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Association of Postoperative Serum Lactate Levels with Acute Kidney Injury in Mexican Patients Undergoing Cardio-Surgery

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Abstract: Acute kidney injury (AKI) is a highly prevalent and a critical complication of cardiac surgery (CS). Serum lactate levels (sLac) have consistently shown an association with morbimortality after CS. We performed a cross-sectional study including 264 adult patients that had a cardiac surgery between January and December 2020. Logistic regression analysis was performed to determine factors associated with AKI development. We measured the postoperative levels of sLac to all participants immediately after CS (T_0) and after 4 hours (T_4) of the surgical intervention. Linear regression model was carried out to identify the factors influencing both levels of sLac. We identified four risk predictors of AKI; one was preoperative (atrial fibrillation), one intraoperative (cardiopulmonary bypass time), and two were postoperative (length of hospital stay and postoperative sLac). T_0 and T_4 sLac levels were higher among CS-AKI patients than in Non-CS-AKI. Postoperative sLac levels were significant independent predictors of CSA-AKI and the sLac levels are influenced by length of hospital stay, the number of packed red blood cells transfused and the use of furosemide in CS-AKI patients. These findings may facilitate the earlier identification of patients susceptible to AKI after CS.

Keywords: cardiac surgery; kidney injury; lactates; postoperative; risk factors

1. Introduction

Acute kidney injury (AKI) comprises a clinical syndrome that is characterized by an abrupt alteration in kidney function as indicated by an increase in serum creatinine (sCr) and/or a reduction of the urine output [1]. AKI represents a common postoperative complication in patients undergoing cardiac surgery (CS) and percutaneous coronary interventions with prolonged intensive care unit (ICU) stays [2–4]. Cardiac surgery associated AKI (CS-AKI) led to increased mortality rates in the postoperative stage [5], and this augmented mortality remains high for 10 years after CS even in patients with complete renal recovery [6]. There is a complex interaction between patient and procedure-related factors that may contribute to the development of CS-AKI and these factors can be grouped into preoperative, intraoperative, and postoperative factors [7].

Regarding the first group, the preoperative variables comprise demographic characteristics such advanced age and sex, but also include preexisting kidney alterations, obesity, hypertension, diabetes mellitus, cardiac dysfunction, sepsis, volume depletion, hepatic failure, and exposure to nephrotoxic substances including drugs [7]. The intraoperative factors comprise hypovolemia, hypotension, kidney ischemia, inflammation, transfusion, decreased cardiac output, the use of diuretics, vasopressors and inotropes, and the use of cardiopulmonary bypass (CPB). Finally, the postoperative

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factors encompass hypovolemia, reduced cardiac output, mechanical ventilation, consumption of potentially nephrotoxic drugs, and urinary obstruction [7,8].

Recently, it has been proposed the use of biomarkers associated with hypoperfusion and ischemia as clinical tool for the prediction of CS-AKI. In this context, serum lactate (sLac) is directly associated to capillary perfusion, and it is a microcirculation biomarker [9,10]. Due to the physiologic interrelation with the kidneys and the production of lactate, this biochemical parameter could be pointed out as a screening tool by identifying and monitoring patients with developing CS-AKI. Also, there are several reports indicating consistently an association of sLac levels with morbidity and mortality after CS [11]. Thereby, we aimed to identify the risk factors related to CS-AKI development and to analyze the association of postoperative sLac levels with CS-AKI in Mexican patients.

2. Materials and Methods

We performed a cross-sectional study and included individuals admitted to the post-surgical unit of the Western National Medical Center of the Mexican Institute of Social Security (Jalisco, México) between January and December 2020. All eligible patients were chosen by consultation of the post-surgical patient records. AKI was defined by current KDIGO (Kidney Disease: Improving Global Outcomes) 2012 guideline [1] that includes: an increase in SCr by ≥ 0.3 mg/dL within 48 hours; or an increase in SCr to ≥ 1.5 times baseline within the previous 7 days; or urine volume <0.5 mL/kg/h for 6 hours. A total of 264 expedients of adult patients (≥18 years of age) that had a cardiac surgery were included, where 66 patients had a postsurgical diagnosis of AKI and 198 had not. Considering a prevalence of 23% of AKI [14], the proportion of patients diagnosed with Cardio-Surgery associate Acute Kidney Injury (CS-AKI) with respect to patients that did not develop CS-AKI (Non-CS-AKI) was 3:1 respectively and it was paired by age. Patients with Chronic Kidney Disease (CKD) or patients who were discharged or died after post-surgical unit admission, were excluded from the study.

