



ORIGINAL INVESTIGATION

Intraoperative fluid balance and cardiac surgery-associated acute kidney injury: a multicenter prospective study



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Abstract

Background: Recent data suggest the regime of fluid therapy intraoperatively in patients undergoing major surgeries may interfere in patient outcomes. The development of postoperative Acute Kidney Injury (AKI) has been associated with both Restrictive Fluid Balance (RFB) and Liberal Fluid Balance (LFB) during non-cardiac surgery. In patients undergoing cardiac surgery, this influence remains unclear. The study objective was to evaluate the relationship between intraoperative RFB vs. LFB and the incidence of Cardiac-Surgery-Associated AKI (CSA-AKI) and major postoperative outcomes in patients undergoing on-pump Coronary Artery Bypass Grafting (CABG).

Methods: This prospective, multicenter, observational cohort study was set at two high-complexity university hospitals in Brazil. Adult patients who required postoperative intensive care after undergoing elective on-pump CABG were allocated to two groups according to their intraoperative fluid strategy (RFB or LFB) with no intervention.

Results: The primary endpoint was CSA-AKI. The secondary outcomes were in-hospital mortality, cardiovascular complications, ICU Length of Stay (ICU-LOS), and Hospital LOS (H-LOS). After propensity score matching, 180 patients remained in each group. There was no difference in risk of CSA-AKI between the two groups (RR = 1.15; 95% CI, 0.85-1.56,

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$p = 0.36$). The in-hospital mortality, H-LOS and cardiovascular complications were higher in the LFB group. ICU-LOS was not significantly different between the two groups. ROCcurve analysis determined a fluid balance above 2500 mL to accurately predict in-hospital mortality.

Conclusion: Patients undergoing on-pump CABG with LFB when compared with patients with RFB present similar CSA-AKI rates and ICU-LOS, but higher in-hospital mortality, cardiovascular complications, and H-LOS.

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Introduction

The hemodynamic status of surgical patients, in particular the intravascular volume, plays a central role in the perioperative period and has a direct influence on their outcome. Additionally, inadequate organ perfusion can have profound implications at the molecular level leading to organ dysfunction.^{1,2} Patients undergoing cardiac surgery are at higher risk of greater intravascular volume changes during surgery and after admission to the Intensive Care Unit (ICU).³ Different aspects inherent to the operation may influence the amount of fluid required perioperatively, however the most crucial period to the risk of developing impaired organ function is the intraoperative phase.⁴ The cornerstone of fluid therapy is to maintain intraoperative adequate tissue perfusion, as malperfusion may progress to organ ischemia and consequently organ dysfunction with further acute and long-term clinical consequences.^{4,5}

A relatively common complication is the development of renal dysfunction after cardiovascular procedures, especially those requiring cardiopulmonary bypass (on-pump procedures).⁶ Postoperatively, the development of Cardiac-Surgery-Associated Acute Kidney Injury (CSA-AKI) has been associated with increased hospital length of stay and increased incidence of nosocomial infections and mortality.^{7,8} The pathophysiological mechanism behind CSA-AKI presents a multifactorial nature and it is not yet fully understood.⁶

Recent data from studies in patients undergoing major abdominal surgery suggests that the regime of intraoperative fluid therapy – i.e., liberal and restrictive strategies – may affect patient outcomes.^{9,10} For instance, the RELIEF trial¹¹ found a higher rate of Acute Kidney Injury (AKI) in patients treated with a restrictive fluid strategy, however more liberal fluid resuscitation has also been described as a risk factor in further studies.¹²

In this context, the benefit or harm of either strategy in patients undergoing cardiac surgery is discussed controversially.¹³ This study aims to evaluate the relationship between both intraoperative fluid regimes and the incidence of CSA-AKI in patients undergoing on-pump Coronary Artery Bypass Grafting (CABG). Furthermore, this study addresses the influence of both intraoperative strategies on in-hospital mortality, cardiovascular complications, Length of Stay in the ICU (ICU-LOS), and length of stay in Hospital (H-LOS).

