.3)	9 (3.70)	14 (2.0)	0.45
ECMO and/or IABP		7 (0.7)	5 (1.7)	2 (0.3)	0.05
ICU stay > 96 hours		115 (11.4)	43 (14.4)	72 (10.2)	0.07
Duration					
Mechanical ventilation	Hours	4 [2-9]	4 [3-10]	4 [2-9]	0.07
ICU stay	Days	2 [1-3]	2 [1-3]	2 [1-3]	0.56
Vasopressors (>24 hours)	n, %	315 (31.3)	127 (42.5)	188 (26.6)	<.001
Whole blood transfusion	n, %	204 (20.3)	68 (22.7)	136 (19.3)	0.42
Laboratory					
Leukocytes	$x10^3/\mu L$	12.7 [10.3-15.4]	13.3 [11.2-16.3]	12.4 [10.2-15.1]	0.001
Neutrophils	$x10^3/\mu L$	10.6 [8.3-12.9]	11.0 [9.0-13.6]	10.3 [8.2-12.7]	0.001
Lymphocytes	$x10^3/\mu L$	1.0 [0.7-1.2]	1.0 [0.8-1.3]	1.0 [0.7-1.2]	0.19
Thrombocytes	$x10^3/\mu L$	154 [121-193]	161 [128-198]	152 [118-190]	0.04
CRP	mg/dL	72.3 [59.0-92.0]	72.0 [60.6-95.2]	72.9 [58.7-91.0]	0.57

CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; ICU: intensive care unit; SIRS: systemic inflammatory reaction syndrome

Table 2. Multivariable Logistic Regression with Backward Elimination for SIRS at POD1

Variable	Estimate	Odds Ratio [95% CI]	p-value
Constant	0.79	2.19 [0.71-6.76]	0.17
Female sex	0.45	1.56 [1.12-2.18]	0.009
Left ventricular ejection fraction (%)	-1.99	0.73 [0.61-0.88]	0.001
Preoperative hemoglobin (g/dL)	-1.66	0.73 [0.56-0.94]	0.02
Preoperative thrombocytes (x10^3/µL)	4.11	1.54 [1.29-1.85]	<.001
Surgery type	0.15	1.34 [0.95-1.89]	0.09
Intraoperative hemoglobin nadir (g/dL)	-8.48	0.42 [0.31-0.57]	<.001
Intraoperative lactates peak (mmol/L)	5.05	1.20 [1.09-1.31]	<.001

Table 3. Multivariable Model for the Occurrence of at Least 1 Event of the Composite Outcome

Variable	Estimate	Odds Ratio	p-value
Constant	-1.07	0.34 [0.12-1.00]	0.05
Postoperative SIRS	1.57	4.81 [3.11-7.49]	<.001
Female sex	0.54	1.72 [1.10-2.69]	0.017
Body Mass Index (kg/m^2)	2.28	1.47 [1.10-1.96]	0.009
Left ventricular ejection fraction (%)	-3.56	0.57 [0.46-0.72]	<.001
Baseline glomerular filtration rate (mL/min)	-4.50	0.45 [0.32-0.62]	<.001
Surgery type	0.24	1.60 [1.04-2.48]	0.03
Intraoperative lactates peak (mmol/L)	3.80	1.14 [1.05-1.25]	0.003
Interaction terms			
Female sex+SIRS	1.55	4.70 [1.69-13.06]	0.003

Table 4. Mediation Analysis for SIRS as Mediator for Composite Outcome

	Estimate	Odds Ratio [95%CI]	p-value
SIRS as Mediator of **Female Sex**			
Total Effect	0.08	1.08 [1.03-1.14]	<.001
Average Causal Mediation Effect	0.04	1.04 [1.03-1.06]	<.001
Average Direct Effect	0.04	1.04 [1.00-1.09]	0.08
Proportion Mediated (Average Causal Mediation Effect/Total Effect): 50.8%			<.001
SIRS as Mediator of **Left Ventricular Ejection Fraction (%)**			
Total Effect	-0.49	0.61 [0.52-0.73]	<.001
Average Causal Mediation Effect	-0.08	0.92 [0.88-0.97]	0.002
Average Direct Effect	-0.41	0.67 [0.56-0.79]	<.001
Proportion Mediated (Average Causal Mediation Effect/Total Effect): 17.0%			0.002
SIRS as Mediator of **Intraoperative Lactates Peak (mmol/L)**			
Total Effect	0.88	2.41 [1.77-2.57]	<.001
Average Causal Mediation Effect	0.27	1.31 [1.14-1.54]	<.001
Average Direct Effect	0.61	1.84 [1.27-2.21]	<.001
Proportion Mediated (Average Causal Mediation Effect/Total Effect): 30.9%			<.001