The analyzed variables were obtained from individual handwritten clinical register and encompassed: demographic variables (sex and age), presence of comorbidities (diabetes mellitus, smoking, hypertension, obesity, atrial fibrillation, left ventricular ejection fraction, and dyslipidemia), presence of infection, the preoperative level of sCr, as well as the preoperative administration of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-II receptor antagonists (ARA), and furosemide; postsurgical transfusion, CPB time, and postsurgical use of antiarrhythmics. Aortic clamp time was not included in regression models due to its high collinearity with CPB time. The postoperative levels of sLac were measured postoperatively at time zero (T_0) after CS and were also quantified at 4 hours (T_4) after CS by chemiluminescence.

Categorical variables were described as the total number and percentage for each category. Continuous variables were indicated as the median and [interquartile range]. Mann–Whitney U test was used to analyze continuous variables that do not fit a normal distribution. Chi-square test was used to compare categorical variables. Univariate and multivariate logistic regression analysis were performed to identify risk factors for AKI. Only variables with statistical significance in the univariate analysis were integrated in the multivariate analysis model (enter model). Data were described as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was established as a p-value < 0.05. Statistical analysis was performed with the statistical software package GraphPad Prism (version 9.5.1).

3. Results

3.1. Clinical Characteristics

The clinical and demographic characteristics of the studied groups are detailed in Table 1. The mean age was 60 and 59 years in the CS-AKI and Non-CS-AKI, respectively (p= 0.4407). The proportion of males was higher in both groups. The prevalence of obesity and atrial fibrillation were significatively higher in the CS-AKI. Eight AKI patients (12%) underwent renal replacement therapy (RRT) and four AKI individuals (6%) had hemodialysis. CPB time was greater in patients that

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developed AKI when compared to patients who did not (p=0.0001). Patients diagnosed with AKI were more likely to require antiarrhythmic and vasopressor drugs (p=0.004 and p=0.001, respectively) when compared to Non-CS-AKI patients. In the same way, the hospital length of stay was longer in patients who developed AKI when compared to Non-CS-AKI (p<0.0001). The use of furosemide was more prevalent in patients who did not developed AKI when compared to CS-AKI group (p<0.0001). As expected, the mean value of sCr was statistically different between groups (0.88 ± 0.25 CS-AKI and 1.54 ± 7.7 Non-CS-AKI, p=0.0091).

Table 1. Baseline characteristics of Cardio-Surgery Acute Kidney Injury (CS-AKI) and without Acute Kidney Disease (Non-CS-AKI) individuals according to the category of risk factors by surgical stage.

Variable	CS-AKI n= 66 (%)	Non-CS-AKI n= 198 (%)	p-value
Preoperative risk factors			
Age	60	59	0.4407
Gender			
Female	12(18.2)	64(32.3)	0.04
Male	54(81.8)	134(67.7)	
T2DM	26(39.4)	53(26.8)	0.07
Smoking	26(39.4)	71(35.8)	0.71
Systemic Arterial Hypertension	42(63.6)	103(52)	0.13
Obesity	34(51.5)	68(34.3)	0.019
Dyslipidemia	16(24.2)	52(26.3)	0.870
Diastolic dysfunction	54(81.8)	136 (68.6)	0.057
Atrial fibrillation	24(36.3)	34(17.2)	0.002
ACEI consumption	17(25.7)	38(19.2)	0.33
ARA consumption	26(39.4)	56(28.3)	0.12
Intraoperative risk factors			
Transfusion	66(100)	185(93.4)	NA
< 3 PRBC	28 (43)	145 (73)	NA
≥ 4 PRBC	37 (56)	53 (27)	NA
CPB time*	156.0 [124.2-191.5]	121.5 [87.25-159.75]	<0.0001
AxC time	109 [88-150]	90 [67.5-116.8]	0.0009
Use of inotropes	54(81.8)	142(71.7)	0.14
Postoperative risk factors			
Use of Furosemide	15(22.7)	178(89.8)	<0.0001
Antiarrhythmics	23(34.8)	34(17.2)	0.004
Use of Vasopressors	56(84.8)	123(62.1)	0.001
Hospital length of stay (days)	5 [3-8]	3 [2-5]	<0.0001