Methods

Study design

This prospective, multicenter, observational cohort study was conducted in two university hospitals from February to December 2017, in São Paulo, Brazil. This study was performed in accordance with the principles of the Declaration of Helsinki and the STROBE guidelines for reporting observational studies.¹⁴ Ethical approval was obtained from the Ethics Committee of the University of São Paulo (USP – CAAE 55828016.1.2007.0068). All enrolled participants or their legal representatives provided written informed consent. Patient clinical, laboratory and outcome data were acquired prospectively. Enrolled patients were followed up to 48 hours after the surgical procedure to assess the primary outcome. Further, all patients were followed up during their hospital stay to assess secondary outcomes. Blood samples were collected and immediately processed in the respective institutes for clinical chemistry and laboratory diagnostics from each university hospital.

Study population, inclusion and exclusion criteria

Patients who received an indication for on-pump CABG were screened for inclusion in this cohort. Moreover, the Parsonnet score was determined preoperatively to assess the risk stratification of the collective.¹⁵ Inclusion criteria were patients with age ≥ 18 undergoing on-pump CABG surgery. Exclusion criteria were severe chronic kidney diseases according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines defined as abnormalities of kidney structure or function, present > 3 months with a category of Glomerular Filtration Ratio (GFR) ≤ 59 mL \cdot min $^{-1}$ /1.73 m 2 . Patients with NYHA class IV, ejection fraction on echocardiography less than 30%, intraoperative blood loss ≥ 750 mL corresponding to shock class II of the classification of hemorrhagic shock,¹⁶ and pregnant or breastfeeding patients were also excluded from the study.

Definition of fluid balance

Lacking a clear definition,⁴ based on the results of our previous studies evaluating fluid balance intraoperatively in patients undergoing noncardiac surgery, patients in this study who received ≤ 2000 mL fluids were defined as Restrictive Fluid Balance (RFB) and those who received > 2000 mL were defined as Liberal Fluid Balance (LFB).¹⁷ For the fluid balance calculation, we considered all types of fluids

administered intraoperatively such as crystalloid solutions, colloids, priming, cardioplegic solutions and Transfusions (Red Blood cells [allogenic and autologous]; Platelets and Coagulator factors). Patients who had intraoperative blood loss of more than 750 mL, classified as grade II hemorrhagic shock, were excluded from the study (see exclusion criteria above). The influence of a specific type and duration of the fluid therapy were not assessed.

Study outcomes

The primary outcome was the development of CSA-AKI within 2 postoperative days. AKI was defined according to the KDIGO-guidelines as stage 1: increase in serum creatinine $\geq 0.3 \text{ mg.dL}^{-1}$ ($\geq 26.5 \text{ }\mu\text{mol.L}^{-1}$) within 48 hours or increase in serum creatinine to $\geq 1.5\text{--}1.9 \times$ baseline or urinary output $< 0.5 \text{ mL.kg}^{-1}.\text{h}^{-1}$ in 6–12 hours.¹⁸ The secondary outcomes were in-hospital mortality, composite cardiovascular complications (postoperative low cardiac output syndrome: decreased Cardiac index [Cardiac index lower than $2.0 \text{ L.min}^{-1}.\text{m}^{-2}$] need of inotropic agent infusion and the use of intra-aortic balloon pump and new onset of Arrhythmias [Atrial fibrillation, Ventricular tachyarrhythmias, bradyarrhythmias]), ICU-LOS, and H-LOS.

Intraoperative fluid management

Intraoperatively, we categorized fluid management according to the American Society of Anesthesiologists (ASA)⁴ and Enhanced Recovery After Surgery (ERAS)¹⁹ guidelines in maintenance and therapy. The maintenance fluid serves to cover insensible loss and urine output with a baseline crystalloid infusion rate 1 to $1.5 \text{ mL.kg}^{-1}.\text{h}^{-1}$. Fluid therapy was performed by an independent anesthesiologist during the surgery regarding invasive, noninvasive hemodynamic parameters, and laboratorial parameters such as lactate and central venous oxygen saturation to assess the requirement of fluid resuscitation. The volume of fluid therapy needed was documented and the amount of fluid needed for maintenance was considered in the calculation of the fluid balance. The insensible loss of fluid was not calculated.

