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Article

A Novel Understanding of Serum Creatinine Levels as a Predictive Factor for Mortality Outcome in Aortic Disease

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Abstract: Acute renal injury (AKI) is a complication that can occur after cardiac surgery, and since technological advancements and knowledge in medicine are exponentially expanding, it requires ongoing research. The study aims to evaluate the outcome of the treated electives of emergency aortic disease with high serum creatinine levels (SCr). **Methods:** The cohort included 183 patients, all of whom had an aortic disease and whose SCr levels were checked upon admission on the first day in the intensive care unit (ICU) and upon discharge from the hospital. We correlated SCr levels with in-hospital mortality and immediate mortality at least six months after discharge, with cross-clamp time and bypass time. **Results:** A high SCr level upon admission significantly predicts in-hospital mortality (p = 0.001) but not immediate mortality (p = 0.409). There is also a statistically significant correlation between the elevated SCr levels on the first day of ICU and aortic disease (p = 0.041) but not with immediate mortality (p = 0.119). We found a significant correlation between aortic disease and in-hospital mortality (p < 0.001) but no correlation between high SCr level on the first day of ICU and immediate mortality (p = 0.119). The cross-clamp time had a statistically significant correlation with elevated SCr level (p = 0.013) and in-hospital mortality (p = 0.001) but not with immediate mortality (p = 0.847). Furthermore, the bypass time was negatively correlated with a high SCr level on the first day of ICU (p = 0.090), with in-hospital mortality (p = 0.410) and immediate mortality (p = 0.625). We also found that patients with an aortic disease were not correlated with elevated creatinine levels at ICU discharge (p = 0.152) or long-term mortality (p = 0.106). **Conclusions:** The study only included a small portion of the elaborate surgical and medical management developed around cardiac patients who received invasive treatment. The conclusions reached were nevertheless clearly relevant, evidenced by the significantly correlated statistics. This element, moving forward, motivates us to expand our research's range, collect the most newly relevant data, and use it to benefit the patient; this work provides the beginning step in this process.

Keywords: aortic diseases; serum creatinine; acute kidney injury; cardiac surgery; in-hospital mortality; cross-clamp time

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1. Introduction

Acute kidney injury (AKI), a common complication following cardiac surgery, still occurs between 30% and 45% of patients and is the second common factor that increases mortality in the intensive care unit (ICU) after infections [1-4].

"Cardiorenal syndrome" is an illness that affects the kidneys and the heart, where one of the organs may become acutely or chronically dysfunctional, leading to the dysfunction of the other organ [5-8].

AKI, formerly known as acute renal failure (ARF), is characterized by the kidneys' rapid failure to maintain water and electrolyte regulation [9]. Compared to non-cardiac surgery, cardiac surgery has special characteristics, such as high rates and volumes of exogenous blood product transfusion, that make patients more susceptible to AKI [10]. Glomerular filtration rate (eGFR) <30-44 mL/min/1.73m^2, is associated with increased in-hospital and long-term mortality rate [5, 11-15].

AKI is characterized by a rise in serum creatinine (SCr) ≥ 0.3 mg/dl (≥26.5 μmol/l) within 48 hours, an increase in SCr of ≥ 1.5 times baseline that is known or suspected to have happened within the previous 7 days, or a rise in SCr of <0.5 ml/kg/h for a period of 6 hours [16].

Studies have shown a strong correlation between mortality rate to a drop in eGFR, with one study showing a 14% mortality risk increase for each 10 mL/min/1.73m^2 decline in eGFR [2,17-19]. Several conditions, such as diabetes mellitus (DM), can predict AKI, which leads to hypoperfusion due to inflammation [20,21].

The most prevalent underlying pathology of coronary artery disease is atherosclerosis, where the innermost layer of large to medium-sized arteries gradually narrows due to the accumulation of plaque over time; this reduces blood flow and culminates in severe tissue hypoxia, which may be the cause of AKI [22,23].

According to studies, preoperative atherosclerosis and inflammation are highly linked to postoperative AKI [24,25]. Extracorporeal circulation (EC) in cardiac surgery allows surgeons to address various heart problems while a heart-lung pump maintains myocardial oxygen and blood oxygenation [26-29]. The improper stimulation of inflammatory markers in patients undergoing cardiac surgery with EC support continues to be a common cause of postoperative complications, including AKI [27,30,31].

The mortality rate in cardiac surgery ranges from 2 to 7%, depending on factors such as race, age, low cardiac output, and associated comorbidities other than cardiac diseases [32,33]. However, the mortality risk increases drastically to over 60% when the patient develops postoperative AKI [34-37]. Currently, more than 6.4 billion people do not have adequate access to cardiac surgery and do not live in developed countries [38]. With cardiac surgery being a global specialty since its origin in 1896, it is imperative to understand correlations to lower mortality risk [39-41].