[1] The quantitative data was presented as median [interquartile range] and were tested by U-Man-Whitney; proportions were indicated as total number (percentage) and analyzed by chi-squared test. Abbreviatures: T2DM: Type 2 Diabetes mellitus; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARA: Angiotensin-II Receptor Antagonist; PRBC: Packed Red Blood Cell; CPB: Cardipulmonary bypass; and AxC: Aortic cross clamp.

The frequency and the types of surgery in the CS-AKI and Non-CS-AKI were as follow: coronary artery bypass surgery (41% and 35%), aortic valve replacement (18% and 20%), replacement of 2 or more valves (17% and 6%), mitral valve replacement (7.5 and 6%), coronary artery bypass surgery and mitral valve (6% and 3.5%), ascending aortic surgery (6% and 5%), mediastinal exploration (1.5% and 4.5%), and others (3% and 20%), respectively.

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3.2. Serum Lactate Levels

Regarding T_0 sLac levels, its concentration was higher among CS-AKI as compared with Non-CS-AKI (4.3 [3.2-7.77] mmol/L vs 2.6 [2.0-2.85] mmol/L, p<0.0001) (Figure 1a). In the same way, the sLac levels at T_4 showed an increase value in patients who developed AKI compared to those who did not (6.55 [3.75-10.0] mmol/L vs 3.0 [2.0-4.0] mmol/L, p<0.0001) (Figure 1b). Also, when we compared the levels of sLac at T_0 and at T_4 in each group, The CS-AKI group showed an increase in the concentration (4.3 mmol/L vs 6.5 mmol/L, p=0.04) as presented in Figure 1d, and this was not observed in the Non-CS-AKI patients (Figure 1c).

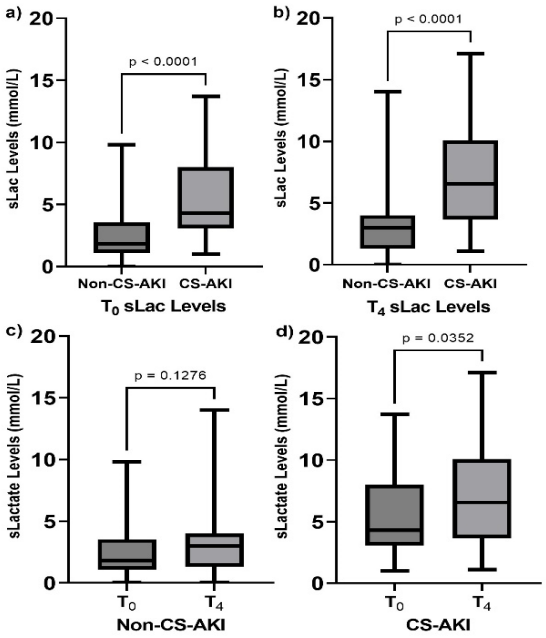

Figure 1. Comparison of postoperative serum lactate (sLac) levels in the studied groups. 1a) sLac levels at T_0 in both groups, 1b) sLac levels at T_4 in both groups, 1c) Comparison of sLac levels in the Non-CS-AKI group at T_0 vs T_4, and 1d) Comparison of sLac levels in the CS-AKI group at T_0 vs T_4. Data presented as median and interquartile range. Data analyzed through Mann-Whitney U test.

3.2. Multivariate Analysis

Furthermore, we evaluated the factors that influence the level of T_0 and T_4 sLac thorough a linear regression model. The variables significantly associated are indicated in Table 2.

Table 2. Linear Regression model of factors influencing postoperative levels of serum lactate.