Statistical analyses

The categorical data in this study are shown as frequencies and percentages. Continuous variables are displayed as means and Standard Deviations (SDs) for normally distributed variables or, otherwise, as medians and Interquartile Ranges (IQRs). The choice of the statistical method used in assessing each variable was based on their distribution pattern. The categorical variables were analyzed by the chi-square test and the continuous variables by means of the Student's *t*-test. Continuous variables with irregular distribution were analyzed by the Mann-Whitney test. Values of $p < 0.05$ were considered significant. The Statistical Package for Social Sciences (IBM Company, version 20.0) was used for statistical analysis.

Based on literature data²⁰ which indicates that 30% of patients undergoing cardiac surgery with cardiopulmonary bypass develop CSA-AKI, and considering a null hypothesis of 80% for CSA-AKI, with type I error of 0.05 and type II error of

0.2 (1-power), at least 124 patients would be necessary to perform the study.

In an attempt to minimize the bias due to confounding variables of this study and mimic randomization, we used a propensity score matching.²¹ First, a logistic regression model was created using the group variable as the dependent variable. Age, sex, body mass index (BMI), Parsonnet score, time of surgery, previous myocardial infarction and baseline creatinine were entered as predictors, and the width of the matching tolerance caliper was set at 0.01 of the logit. Then, a match for each group patient was selected based on the closest logit. This model was constructed based on a sample of patients matched by propensity score 1:1 without replacement or repetition. The matching procedure was performed before the analysis of the study outcomes.

A Chi-Square analysis was conducted comparing the treatment groups for the primary and secondary outcomes, and the corresponding Relative Risk (RR) and 95% Confidence Interval (95% CI) calculated. Finally, the analysis of sensitivity and specificity considered the value of fluid balance with best accuracy to predict hospital mortality, and the value was chosen by Youden's index (sensitivity + specificity - 1) and disposed as a ROC curve.

Results

Figure 1 shows the study flowchart. Initially, 669 patients who underwent CABG were selected from a group of 1143 patients who underwent cardiac surgery. According to the aforementioned exclusion criteria, 83 patients had to be excluded from the cohort. Then, 586 patients were enrolled and divided into two groups: RFB and LFB. A propensity score matching was performed based on demographic and clinical characteristics, finally presenting two groups of 180 patients.

Patient demographics

Table 1 shows the perioperative demographic and clinical data of the patient population separated by original cohort and matched cohort. Patients of the RFB group included more males and Caucasians, had significantly lower prior cardiac surgery, higher prior myocardial infarction, lower baseline glycemia levels, and slightly lower creatinine levels. There were no differences regarding age, BMI, Parsonnet score, hypertension, chronic heart failure, cardiopulmonary bypass time, and left ventricular ejection fraction. After propensity score matching, all the baseline characteristics regarding demographic data, comorbidities, Parsonnet score, frequency of prior cardiac surgery, cardiopulmonary bypass time, clinical and laboratory data showed no significant differences between the groups.

Primary and secondary outcomes

Table 2 summarizes the key outcomes. No significant difference was found between the two groups regarding the creatinine values 48 hours postoperatively (Fig. 2). There was neither a significant difference in the incidence nor in the relative risk (RR = 1.15; 95% CI 0.85–1.56, $p = 0.36$) of CSA-AKI between the two groups (Fig. 3).

