Scientific Research Publishing

World Journal of Cardiovascular Diseases, 2024, 14, 363-373
https://www.scirp.org/journal/wjcd
ISSN Online: 2164-5337
ISSN Print: 2164-5329

Exploring the Role of Serum Cystatin C in Early Detection of Acute Kidney Injury among On-Pump Cardiac Surgery Patients: A Single-Center Investigation in Bangladesh

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How to cite this paper: Ahaduzzaman, Md., Chowdhury, Md.A.T., Magdum, M., Khan, Md.S.I., Sharma, S., Tiwari, M., Maruf, Md.A.B., Alauddin, Md., Khan, O.S., Rahman, Md.M. and Saquib, M.Md.N. (2024) Exploring the Role of Serum Cystatin C in Early Detection of Acute Kidney Injury among On-Pump Cardiac Surgery Patients: A Single-Center Investigation in Bangladesh. *World Journal of Cardiovascular Diseases*, **14**, 363-373.
https://doi.org/10.4236/wjcd.2024.146030

Received: May 17, 2024
Accepted: June 24, 2024
Published: June 27, 2024

Abstract

Background: Acute Kidney Injury (AKI) stands as a prominent postoperative complication in on-pump cardiac surgery, with repercussions on morbidity, mortality, and hospitalization duration. Current diagnostic criteria relying on serum creatinine levels exhibit a delayed identification of AKI, prompting an exploration of alternative biomarkers. **Aims and Objectives:** This study is designed to overcome diagnostic constraints and explore the viability of serum Cystatin C as an early predictor of Acute Kidney Injury (AKI) in individuals undergoing on-pump cardiac surgery. The investigation aims to establish the relationship between serum Cystatin C levels and the onset of AKI in patients subjected to on-pump cardiac surgery. Primary objectives involve the assessment of the diagnostic effectiveness of serum Cystatin C, its comparison with serum creatinine, and the exploration of its potential for the early identification and treatment of AKI. **Methodology:** Conducted as a single-center study at the cardiac surgery department of BSMMU in Bangladesh from September 2020 to August 2022, a comparative cross-sectional analysis involved 31 participants categorized into No AKI and AKI groups based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Data collec-

tion encompassed preoperative, post-CBP (cardiopulmonary bypass) conclusion at 2 hours, postoperative day 1, and postoperative day 2 intervals. Statistical analyses included Chi-squared tests, independent Student's t-tests, and one-sample t-tests. Significance was set at $P < 0.05$, and the study utilized Statistical Package for the Social Sciences (SPSS) version 29.0 for data analysis. **Results:** The study revealed no significant differences in baseline characteristics between the No AKI and AKI groups, except for CPB time and cross-clamp time. Serum Cystatin C levels in the AKI group exhibited statistical significance at various time points, highlighting its potential as an early detector. Conversely, Serum Creatinine levels in the AKI group showed no statistical significance. The Receiver Operating Characteristic (ROC) curve analysis further supported the efficacy of serum Cystatin C, with an Area under the ROC Curve of 0.864 and a cut-off value of 0.55 ($p < 0.05$). **Conclusion:** This study supports the superior utility of serum Cystatin C as an early detector of AKI in on-pump cardiac surgery patients compared to serum creatinine. Its ability to identify AKI several hours earlier may contribute to reduced morbidity, mortality, and healthcare costs. The findings underscore the significance of exploring novel biomarkers for improved post-cardiac surgery renal function assessment.

Keywords

Acute Kidney Injury (AKI), On-Pump Cardiac Surgery, Serum Cystatin C, Serum Creatinine, Diagnostic Biomarkers, Early Detection, Cardiopulmonary Bypass, Single-Center Study, Bangladesh

1. Introduction

Cardiac surgery, encompassing procedures such as Coronary Artery Bypass Grafting, congenital heart diseases, and valvular disease interventions, ranks among the most common surgical interventions worldwide, surpassing 2 million surgeries annually [1]. Cardiopulmonary bypass (CPB), a form of extracorporeal circulation bypassing the heart and lungs, facilitates circulatory and respiratory support and temperature control during heart surgeries [2]. CPB-associated systemic inflammatory response syndrome is primarily attributed to blood contact with the artificial surface of the bypass circuit and mechanical shear [2].