Variable	T_0 serum lactate level			T_4 serum lactate level		
	β	OR [95%CI]	p-value	β	OR [95%CI]	p-value
Hospital length of stay	0.11	1.11 [1.05, 1.17]	0.0002	0.08	1.10 [1.03-1.18]	0.009
Transfusion ≤ 3 PRBC	-1.16	0.31 [0.18, 0.53]	<0.0001	-1.64	0.17 [0.08, 0.34]	<0.0001
Furosemide use ≤ 40 mg	-0.95	0.38 [0.16, 0.89]	0.027	-2.20	0.12 [0.04, 0.36]	<0.0001

T_0 serum lactate adjusted R-squared model: 0.33, p<0.0001; T_4 serum lactate adjusted R-squared model: 0.34, p<0.0001. Abbreviatures. PRBC: Packed red blood cells. T_0: quantification of serum lactate immediately after cardio surgery, T_4: quantification of serum lactate after 4 hours of the cardio surgery.

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Additionally, according to the multivariate analysis, the occurrence of AKI was influenced by sex, the hospital length of stay, both postoperative times of quantification of sLac levels, the use of furosemide, and the presence of atrial fibrillation. The statistical parameters for the logistic regression model are indicated in Table 3. As the presence of obesity and atrial fibrillation influenced the risk of CS-AKI, we analyzed the levels of sLac in these subsets of patients. When comparing the level of sLac at T_0 in CS-AKI individuals with obesity (n=34, 4.85 [3.60-8.22] mmol/L) and in the Non-CS-AKI individuals with the presence of obesity (n=68, 2.4 [1.8-3.3] mmol/L), there was a significative difference ($p<0.0001$). In the same subset, the levels of T_4 sLac in the CS-AKI and Non-CS-AKI were 6.0 [3.77-10.00] mmol/L and 3.0 [2.0-4.0] mmol/L, respectively. Concerning the presence of atrial fibrillation there were significative differences when comparing the level of T_0 sLac in the subset of CS-AKI group (n= 24, 5.0 [2.97-10.00] mmol/L) and Non-CS-AKI (n= 34, 2.0 [1.7-3.0] mmol/L) with the presence of this risk factor ($p<0.0001$). Moreover, when adjusting for independent variables, the levels of both times of measurement of sLac levels were not predicted by the presence of obesity neither atrial fibrillation (Table 3).

Table 3. Logistic Regression Model of factors influencing the risk of cardiac surgery associated acute kidney injury.

Variable	β coefficient	OR [95% CI]	p-value
Female gender	-1.46	0.23 [0.06, 0.71]	0.015
Hospital length of stay	0.13	1.15 [1.04, 1.29]	0.013
CPB time	0.02	1.03 [1.01-1.05]	0.008
Atrial Fibrillation	1.13	3.11 [1.08-9.40]	0.037
T_0 serum lactate	0.36	1.44 [1.12, 1.91]	0.007
T_4 serum lactate	0.31	1.38 [1.13, 1.69]	0.001
Use of furosemide ≤ 40 mg	-2.52	0.08 [0.02, 0.31]	0.0005

Abbreviatures. CPB: cardiopulmonary bypass, T_0: quantification of serum lactate immediately after cardio surgery, T_4: quantification of serum lactate after 4 hours of the cardio surgery.

3.4. Receiver Operating Characteristic Curve of Serum Lactate Levels

Finally, to estimate the predictive accuracy of the T_0 and T_4 sLac levels for the development of CS-AKI, receiver operating characteristic analysis was performed (Figure 2). The area under the curve (AUC) of T_0 sLac level was 0.814 (95% CI: 0.756-0.872), and for T_4 sLac was 0.818 (95% CI: 0.755-0.882). The optimum cut-off points and the values of sensitivity-specificity were T_0 sLac, 3.45 mmol/L (72%-74%), and T_4 sLac: 4.05 (70%-83%). According to the sLac level based on the optimal cut-off values, we observed that 72.7% of patients (n=48) had a T_0 sLac level ≥3.45 mmol/L, and 73.7% of individuals in the Non-CS-AKI (n=146) had a sLac level <3.45 mmol/L. Concerning T_4 sLac level, 69.7% (n=46) of patients of the CS-AKI group had a sLac level ≥4.05 mmol/L and 80.3% (n=158) showed a sLac concentration <4.05 mmol/L.