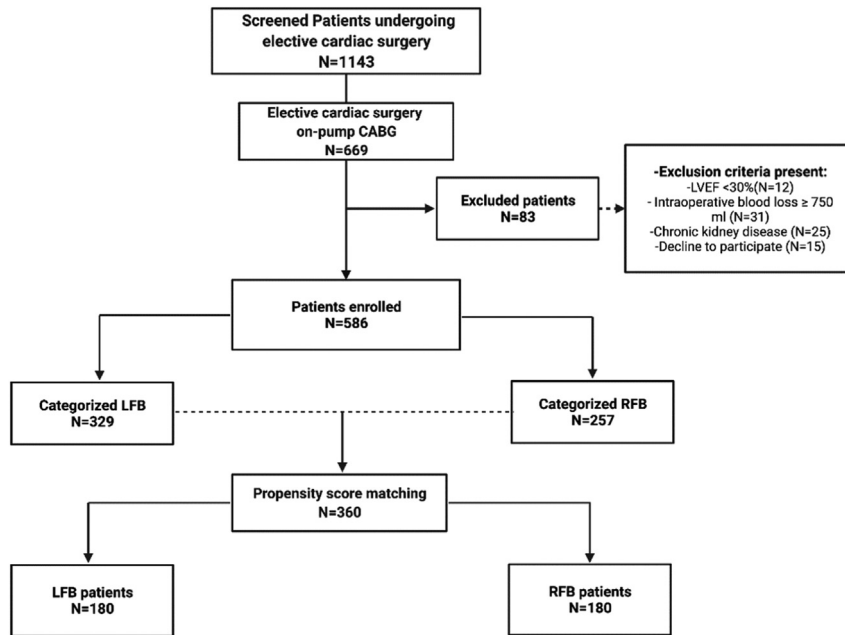


Figure 1 Study flow diagram. Patients involved in the study and the respective groups analyzed. CABG, Coronary Artery Bypass Grafting; LFB, Liberal Fluid Balance; RFB, Restrictive Fluid Balance.

The in-hospital mortality was higher in the LFB group in the matched cohort (RR = 2.6, 95% CI 1.10–6.0, $p = 0.02$). The composite cardiovascular complications were higher in the LFB group in the original and in the matched cohort (RR = 1.52, 95% CI 1.19–1.94, $p = 0.0006$).

ICU-LOS was not significantly different between the two groups (RFB vs. LFB, 3 ± 0.75 vs. 2 ± 0.75 , $p = 0.29$). Finally, H-LOS was higher in the LFB group in the matched population (RFB vs. LFB, 15 ± 3.7 vs. 22 ± 4.4 , $p = 0.01$).

Table 1 Demographic, clinical and laboratorial data before and after propensity score matching.

	Original Cohort			Matched Cohort		
	RFB (n = 257)	LFB (n = 329)	p-value	RFB (n = 180)	LFB (n = 180)	p-value
Male, n (%)	154 (59.9%)	230 (69.9%)	0.01	117 (65.0%)	115 (63.9%)	0.83
Age (y), mean ± SD	62.6 ± 10.8	63.4 ± 10.7	0.35	63.1 ± 11.1	63.3 ± 1.0	0.89
BMI (kg.cm ⁻²), mean ± SD	27.8 ± 5.2	27.3 ± 4.4	0.19	27.4 ± 5.4	27.9 ± 4.9	0.27
Race			0.0001			0.16
Caucasian, n (%)	184 (71.8%)	292 (88.8)		143 (79.4%)	153 (85%)	
Black, n (%)	73 (28.4%)	37 (11.3%)		27 (15.0%)	37 (20.5%)	
Parsonnet score	13.6±8.0	14.0±6.1	0.72	14.1±2.0	14.0±2.1	0.99
Comorbidities						
Previous cardiac surgery, n (%)	7 (2.7%)	25 (7.6%)	0.01	7 (3.9%)	10 (5.6%)	0.45
Hypertension, n (%)	112 (76.2%)	88 (71.6%)	0.40	64 (76.2%)	65 (77.4%)	0.85
Prior myocardial infarction, n (%)	105 (40.9%)	58 (17.6%)	0.001	49 (26.7%)	48 (26.7%)	0.90
Chronic heart failure, n (%)	24 (9.3%)	31 (9.4%)	0.97	20 (11.1%)	11 (6.1%)	0.14
Intraoperative fluid balance mL, median (IQR)	497 (-440–1700)	3700 (3150–4500)	0.001	900 (-157.5–1700)	3740 (3105–4700)	0.001
Cardiopulmonary bypass time (min), median (IQR)	85 (65.0–110)	85 (53.5–115)	0.58	90 (69.2–109.8)	88 (69.7–115)	0.59
Preoperative tests						
Left ventricular ejection fraction						
> 50%	175 (68.1%)	230 (69.9%)	0.64	121 (67.2%)	136 (75.6%)	0.08
< 50%	82 (31.9%)	99 (30.1%)		59 (32.8%)	44 (24.4%)	0.76
Glycemia (mg.dL ⁻¹), mean ± SD	131.8 ± 79.1	146.1 ± 94.6	0.05	133.9 ± 83.4	129.7 ± 0.63	0.17
Baseline creatinine (mg.dL ⁻¹)	1.05 ± 0.5	1.16 ± 0.4	0.002	1.06 ± 0.5	1.16 ± 0.4	0.3

RFB, Restrictive Fluid Balance; LFB, Liberal Fluid Balance; BMI, Body Mass Index; IQR, Interquartile Range; SD, Standard Deviation. The categorical variables were analyzed by Chi-Square test and the continuous variables by mean with the Student's *t*-test. Continuous variables with irregular distribution were analyzed by the Mann-Whitney test (< 0.05 marked in bold).