Medical records of 183 patients who received medical and surgical care for aortic disease in a tertiary center were analyzed retrospectively, and our primary objective was to establish if a high SCr level influences mortality following the treatment of aortic disease.

The study's idea came from the need to continue studying possible predictors factors which occur after surgical treatment of aortic disease due to a mortality rate that is still high in the in-hospital and immediate, even though experience and technological advancements have made significant progress in the 21st century.

We aimed to determine if the medical approach used in the study group from a tertiary center from Eastern Europe continues to produce favorable outcomes for surgical patients and if it can serve as a starting point for extensive research to reduce postoperative mortality in patients undergoing cardiac surgery. If it can, this would be a step in the right direction.

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2. Materials and Methods

Between 2019 and 2022, 185 patients who presented for elective or emergency aortic disease treatment at Targu Mures Emergency Institute for Cardiovascular Diseases and Transplant were the subjects of this retrospective study.

The main inclusion criterion in the analyzed groups was the presence of an ascending aortic disease who required elective (aortic aneurysms) or urgent (acute aortic syndrome) surgery and serum creatinine value above the reference values of 1.25 mg/dl.

We used the Abbott Creatinine 2 R1 8x53.9ml/R2 8x21.4ml kit for SCr dosing, with reference values ranging from 0.74 mg/dl to 1.25 mg/dl for Processing Module Architect c 4000, manufactured by Abbott Diagnostics (USA).

Patients whose consent could not be obtained or who refused surgery were excluded from the study ($n = 2$), as well as patients with New York Heart Association (NYHA) class III (severe heart failure) established cardiac failure with functional status, those with established renal failure necessitating replacement therapy, and patients under 18 years old. All patient data were analyzed in agreement with the ethical code and current legal requirements.

All maneuvers were performed in line with the local standard protocols during surgery and the ICU. SCr level was assessed in every patient at three different moments: admission, on the first day in ICU, and discharge.

In-hospital mortality is the term we use to describe patients who pass away while hospitalized, and immediate mortality is when patients pass away more than six months following discharge.

Statistical analysis was performed using the IBM SPSS 23.0 Statistics program (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp., USA). When dealing with categorical variables, the findings of descriptive statistics are often reported in the form of absolute and relative frequencies. The mean ± standard deviation (minimum-maximum) was used for continuously collected data. The Skewness test was applied to measure the symmetry of the distribution, and the Kurtosis test was applied to determine the heaviness of the distribution tails. The Spearman RHO non-parametric test was carried out to measure the strength and direction of the linear association relationship between the ranked variables.

The flatness and skewness distribution (Kurtosis and Skewness tests) found that the data was not parametric. As a result, Spearman's rank correlation coefficient was applied, which is used when data is non-parametric.

At least 30 measurements or surveys out of the total 183 subjects were needed to achieve a confidence level of 95% and to ensure that the actual value was within 5% of the value measured or surveyed using the Minitab software. This amount was the minimum number of required measurements or surveys (Minitab 20 Statistical Software, 2020. State College, PA: Minitab, Inc., www.minitab.com). Since we got a more significant than (>) alternative hypothesis, we presented one as a counterpoint to the alternative hypothesis. The number 183 was chosen as the appropriate sample size, leading to a statistical power of 0.853283, or 85%. It was determined that the statistical power (S.P.) needed to identify the proper effect needed to be at least 0.8.

Data were collected over time from 183 patients who got thoracic aorta treatment, patients with an average age of 62 years (ranging from 22 to 85 years) and 54 (29.5%) women, and 129 (70.5%) men. There were 73 cases with aortic aneurysms and 110 with acute aortic dissection. The group's mortality is determined based on the 16 patients (8.74%) who passed away at least 6 months after discharge and the 50 patients (27.3%) who passed away while hospitalized. Table 1 details the clinical and patient characteristics.

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3. Results

Data were collected over time from 183 patients who got thoracic aorta treatment, patients with an average age of 62 years (ranging from 22 to 85 years) and 54 (29.5%) women, and 129 (70.5%) men. There were 73 cases with aortic aneurysms and 110 with acute aortic dissection. The group's mortality is determined based on the 16 patients (8.74%) who passed away at least 6 months after discharge and the 50 patients (27.3%) who passed away while hospitalized. Table 1 details the clinical and patient characteristics.