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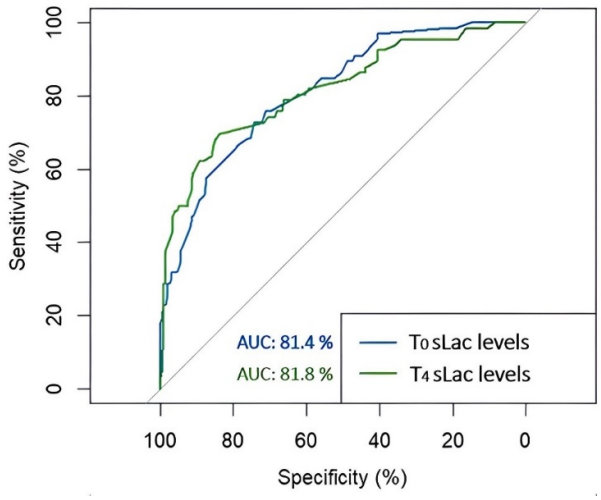

Figure 2. Receiver operating characteristic (ROC) curve for the development of acute kidney injury after cardio surgery according to the levels of T_0 and T_4 serum lactate (sLac). The area under the ROC curve was 0.814 for T_0 sLac (blue) and it was 0.818 for T_4 sLac (green).

4. Discussion

The incidence and mortality of AKI has been increasing during the past few decades, even though there have been advances in critical care and treatment technologies. The actual assumption about its physiopathological mechanisms is that hypoperfusion to the kidney, because of decreased cardiac output, decreased mean arterial pressure, or both, are the main causes of injury in patients undergoing CS [6]. Also, it has been pointed out that a complex interaction between patient and procedure-related factors contribute to the development of AKI after CS [15,16].

Concerning the preoperative risk factors, the male sex was predominant compared to women in both groups (p=0.04). There are controversies regarding the role of sex in the pathophysiology, prevalence, and progression of renal disorders. Some reports suggest that the female sex presents an elevated tendency to develop AKI compared to men [2,6], but reports also exist suggesting that female sex is a protective factor in renal disease [17]. In concordance with the latest, in the present study and as indicated by the multivariate analysis, the female sex was associated as a protector factor in the development of AKI after CS (OR:0.24, 95% CI:0.07-0.68, p=0.011). In this setting, the female sex protective association with the development of CS-AKI may be related to protective effects of estrogen as it has been reported that this type of hormones decreases renal oxidative stress [18].

Moreover, obesity was more frequent in the CS-AKI group when compared to the Non-CS-AKI (51.5% vs 34%, p=0.001) and in the same way, atrial fibrillation was more prevalent in CS-AKI group than in the Non-CS-AKI (36% vs 17%, p=0.001). However, after adjustment only atrial fibrillation was independently associated with the development AKI in patients undergoing CS (OR: 3.11, 95% CI:1.08-9.40, p=0.037). In concordance with this finding, Wang et al. reported that the risk of in-hospital AKI increased significantly in patients hospitalized for atrial fibrillation [19]. Furthermore, the presence of risk factors for atrial fibrillation often coexists and may predispose to the development of kidney disease and vice versa. However, it is worth noting that AKI itself is linked to a higher mortality and so, the coexistence of these two diseases significantly reduces the life expectancy of the individuals. For this reason, understanding this pathophysiologic interaction deserves further investigation.

Regarding the intraoperative factors, in the multivariate analysis we identify that CPB time was higher in CS patients that developed AKI when compared to patients who did not develop AKI (p<0.0001 and p=0.0009, respectively) and this association has been consistent among several reports [5,20,21]. The deleterious effect of CPB on kidney function is multifactorial and it is now well-stablished that a long CPB time is considered as a potential modifiable risk factor [20].