CPB induces a 30% reduction in renal perfusion pressure, contributing to ischemic reperfusion damage [3]. Acute Kidney Injury (AKI) is a prevalent and potentially fatal complication following cardiac surgery and CPB [4]. AKI is characterized by an abrupt decline in kidney function, leading to urea accumulation and disruption of extracellular volume and electrolyte balance. Approximately 2% - 30% of CPB patients develop AKI, with 1% requiring renal replacement therapy [5].

The complex etiology of post-cardiac surgery AKI involves exogenous and endo-

genous toxins, metabolic anomalies, ischemia-reperfusion injury, neuro-hormonal activation, inflammation, and oxidative stress [6]. CPB-related AKI is associated with higher morbidity, mortality, prolonged critical care unit and hospital stays, with acute tubular necrosis being a common cause [7].

Serum Cystatin C (S. cysC) emerges as a promising biomarker for predicting all-cause AKI after CPB, offering superior diagnostic performance compared to serum creatinine [7]. Despite cardiac surgery's frequency, AKI remains a significant concern for patient survival, emphasizing the need for early detection. Unlike serum creatinine, S. cysC remains unaffected by age, sex, or muscle mass, making it a more reliable biomarker for early AKI diagnosis [8].

The study explores the potential of S. cysC in the early diagnosis of AKI according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria in patients undergoing on-pump cardiac surgery. The investigation aims to contribute to the identification of reliable biomarkers for timely AKI detection and risk stratification, crucial for successful treatment and patient outcomes.

2. Materials and Methods

The study, spanning a 24-month period from September 2020 to August 2022, was conducted at the Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), utilizing a comparative cross-sectional design to assess 31 patients undergoing on-pump cardiac surgery with cardiopulmonary bypass. Following post-operative categorization based on Kidney Disease Improving Global Outcomes (KDIGO) criteria, patients were divided into two groups: Group A, comprising individuals without acute kidney injury (No AKI), totaling 23 patients, and Group B, consisting of those with acute kidney injury (AKI), totaling 8 patients. Its primary focus was to investigate the potential of serum Cystatin C as an early predictor of Acute Kidney Injury (AKI) in this patient cohort. The study aimed to establish the correlation between serum Cystatin C levels and the onset of AKI following on-pump cardiac surgery, with objectives centered on evaluating the diagnostic efficacy of serum Cystatin C compared to serum creatinine and exploring its utility in early AKI detection and management. Notably, the decision to employ a smaller sample size was made in light of the challenges posed by the COVID-19 pandemic and was carefully considered by both the investigators and the institutional review board. As previously stated, patients were categorized post-operatively according to KDIGO criteria, with convenient sampling methodology utilized. Inclusion criteria encompassed patient consent for cardiac surgery participation, while exclusion criteria included specific medical conditions and refusal to consent. Data collection involved various methods, including face-to-face interviews, standardized questionnaires, and investigation reports, with serum creatinine and cystatin C levels measured at specified intervals. Ethical considerations were meticulously followed, including obtaining ethical approval, informed consent, confidentiality assurances, and the provision for withdrawal. Data analysis utilized Statistical Package for the Social Sciences (SPSS) ver-

sion 29, employing statistical techniques with a predefined significance level of P-value < 0.05.

Regarding the definition of acute kidney injury (AKI), the study adhered to the KDIGO classification criteria, which includes: an increase in serum creatinine by 0.3 mg/dL or more within 48 hours; an increase in serum creatinine to 1.5 times baseline or more within the last 7 days; or urine output less than 0.5 mL/kg/h for 6 hours. The KDIGO staging system for AKI is as follows: Stage 1 involves a serum creatinine increase of 1.5 - 1.9 times baseline or ≥0.3 mg/dL, coupled with urine output less than 0.5 mL/kg/h for 6 hours. Stage 2 comprises a serum creatinine increase of 2 - 2.9 times baseline, with urine output remaining below 0.5 mL/kg/h for 12 hours. Stage 3 encompasses a serum creatinine increase to 3 times baseline, an increase to ≥4 mg/dL, or the initiation of renal replacement therapy, along with significantly reduced urine output (<0.3 mL/kg/h for 24 hours or anuria for ≥12 hours). As highlighted in the study, serum cystatin C, a cysteine protease inhibitor protein produced in nucleated cells, was utilized. It undergoes free filtration by the glomerulus and subsequent reabsorption in the proximal tubule. Elevated levels correlate with deteriorating kidney function, indicating a decline in glomerular filtration rate. The typical normal range for cystatin C falls between 0.62 to 1.15 mg/L.C [4] [9].