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Table 1. Summary of the research participants' clinical and baseline characteristics (N=183).

	n =	Std. Deviation	Skewness		Kurtosis	
				Std. Error		Std. Error
Urgency	110	0,49	-0,41	0,18	-1,84	0,35
Chronic	73	0,49	0,41	0,18	-1,84	0,35
Hemopericardium	36	0,39	1,53	0,18	0,37	0,35
Cardiac tamponade	16	0,28	2,94	0,18	6,74	0,35
Cardiogenic shock	13	0,25	3,36	0,18	9,44	0,35
Cardiac arrest	4	0,14	6,59	0,18	41,94	0,35
Peripheral artery disease	7	0,19	4,85	0,18	21,80	0,35
Diabetes mellitus	8	0,20	4,50	0,18	18,45	0,35
Chronic obstructive pulmonary disease	9	0,21	4,20	0,18	15,84	0,35
Asthma	3	0,12	7,68	0,18	57,61	0,35
Kidney disease	28	0,36	1,94	0,18	1,798	0,35
Polycystic kidney disease	5	0,16	5,84	0,18	32,54	0,35

The statistically significant positive correlation between a high SCr level at admission and in-hospital mortality was $r = 0.29$, $p < 0.001$ (Table 2).

Table 2. Relationship between high SCr level on admission and in-hospital mortality.

			In-hospital mortality
Spearman's rho test	High SCr level	Correlation Coefficient	0,29**
		Sig. (2-tailed)	0,000

**. Correlation is significant at the 0.01 level (2-tailed).

According to our research, a high SCr level at admission did not significantly correlate with immediate mortality ($r = 0.06$, $p = 0.409$) (Table 3).

Table 3. Relationship between SCr level on admission and immediate mortality.

			Immediate mortality
Spearman's rho test	High SCr level on admission	Correlation Coefficient	0,06
		Sig. (2-tailed)	0,409

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Statistically significant negative correlations were identified between aortic disease and high SCr levels on the first day in ICU (r = -0.15, p = 0.041) and between aortic disease and in-hospital mortality (r = -0.38, p <0.001). Furthermore, a statistically significant positive correlation was found between high SCr levels on the first day in ICU and in-hospital mortality (r = 0.36, p <.001) (Table 4).

Table 4. Relationship between the presence of aortic, high SCr value in the first day in ICU, in-hospital mortality, and long-term mortality.

			Aortic disease	High SCr on the first ICU day
Spearman's rho	High SCr level on the first ICU day	Correlation Coefficient	0,15*	
		Sig. (2-tailed)	0,041	
	In-hospital mortality	Correlation Coefficient	0,38**	0,36**
		Sig. (2-tailed)	0,000	0,000
	Immediate mortality	Correlation Coefficient	0,12	0,116
		Sig. (2-tailed)	0,106	0,119

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

The results show no statistically significant correlation between high SCr levels on the first ICU day and immediate mortality (r = 0.11, p = 0.119) (Table 5).

Table 5. Relationship between high SCr level on the first day in ICU and immediate mortality.

			Immediate mortality
Spearman's rho	High SCr level on the first ICU day	Correlation Coefficient	0,11
		Sig. (2-tailed)	0,119

In table 6, it can be observed that cross-clamp time correlates negatively with high SCr levels on the first ICU day (r = 0.18, p = 0.013) and strongly positively with in-hospital mortality (r = 0.36, p <.001).

Table 6. Relationship between cross-clamp time with high SCr level on the first ICU day and in-hospital mortality.

			Cross-clamp time
Spearman's rho	High SCr level on the first ICU day	Correlation Coefficient	0,18*
		Sig. (2-tailed)	0,013
	In-hospital mortality	Correlation Coefficient	0,36**
		Sig. (2-tailed)	0,000

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Regarding the relationship of immediate mortality, we observed no statistically significant correlation related to cross-clamp time (r = 0.01, p = 0.847) (Table 7).

Table 7. Relationship between cross-clamp time and immediate mortality.

	Immediate mortality

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Spearman's rho	Cross-clamp time	Correlation Coefficient	0,01
		Sig. (2-tailed)	0,847

We found no significant correlation between total bypass time with high SCr level on the first ICU day (r = -0.12, p = 0.090), in-hospital mortality (r = 0.06, p = 0.410), and immediate mortality (r = 0.03, p = 0.625) (Table 8).

Table 8. Relationship between total bypass time with high SCr level on the first ICU day, in-hospital mortality, and immediate mortality.

			Total bypass time
Spearman's rho	High SCr level on the first ICU day	Correlation Coefficient	0,12
		Sig. (2-tailed)	0,090
	In-hospital mortality	Correlation Coefficient	0,06
		Sig. (2-tailed)	0,410
	Immediate mortality	Correlation Coefficient	0,03
		Sig. (2-tailed)	0,625

There was also no correlation between immediate mortality (r = 0.12, p = 0.106) and aortic disease with high SCr level at ICU discharge (r = 0.10, p = 0.152) (Table 9).