Graphical Abstract. Outline of the Sex-Hyperlactatemia-Inflammation-Outcome Axis

Figure 1. Mediation Effect Plot

Figure 2. Moderation Effect of Female Sex on the Impact of SIRS on the Composite Outcome

Figure 1

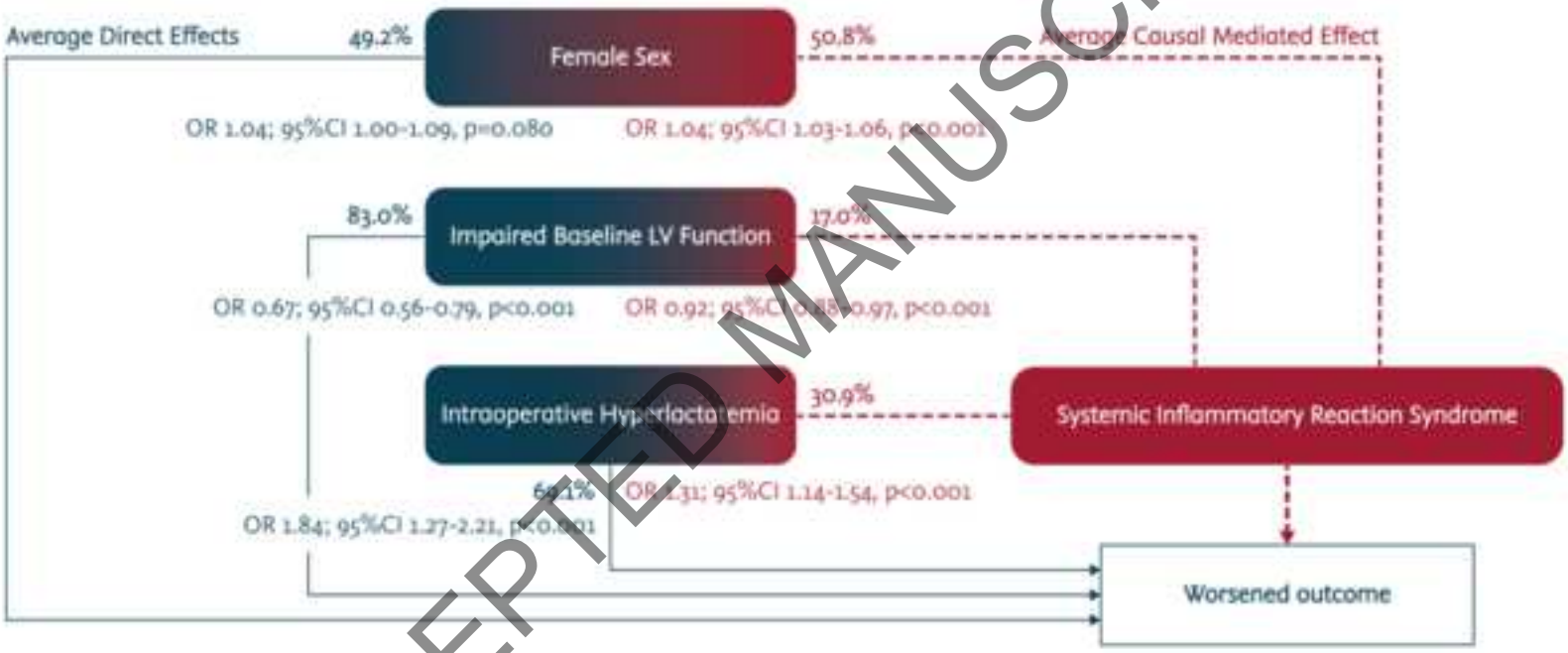
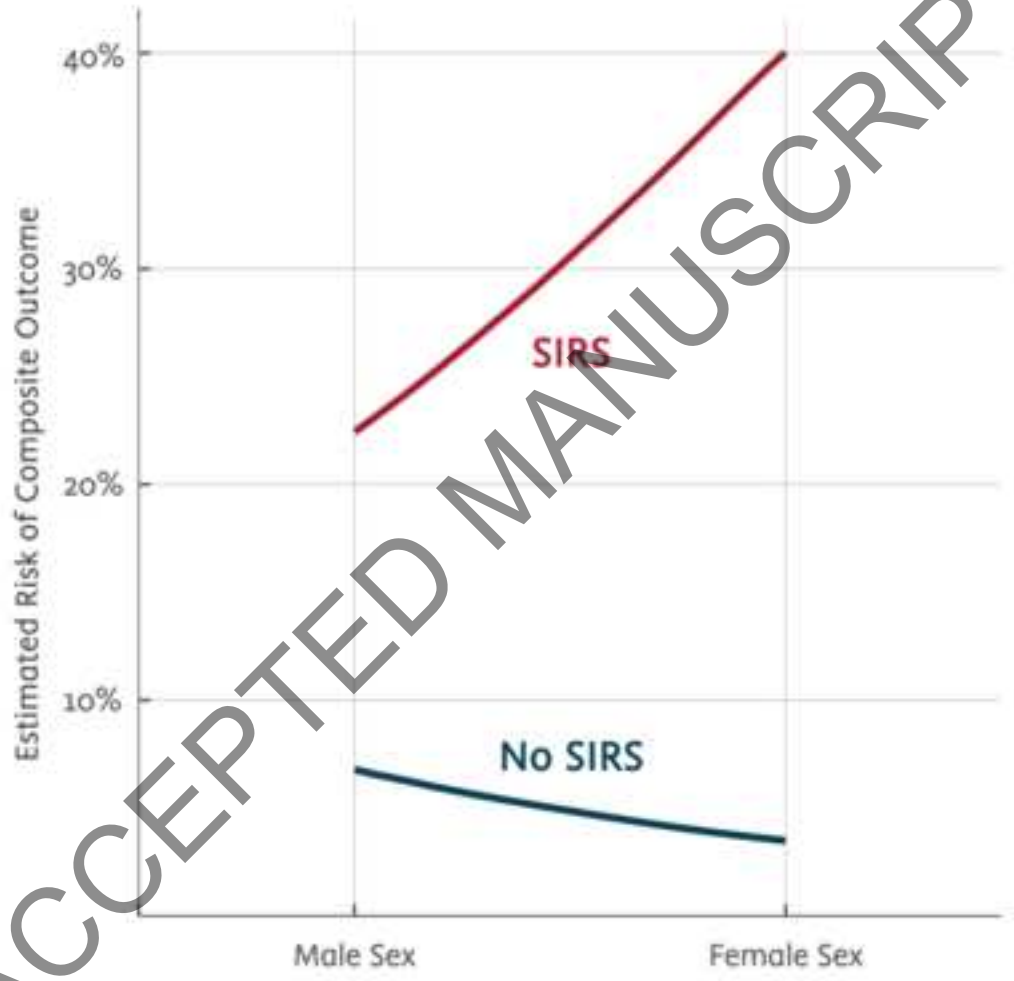