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In addition, concerning the drugs that were part of the intraoperative and postoperative stages, patients diagnosed with CS-AKI were more likely to require antiarrhythmic and vasopressor drugs (p=0.004 and p=0.001, respectively) when compared to Non-CS-AKI. On the other hand, the use of furosemide was more frequent in Non-CS-AKI than in patients who developed AKI (p<0.0001). Though, only the administration of furosemide influenced the risk of AKI after adjusting in the corresponding model. In fact, the administration of diuretics has a controversial association on the risk of developing AKI after CS. On the one hand, according to retrospective studies on patients undergoing CS the use of furosemide may lead to hypercreatinemia [22] and it was associated with worse renal function [23]. On the other hand, the use of furosemide has been suggested to have a nephroprotective effect [5]. In studies including healthy subjects, the diuresis effect is produced by 10 mg of furosemide with its maximal effect at 40 mg when is intravenously administered [24]. In the present investigation, the furosemide dose ranged from 10 to 100 mg, and we observed that at ≤40 mg the use of furosemide had a protective association on the risk of CS-AKI (OR: 0.09, 95% CI:0.02-0.36, p=0.001) as indicated by the multivariate analysis. In this context, the variability among reports, may reflect in part, the variable dosing that is usually employed based on disease severity.

Several reports have supported the use of sLac concentration as a measure of inadequate perfusion and tissue hypoxia, and this biochemical parameter has been proposed as a screening tool by identifying patients with underlying tissue hypoperfusion and it could be used to distinguish critically ill patients from those less critically ill individuals [25]. Nevertheless, it is currently not possible to define the best time interval between lactate measurements [26] and so, a dynamic assessment of serial lactate levels may therefore be more informative than a single measurement. According to a systematic review, the lactate quantification every 1–2 hours are probably sufficient in most acute conditions [26]. According to the latest, in the logistic regression model both postoperative times of measurement of sLac were independent risk factors for CS-AKI development. Previously, Zhang et al. reported that postoperative normalized lactate load was independently associated with postoperative AKI in patients undergoing CPB [27]. Additionally, in the particular setting of CS-AKI, Radovic et al. evaluated NGAL (Neutrophil Gelatinase-Associated Lipocalin), KIM-1 (Kidney Injury Molecule-1) and sLac levels in CS patients assessed as low-risk for developing CS-AKI and they found out that postoperative sLac was a better predictor of CS-AKI than NGAL and KIM-1 [28]. It is worth mentioning that in such study, the researchers included a relatively small number of CS-AKI patients (n=15) and they evaluated only low-risk CS-AKI patients and they measured lactate levels in arterial blood sample.

Additionally, we evaluated the factors influencing T_0 and T_4 levels of sLac. We found out that transfusion, the use of furosemide and the length of hospital stay influenced the concentrations of sLac. In the present study, the median number of PRBC transfused was 5 and 3 units in the CS-AKI and Non-CS-AKI, respectively. Surgenor et al. described the use of ≤ 3 PRBC units as the reflect of the management of routine intraoperative anemia during CS and the transfusion of >3 RBCP represents the management of active hemorrhage or severe anemia [29]. As the number of PRBC ranged from 0 to 10, we grouped those patients receiving ≤ 3 units and those individuals who received more than 4 units of PRBC. In the linear regression model, we observed that the use of ≤ 3 units was associated negatively with the levels of sLac at two times of quantification (T_0 β= -1.16, p<0.0001; T_4 β= -1.64, p<0.0001 respectively). Transfusion of PRBC units is used to improve oxygen delivery (DO_2) and increase the proportion of global DO_2 and global oxygen consumption (VO_2). Lactate is the most commonly available surrogate of the DO_2-VO_2 balance, and it has been proposed as a PRBC transfusion trigger [26]. In this context, if hemoglobin decreases to such an extent that tissue DO_2 can no longer be met, tissue hypoxia occurs resulting in a rise in lactate levels [30]. In our study´s observations, the use of ≤ 3 PRBC units was associated negatively with the postoperative levels of sLac, and this may reflect an improvement on the DO_2-VO_2 balance during CS due to transfusion when the number of PRBC was ≤ 3.