Table 2 Outcomes summary.

	Original Cohort			Matched Cohort			
	RFB (n = 257)	LFB (n = 329)	p-value	RFB (n = 180)	LFB (n = 180)	RR (95% CI)	p-value
CSA-AKI (%)	209 (37.9%)	207 (35%)	0.32	61 (33.9%)	53 (29.4%)	1.15 (0.85–1.56)	0.36 ^a
Creatinine (mg.dL ⁻¹) median (IQR) ^c	1 (0.9–2.2)	1.3 (0.8–2.1)	0.56	1.3 (1.2–2.4)	1.4 (1.3–2.7)		0.24 ^b
Urinary output (mL) median (IQR) ^d				650 (30–2765)	1337.5 (1000–2235)		0.001^b
In-hospital mortality	53 (9.0%)	66 (12%)	0.10	7 (3.9%)	18 (10.0%)	2.6 (1.10–6.0)	0.02^a
Cardiovascular complications, n (%)	190 (34.4%)	270 (45.7%)	< 0.001	63 (35.0%)	96 (53.3%)	1.52 (1.19–1.94)	0.0006^a
ICU-LOS (d), median (IQR)	2 (1–4)	2 (1–4)	0.59	3 (1–4)	2 (1–4)	–	0.29 ^b
H-LOS (d), median (IQR)	17 (11–26)	16 (9–25)	0.30	15 (9–23.75)	22 (13–30.75)	–	0.01^b

RFB, Restrictive Fluid Balance; LFB, Liberal Fluid Balance; RR, Relative Risk, 95% CI, Confidence Interval 95%; CSA-AKI, Cardiac Surgery-Associated Acute Kidney Injury; ICU-LOS, Intensive Care Unit Length of Stay; d, days, H-LOS, Hospital Length of Stay; IQR, Interquartile Range.

^a p-values of Chi-Square.

^b p-values of Mann-Whitney-U test (< 0.05 marked in bold).

^c serum creatinine $\geq 0.3\text{mg.dL}^{-1}$ ($\geq 26.5 \mu\text{mol.L}^{-1}$) within 48 hours or increase in serum creatinine to $\geq 1.5\text{--}1.9 \times$ baseline.

^d Urinary output in 12 hours.

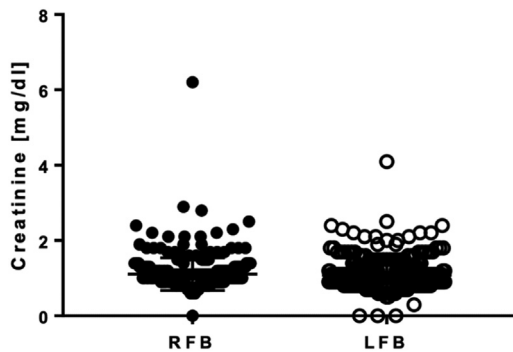


Figure 2 Creatinine values 48 hours postoperatively. Distribution of creatinine values (mg.dL⁻¹) among the evaluated groups. LFB, Liberal Fluid Balance; RFB, Restrictive Fluid Balance.