3. Results

In the current study, patients were categorized post-operatively based on KDIGO criteria into two groups: Group A, encompassing individuals without acute kidney injury (No AKI), totaling 23 patients (74.2%), and Group B, consisting of those with acute kidney injury (AKI), totaling 8 patients (25.8%). This distribution is visually depicted in **Figure 1**. **Table 1** presents the distribution of patients studied by age. In the No AKI group, the mean age was 25.83 ± 7.13 years, contrasting with 34.63 ± 15.75 years in the AKI group. The majority of patients in the No AKI category were aged between 21 and 40 years, while those in the AKI group were mostly between 41 and 60 years old. Despite these variations, the difference in age between the groups did not reach statistical significance (P > 0.05).

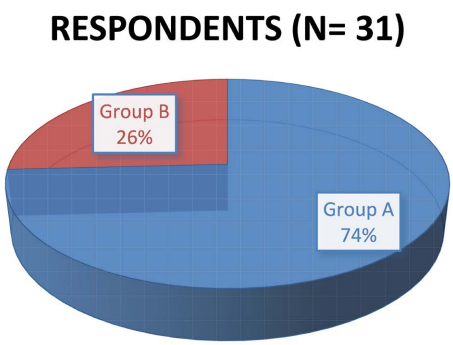

Figure 1. Distribution of study participants in Group A (without AKI) and Group B (with AKI).

Table 1. Comparison of age between two groups.

Age group (in years)	Respondents (N = 31)		
	Group A f (%) $n_1 = 23$	Group B f (%) $n_2 = 8$	P value
01 - 20	5 (21.7)	2 (25)	
21 - 40	18 (78.7)	2 (25)	0.373 [ns]
41 - 60	0 (0)	4 (50)	
Age Mean ± SD	25.83 ± 7.13	34.63 ± 15.75	

N = Total number of respondents; n_1 = Participants in Group A; n_2 = Participants in Group B; f = Frequency; ns = Not significant; SD = Standard Deviation; Data were presented as frequency and mean and ±SD; Statistical analysis was done by Chi square-test; P value ≤ 0.05 was considered as significant.

Table 2 presents the gender distribution of the study population. In the No AKI group, 11 individuals (47.83%) were male and 12 (52.17%) were female. In the AKI group, both males and females were evenly represented, with 4 individuals (50.0%) in each category. The P-value was 0.618, indicating no statistically significant difference in gender distribution between the two groups.

Table 2. Comparison of gender between two groups.

Gender	Respondents (N = 31)		
	Group A f (%) $n_1 = 23$	Group B f (%) $n_2 = 8$	P value
Male	11 (47.83)	4 (50)	0.618 [ns]
Female	12 (52.17)	4 (50)	

N =Total number of respondents; n_1 = Participants in Group A; n_2 = Participants in Group B; f = Frequency; ns = Not significant; SD = Standard Deviation; Data were presented as frequency and mean and ±SD; Statistical analysis was done by Chi square-test; P value ≤ 0.05 was considered as significant.

Table 3 indicates that the majority of subjects in both groups had a normal BMI. Specifically, 21 individuals (91.3%) in the No AKI Group And 7 individuals (87.5%) in the AKI group fell within the normal BMI range. The mean BMI was 22.32 ± 2.21 for the No AKI Group And 22.33 ± 2.09 for the AKI group. There was no significant difference in BMI between the two groups ($P > 0.05$).

Table 4 presents the distribution of risk factors among the study participants. The comparison of diabetes mellitus, hypertension, thyroid abnormalities, and LVEF < 40% between the No AKI and AKI groups showed no statistically significant differences ($P > 0.05$).

Table 5 compares the Mean ± SD of Total CPB Time and Cross Clamp Time between patients in the No AKI and AKI groups. For the No AKI group (n = 23), the Mean ± SD CPB Time was 117 ± 10.96 minutes, while for the AKI group

(n = 8), it was 165 ± 9.03 minutes, with a P-value of <0.001, indicating statistical significance. Similarly, the Mean ± SD Cross Clamp Time was 75.96 ± 6.74 minutes for the No AKI Group And 97.75 ± 11.85 minutes for the AKI group, also with a P-value of <0.001, indicating statistical significance. Both variables showed statistically significant differences with p-values < 0.05.

Table 3. Comparison of body mass index (BMI) between two groups.