Moreover, according to regression linear analysis, when furosemide was not administered, the level of sLac decreased (T_0 sLac: -1.31, p=0.003 and T_4 sLac: -2.76, p<0.0001). However, when furosemide was used at dose ≤ 40 mg also had a negative effect over the levels of sLac, and in

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concordance with the result of the logistic regression model, the use of such dose of furosemide had a protective association on the risk of CS-AKI as mentioned above. Considering that the administration of furosemide before and after CS is a method to decrease the risk of fluid overload [6,31], and that fluid overload has been reported as an independent risk factor for AKI [32], in our cohort the association between furosemide use and sLac levels may suggest that there is a relationship between fluid balance and sLac levels. However, further investigation regarding this association in CS-AKI patients' needs to be explored.

Finally, in the current study the length of stay in postsurgical unit was longer in patients who developed AKI when compared to Non-CS-AKI (5 vs 3 days, $p<0.0001$ respectively). Several studies had consistently reported this observation and in addition, in those patients with CS-AKI the longer length of stay in ICU as well as in hospital was associated with an increased risk of death [5–7,33,34]. Also, the hospital length of stay influenced the levels of sLac. In accordance with these observations, Andersen et al. reported that increased postoperative sLac levels were associated with increased hospital length of stay for patients undergoing major CS [11]. Given the fact that sLac levels had shown to be independently associated with the risk of CS-AKI and there is a relationship between sLac concentration, and the length of hospital stay which in turn is associated with high morbidity and mortality [35] this points out that the underlying mechanisms of lactate increase could be a promising target for further investigation and as an intervention target to improve patient life expectancy.

The findings of the present study should be understood in the context of the study's design and limitations. As the data was collected retrospectively, the investigation was limited by the variables collected, and potential confounding by unreported variables and so, multiple other possible causes of raised sLac levels may be present in the postsurgical patient. As well, the current study had a relatively short observational period and for this reason we were unable to perform statistical analysis related to the association between sLac levels and mortality. Preoperative sLac levels were not available, and we were unable to adjust for this variable. Nevertheless, Radovic et al. reported that postoperative sLac was a better predictor of CS-AKI risk than preoperative sLac values [28]. Regarding the use of furosemide, we do not have a precise chronology of the time of its administration. Also, we did not obtain information about urinary output for the adjusting in the effect of renal function of furosemide. For these reasons, our observations need to be confirmed by additional studies with larger patient size.

5. Conclusions

Postoperative sLac levels were significant independent predictors of CSA-AKI and the sLac levels are influenced by length of hospital stay, the number of PRBC transfused and the use of furosemide in CS-AKI patients. These findings may facilitate the earlier identification of patients susceptible to AKI after CS.

Author Contributions: Conceptualization, Héctor-Enrique Flores-Salinas, Yeminia Valle and Jorge-Ramón Padilla-Gutiérrez; Formal analysis, Anahí de Jesús Zambada-Gamboa and Texali-Candelaria Garcia-Garduño; Funding acquisition, Héctor-Enrique Flores-Salinas; Methodology, Guillermo Rodríguez-Zavala, Juan-Carlos Chávez-Herrera, Porfirio-Eduardo Martinez-Gutierrez, Arturo Godinez-Flores and Salvador Jiménez-Limón; Supervision, Jorge-Ramón Padilla-Gutiérrez; Writing – original draft, Héctor-Enrique Flores-Salinas, Anahí de Jesús Zambada-Gamboa and Texali-Candelaria Garcia-Garduño; Writing – review & editing, Guillermo Rodríguez-Zavala, Yeminia Valle, Juan-Carlos Chávez-Herrera, Porfirio-Eduardo Martinez-Gutierrez, Arturo Godinez-Flores, Salvador Jiménez-Limón and Jorge-Ramón Padilla-Gutiérrez. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the 1975 Declaration of Helsinki and approved by the Ethics Committee of Instituto Mexicano del Seguro Social (protocol code R-2021-1301-181). All subjects gave their informed consent for inclusion before they participated in the study.

Informed Consent Statement: Every individual enrolled in the present study was entirely informed about the risks and benefits implicated, and they were also notified about the possibility of publishing. Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Dataset available on request from the authors

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