Figure 4 correlates the fluid balance volume in milliliters with the main outcomes. Patients who received volumes greater than 2500 mL had higher rates of intra-aortic balloon pump use, composite cardiovascular complications, and in-hospital mortality. Figure 5 shows a ROC Curve which correlates sensitivity and specificity, and provides a cut-off value

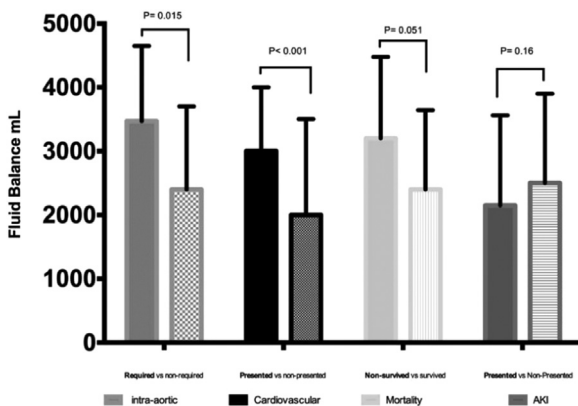


Figure 4 Intraoperative fluid balance and major postoperative outcomes. Bar graph showing the mean value and standard deviation of intraoperative fluid balance according to different outcomes. AKI, Acute Kidney Injury.

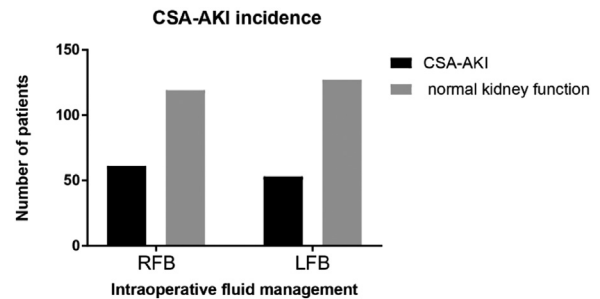


Figure 3 Primary outcome: incidence of cardiac surgery-associated acute kidney injury. Bar graph demonstrating the incidence of acute kidney injury during the study follow-up. CSA-AKI, Cardiac Surgery-Associated Acute Kidney Injury; LFB, Liberal Fluid Balance; RFB, Restrictive Fluid Balance.

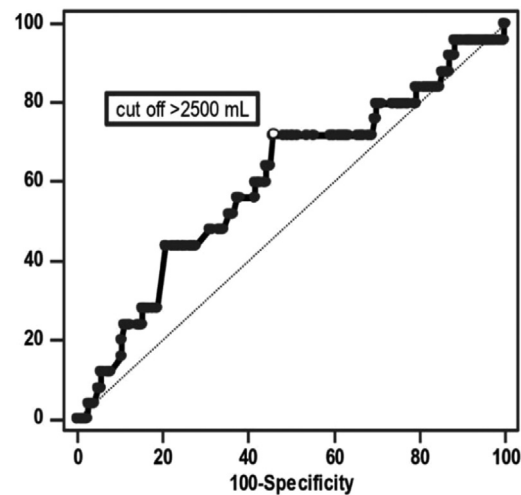


Figure 5 ROC Curve according to intraoperative fluid balance and in-hospital mortality. ROC curve correlating intraoperative fluid balance values with specificity and sensitivity for the end-point in-hospital mortality. The area under the ROC was 0.62 (0.55 to 0.66), and the optimal fluid balance value found to discriminate hospital mortality was 2500 mL (sensitivity of 72% and specificity of 55%).

of 2500 mL with the best accuracy to predict in-hospital mortality. The area under the ROC was 0.62 (0.55 to 0.66) with sensitivity of 72% and specificity of 55%.

Discussion

In view of our primary outcome, our prospective longitudinal, multicenter cohort study found no significant difference in the incidence of CSA-AKI among patients receiving either liberal or restrictive intraoperative fluid balance after on-pump CABG. Therefore, we found no significant difference regarding relative risk of CSA-AKI under different regimes. Nevertheless, we found a higher relative risk towards in-hospital mortality and cardiovascular complications among patients under liberal fluid balance in comparison with those in the restrictive matched group.