BMI	Respondents (N = 31)		
	Group A f (%) n_1 = 23	Group B f (%) n_2 = 8	P value
Male	11 (47.83)	4 (50)	0.618 [ns]
Female	12 (52.17)	4 (50)	

N =Total number of respondents; n_1 = Participants in Group A; n_2 = Participants in Group B; f = Frequency; ns = Not significant; SD = Standard Deviation; Data were presented as frequency and mean and ± SD; Statistical analysis was done by Chi square-test; P value ≤ 0.05 was considered as significant.

Table 4. Comparison of pre-operative risk factors between two groups.

Preoperative Risk Factors	Respondents (N = 31)		
	Group A f (%) n_1 = 23	Group B f (%) n_2 = 8	*P* value
Diabetes Mellitus	2 (9.69)	3(37.5)	0.093 [ns]
HTN	2 (8.70)	1 (12.5)	0.606 [ns]
Thyroid Dysfunction	0 (0)	2 (25)	0.060 [ns]
LVEF < 40	0 (0)	1 (12.5)	0.258 [ns]

N = Total number of respondents; n_1 = Participants in Group A; n_2 = Participants in Group B; f = Frequency; ns = Not significant; SD = Standard Deviation; Data were presented as frequency and mean and ±SD; Statistical analysis was done by Chi square-test; P value ≤ 0.05 was considered as significant.

Table 5. Comparison of per-operative risk factors between two groups.

Per-operative Risk Factors	Respondents (N = 3 1)		
	Group A n_1 = 23	Group B n_2 = 8	P value
CPB Times (minutes)	117 ± 10.96	165 ± 9.03	<0.001 [s]
Cross Clamp time (minutes)	75.96 ± 6.74	97.75 ± 11.85	<0.001 [s]

N = Total number of respondents; n_1 = Participants in Group A; n_2 = Participants in Group B; s = Significant; SD = Standard Deviation; Data were presented as mean and ±SD; Statistical analysis was done by independent t-test.

Table 6 compares the mean ± SD values of serum creatinine and serum cystatin C in AKI patients at different time points: pre-operative, 2 hours after CPB, 24 hours after CPB, and 48 hours after CPB. The mean ± SD of serum creatinine was 0.98 ± 0.20 pre-operatively, 1.09 ± 0.22 at 2 hours post-CPB, 1.15 ± 0.19 at 24 hours post-CPB, and 2.09 ± 0.35 at 48 hours post-CPB, with no statistically significant differences ($P > 0.05$). Similarly, the mean ± SD of serum cystatin C was 0.95 ± 0.20 pre-operatively, 0.90 ± 0.25 at 2 hours post-CPB, 1.39 ± 0.35 at 24 hours post-CPB, and 2.00 ± 0.63 at 48 hours post-CPB, also showing no statistically significant differences ($P > 0.05$).

Table 6. Comparison of plasma cystatin C concentrations at various perioperative time points between two groups.

Perioperative plasma cystatin C	Respondents (N = 31)		
	Group A $n_1 = 23$	Group B $n_2 = 8$	*P* value
Pre-operative	0.75 ± 0.12	0.90 ± 0.14	0.009[s]
2 hours after CPB	0.64 ± 0.11	0.81 ± 0.15	0.003[s]
24 hours after CPB	0.71 ± 0.10	1.39 ± 0.24	<0.0001[s]
48 hours after CPB	0.79 ± 0.14	2.00 ± 0.63	<0.0001[s]

N = Total number of respondents; n_1 = Participants in Group A; n_2 = Participants in Group B; s = significant; SD = Standard Deviation; Data were presented as mean and ±SD; Statistical analysis was performed with the unpaired t-test; P value ≤ 0.05was considered as significant; CPB = Cardiopulmonary bypass.

Table 7 presents the plasma cystatin C concentrations at various perioperative time points for patients with and without AKI. In the No AKI group, the mean ± SD concentrations were 0.75 ± 0.12 pre-operatively, 0.64 ± 0.11 at 2 hours post-CPB, 0.71 ± 0.10 at 24 hours post-CPB, and 0.79 ± 0.14 at 48 hours post-CPB. In the AKI group, the concentrations were 0.90 ± 0.14 pre-operatively, 0.81 ± 0.15 at 2 hours post-CPB, 1.39 ± 0.24 at 24 hours post-CPB, and 2.00 ± 0.63 at 48 hours post-CPB. The P-values for pre-operative, 2 hours post-CPB, 24 hours post-CPB, and 48 hours post-CPB were 0.009, 0.003, 0.0001, and <0.0001, respectively, indicating that plasma cystatin C concentrations were significantly associated with the AKI status of the participants.