Table 9. Relationship between aortic diseases with high SCr levels at discharge from the ICU and immediate mortality.

			High SCr level at discharge from the ICU	Immediate mortality
Spearman's rho	Aortic diseases	Correlation Coefficient	0,10	0,12
		Sig. (2-tailed)	0,152	0,106

4. Discussion

Acute kidney injury is still a significant complication of heart surgery. To enhance outcomes, early detection and effective management are necessary. We propose extending the research area since a high rate of in-hospital mortality still occurs despite the advanced treatment options for AKI after cardiac surgery.

Even though a lot of information regarding the etiology of postoperative AKI exists (older patients with multiple comorbidities, urinary tract obstruction, preexisting chronic kidney disease, acute infections, sepsis, acute organ failure, hypovolemia, nephrotoxic drugs, and many more), there are still a lot of unknown factors that can influence the AKI commencement, progression and its outcomes following cardiac surgery [42,43].

Preoperatively, patients at risk can be identified, and an individual approach can be provided to adjust circulatory support during surgery and with renoprotective postoperative therapy [44,45].

As it is influenced by muscle mass, fragility, and body weight and does not fluctuate outside of typical values until at least 50% of the functioning renal mass has been impacted, serum creatinine is not a reliable indicator of acute kidney injury [15]. However,

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since it positively correlates with in-hospital mortality, it may be used as an indicator of postoperative mortality [46].

Mortality is a key metric for measuring the success of surgical and medical treatments, and studies like this have revealed a correlation between mortality that occurs shortly after surgery or later and the development of AKI [2,47-49].

According to our research, a high SCr level upon admission correlates statistically significantly with in-hospital mortality but not with immediate mortality.

The multidisciplinary team monitoring this type of patient by restoring postoperative hemodynamic and tissue perfusion parameters may have resulted in our lack of correlation to immediate mortality. The cardiac patient is a complex patient requiring much more careful postoperative monitoring due to the associated comorbidities and the slightly more extended recovery period [10,50-52].

To prevent the development of life-threatening complications like AKI, cardiac patients require a multidisciplinary and preventative strategy, according to the results of the interdisciplinary research conducted on patients over time [53-56]. From a surgical standpoint, the use of a preventive renal strategy that involves delaying elective surgery until the renal problems are resolved, using less nephrotoxic treatments, treating infections and other comorbidities that negatively affect the kidneys and other organs, reducing the time of ischemia, preventing blood pressure variations, and using as little blood transfusions as possible is required [57-63]. If the patient's postoperative SCr level is maintained within the accepted reference ranges, the above factors will directly affect the patient's outcome [64].

The inflammatory processes, humoral factors, and cellular immune responses rapidly increased after cardiac surgery by using extracorporeal circulation. As a result, organ dysfunction may occur, where one or more organs fail. The SCr level can be managed in this context through preventive and therapeutic measures and prompt medical assistance. However, if a multi-organ dysfunction occurs, the management aspect evidently becomes harder from the increased mortality [65,66].

Extracorporeal circulation determines a special status for the operated patient. Still, it has been observed that through preventive, therapeutic measures, there is a constant improvement in the patient's postoperative evolution. The essential aspect that actively contributes to mortality is the cross-clamp time, which can distinguish between a favorable and negative operative result [67-69].

In-hospital mortality tends to decrease when a patient is properly managed, and the patient will gain the maximum benefit from the surgical act at the time of discharge [29,59,62,70].

In light of the correlation between prolonged cross-clamp time and elevated SCr levels and between this biochemical parameter and in-hospital mortality, we can conclude that a preventive strategy applied as early as possible following surgery in patients at risk can significantly improve their outcome. To quantify the risk aspect, additional research will be necessary.

5. Limitations

It was decided to use the SCr level above the reference value as an independent predictor of death rather than evaluating renal function according to the glomerular filtration rate. This study was carried out in a tertiary center in Eastern Europe where medical resources, patients' medical service addressability, and medical education programs are not comparable to those in Western European nations.

6. Conclusions

In this current study, we found that a high SCr level negatively impacted in-hospital-term mortality but not immediate mortality. Science and medicine are progressing, and the criterion that was earlier considered to be directly correlated to the death rate following cardiac surgery now appears to be unclear. To successfully contribute to

decreasing mortality and developing efficient renoprotective treatment, we consider that determining risk factors is essential in these circumstances.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the George Emil Palade University of Medicine, Pharmacy, Science and Technology from Targu Mures (UMFST) as well as the Emergency Institute for Cardiovascular Diseases and Transplant from Targu Mures (Resolution No. 878/23.04.2020 and 1359/10.05.2021)

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical reasons.

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Conflicts of Interest: The authors declare no conflict of interest.

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