In accordance with previous described epidemiologic data of CSA-AKI,²⁰ with some incidences being reported in a range of 10% to 30%, our cohort shared similar findings among both studied collectives. In our matched cohort, we found an incidence of 33.9% and 29.4% in patients receiving restrictive and liberal strategies, respectively. The risk association between the development of acute kidney injury after cardiac procedures and some related pathophysiologic mechanisms have been extensively studied.²² Different demographic, clinical and laboratory variables are proposed as risk factors or predictive factors for the occurrence of postoperative CSA-AKI, but the role of the influence of intraoperative fluid balance remains unclear and not yet studied in patients undergoing cardiac surgery.^{22,23}

Interestingly, we found no risk difference concerning the development of postoperative CSA-AKI after on-pump CABG in the 2-day follow-up. Possibly, these findings may suggest that, in the studied cohort, both intravascular fluid shortage and overload intraoperatively could contribute to the impairment of the renal function. Not only intraoperative hypotension during cardiopulmonary bypass is associated with increased incidence of AKI after CABG due to hypoperfusion, but also fluid overload has been described as risk factor for the development of CSA-AKI as a result of endothelial and glycocalyx injury.²⁴⁻²⁶ Our findings may indicate that in moderate and high-risk patients undergoing on-pump CABG, both extremes of fluid balance may contribute to the development of CSA-AKI.

The current data regarding which intraoperative strategy is associated with clinical benefit are scarce and difficult to compare as a consequence of a variety of definitions regarding restrictive and liberal strategies as well different study applied methodologies in patients undergoing cardiac surgery.^{4,9} A prospective observational study with 1280 enrolled patients undergoing on-pump CABG showed that intraoperative highly positive fluid balance (a total fluid balance of > 500 mL at the end of surgery) is associated with adverse outcomes such as increased length of stay.²⁷ Furthermore, another randomized study with 192 patients submitted to elective on-pump cardiac surgery receiving either restrictive or liberal intraoperative fluid administrations had observed that restrictive balance intraoperatively with autologous transfusion reduces the intraoperative allogenic

red blood cell transfusions without an increase of postoperative requirement of transfusion.²⁸ The majority of the current studies observed the influence of postoperative fluid balance on cardiac-surgical patients with most evidence showing a negative influence of fluid overload on patient outcome,²⁵ and an increased incidence of AKI²⁹ and mortality.³⁰

Our study showed findings similar to those described in the literature regarding the influence of fluid balance, especially fluid overload, on patient morbidity and mortality.²⁵ In our collective, a cut-off of 2500 mL intraoperative fluid was a predictor for in-hospital mortality. Fluid overload is associated with tissue edema, distortion of tissue architecture, capillary, and blood flow obstruction resulting in poor diffusion of oxygen and metabolites, contributing to the development and progression of organ dysfunction.³¹

Myocardial edema may worsen ventricular function, resulting in the deterioration of oxygen supply, pulse conduction, and cardiac contraction leading to cardiovascular dysfunction.³² Excessive intraoperative volume can also lead to increased demand for cardiac function, displacing the heart's Starling curve and culminating in increased cardiac morbidity. Indeed, in the current study, we observed not just a significant incidence of cardiovascular complications in the group receiving the LFB, but also an increased relative risk of cardiovascular complications, H-LOS, and in-hospital mortality.

There are only few multicenter studies that prospectively observed and compared the influence of intraoperative fluid regimes in a large cohort of patients undergoing cardiac surgery, especially in patients receiving on-pump CABG on the incidence of CSA-AKI, therefore our study offers valuable results to the scientific community. Moreover, a propensity score was used to match and attempts to limit bias due to confounding variables in this observational study. Nevertheless, this study has some limitations. First, the quantification and evaluation of fluid balance performed postoperatively (based on the postoperative timepoints from the KDIGO criteria) without prior randomization and differentiation in two studied groups. Second, the influence of the type of fluid used on CSA-AKI was not addressed and an absence of a goal-directed therapy protocol for intraoperative fluid resuscitation as well as monitoring of intraoperative hemodynamic parameters could limit the interpretation of our results. Finally, the degree of atherosclerotic plaques in the aorta, aortic cross clamping time, the duration of the surgical procedure, and the postoperative fluid management were also not specifically assessed.

Conclusions

Patients undergoing on-pump coronary artery bypass grafting with liberal fluid balance when compared with patients with restrictive fluid balance present similar acute kidney injury rates and length of stay in ICU, but higher in-hospital mortality, cardiovascular complications, and length of stay in hospital. Additionally, in our cohort the cut-off value of 2500 mL showed the best accuracy to predict in-hospital mortality.

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Conflicts of interest

The authors declare no conflicts of interest.

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