Table 8 presents the findings of Receiver Operating Characteristic (ROC) analysis for predicting acute kidney injury (AKI) after on-pump cardiac surgery using serum creatinine and serum cystatin C. Serum cystatin C demonstrated a higher Area Under the Curve (AUC) of 0.864 compared to serum creatinine's AUC of 0.761. This indicates that serum cystatin C has better discriminatory ability in identifying AKI. Furthermore, serum cystatin C exhibited higher sensitivity (87.5%) but lower specificity (23%) compared to serum creatinine (sensitivity: 75%, specificity: 40%). Both serum creatinine and serum cystatin C showed statistically significant predictive ability for AKI (p-values of 0.03 and

0.002, respectively). Figure 2 illustrates the Receiver Operating Characteristic (ROC) curve, depicting the diagnostic performance of serum creatinine and serum cystatin C concentrations measured 2 hours after cardiopulmonary bypass for identifying acute kidney injury.

Table 7. Comparison of the ICU and Hospital stays between two groups (days) (n = 31).

ICU & Hospital Stays in days	Respondents (N = 31)		
	Group A $n_1 = 23$	Group B $n_2 = 8$	P value
Mean ± SD of ICU Stays (Minimum & Maximum)	2.52 ± 0.51 (2 & 3)	4.6 ± 0.74 (2 & 3)	<0.001 ^{s}
Mean ± SD of Hospital Stays (Minimum & Maximum)	6.56 ± 0.99 (5 & 9)	10.5 ± 1.51 (9 & 13)	<0.001 ^{s}

ICU = Intensive care unit; N =Total number of respondents; n_1 = Participants in Group A; n_2 = Participants in Group B; s = Significant; SD = Standard Deviation; Data were presented as mean ±SD; Statistical analysis was done by independent t-test; P value & < 0.05 was considered as significant.

Table 8. Area under the Curve (AUC) of Receiver Operating characteristic (ROC) curve of serum cystatin C for the prediction of AKI after on-pump cardiac surgery.

Test Result Variable(s)	Area	Cut-off value	Sensitivity	Specificity	P value	95% Confidence Interval	
						Lower Bound	Upper Bound
Serum Creatinine	0.761	0.86	75	40	0.03^s	0.556	0.965
Serum Cystatin C	0.864	0.55	87.5	23	0.002^s	0.676	1.000

ICU = Intensive Care Unit; Null hypothesis: true area = 0.5; <0.05 was considered not to be significant; s = Significant.

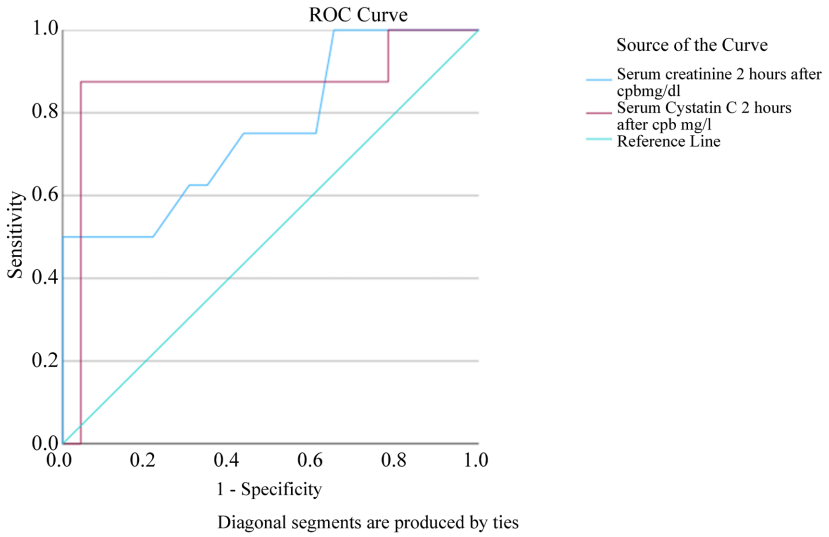

Figure 2. Receiver operating characteristic curve depicting the performance characteristics of serum creatinine and serum cystatin C concentration measured 2 hours after cardiopulmonary bypass in the diagnosis of acute kidney injury.