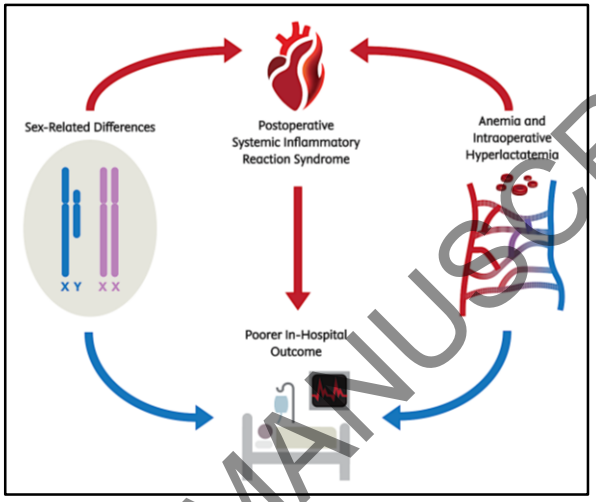
Figure 2



Sex-Related Differences and Systemic Inflammatory Response in Cardiac Surgery

Summary

In a cohort of 1,005 cardiac surgery patients, women, compared to men, showed a higher incidence of SIRS and worse outcomes. SIRS mediated over 50% of the sex-related risk, with anemia and hyperlactatemia contributing to poorer outcomes in women.



Legend: Systemic Inflammatory Response Syndrome (SIRS)