4. Discussion

The study aimed to elucidate the role of serum Cystatin C in the early detection of Acute Kidney Injury (AKI) among patients undergoing on-pump cardiac surgery. Conducted at the Department of Cardiac Surgery, BSMMU, Shahbag, Dhaka, the research enrolled a total of 31 patients who met the predefined inclusion and exclusion criteria. Patients were stratified into two groups based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria: No AKI and AKI. Among the cohort, 23 patients (74.2%) belonged to the No AKI group, while 8 patients (25.8%) were classified in the AKI group. This distribution was consistent with similar investigations conducted by Wald *et al.* [4] and Krawczeski *et al.* [9], which reported AKI incidence rates of 31.3% and 32%, respectively, in cardiac surgery patients. Analysis of demographic attributes revealed no statistically significant difference in age distribution between the two groups, aligning with the findings of previous studies by Wald *et al.* [4] and Yong Zheng *et al.* [7]. Similarly, gender distribution demonstrated no significant discrepancy, in accordance with observations made by Rosner *et al.* [10] and Krawczeski *et al.* [9]. Furthermore, Body Mass Index (BMI) distribution did not show a significant association with AKI, consistent with the conclusions drawn by Hošková *et al.* [11]. Exploration of risk factors such as diabetes mellitus, hypertension, and thyroid abnormalities did not reveal any significant differences between the two groups, in line with the findings of Wald *et al.* [4] and Didier *et al.* [12]. However, prolonged durations of cardiopulmonary bypass (CPB) and cross-clamp times were noted in the AKI group, echoing the findings of studies conducted by Krawczeski *et al.* [9] and Karim *et al.* (2012) [13].

Furthermore, an analysis of serum creatinine and cystatin C levels revealed a significant increase in cystatin C within 24 hours post-CPB. This finding aligns with observations made by Wald *et al.* [4] and Momeni *et al.* [14].

In our study, the study population according to Plasma cystatin C concentrations at various perioperative time points between two groups were analyzed and found statistically significant. The P value of Pre-operative, 2 Hours after CPB, 24 Hours after CPB and 48 Hours after CPB were 0.009 s, 0.003 s, <0.0001 s and <0.0001 s respectively. In previous study conducted by Wald *et al.* [4] demonstrated plasma cystatin C was higher at all times among the patients who developed AKI compared with those who did not (P value < 0.0001).

Patients who developed AKI experienced longer Intensive Care Unit (ICU) and hospital stays, corroborating findings reported by Wald *et al.* [4] and Krawczeski *et al.* [9]. Receiver Operating Characteristic (ROC) Curve analysis unveiled serum cystatin C as a more sensitive predictor of AKI compared to serum creatinine, aligning with the conclusions drawn by Wald *et al.* [4]. While serum creatinine remains a widely utilized biomarker for AKI diagnosis, its limitations in early detection underscore the potential utility of serum cystatin C, which remains unaffected by factors such as age and muscle mass. The early identification of AKI could potentially mitigate its adverse impact on patient outcomes by facilitating timely intervention.

5. Conclusion

In conclusion, our study underscores the significance of serum cystatin C as an early diagnostic marker for acute kidney injury (AKI) among patients undergoing on-pump cardiac surgery, demonstrating its superiority over serum creatinine. The findings suggest that serum cystatin C has the potential to detect AKI several hours earlier than serum creatinine, offering a valuable window for timely intervention. Utilizing serum cystatin C as a diagnostic tool may contribute to reducing morbidity, mortality, and healthcare costs associated with AKI in this patient population. This underscores the importance of integrating serum cystatin C measurement into routine clinical practice for the early detection and management of AKI following cardiac surgery.

Limitation of the Study

Limitations of the study include its reliance on a small sample size, particularly notable due to the constraints imposed by the COVID-19 pandemic. Additionally, the study was conducted at a single center, potentially limiting the generalizability of the findings. Moreover, no follow-up was conducted post-discharge, which could have provided valuable insights into the longer-term outcomes of the patients. Furthermore, the definition of AKI based solely on elevations in Serum Creatinine may present limitations, as this marker can lack accuracy, leading to potential false positives or false negatives, thus affecting the precision of the diagnosis.

Recommendation of the Study

Recommendations stemming from the study include the routine post-operative assessment of serum cystatin C, which could significantly aid in the early detection of acute kidney injury and subsequently enhance patient management protocols. Furthermore, there is a pressing need for a comprehensive prospective study with a larger sample size, ideally conducted across multiple centers, to validate and further elucidate the findings of this investigation.

Acknowledgements

The authors extend their heartfelt gratitude to the patients whose participation made this study possible, recognizing their invaluable time and cooperation. Special appreciation is also extended to the dedicated teaching staff, colleagues, and medical personnel whose unwavering support and assistance significantly contributed to the success of this research endeavor.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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