

ORIGINAL ARTICLE

Correlation of C Reactive protein with acute kidney injury after coronary artery bypass grafting.

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ABSTRACT... Objective: To determine the correlation of preoperative CRP level with cardiac surgery associated AKI, morbidity and mortality after CABG Surgery. **Study Design:** Prospective Comparative study. **Setting:** Department of Cardiac Surgery, Faisalabad Institute of Cardiology, Faisalabad. **Period:** January 2023 to December 2023. **Methods:** After approval from the Ethical Review Committee, informed consent from patients was taken and they were included in this study. Patients were interviewed, explained and counseled about the procedure of the study. Routine Investigations including CRP levels were performed. Patients were divided into 2 groups as Group A (with Raised CRP (More than 5.0mg/L) and Group B (with Normal CRP (Less than 5.0mg/L) and CABG was performed. Post-operative outcomes in term of serum creatinine levels, length of ICU and hospital stay and mortality in early post-operative period was recorded and compared between the two groups. **Results:** Mean age was determined as 56.01 ± 7.07 years in Group A and 54.66 ± 7.3 ($p < 0.001$) in Group B. Mean CRP of the population at the time of admission was determined as 6.8 ± 0.97 mg/L in Group A and 2.70 ± 0.97 ($p < 0.001$) in Group B. Mean of baseline serum creatinine was determined as 1.107 ± 0.04 in Group A as compared to 1.199 ± 0.03 in Group B ($p < 0.001$). Mean of peak serum creatinine were observed which were same as the values on the first day i.e., 1.39 ± 0.028 in Group A and 1.31 ± 0.030 in Group B. A significant correlation ($p < 0.001$) was found in higher CRP levels and higher incidence of AKI in Group A and AKI was lower in case of group B. Chi-square test was used to determine that the incidence of AKI was greater in males in both groups as compared to females. Moreover, patients were distributed based on the follow-up treatments and outcomes, they received, and it was observed that majority of patients suffered AKI followed by medication, dialysis and death respectively in case of both Groups A and B. **Conclusion:** Conclusively, it can be stated that CRP levels at presentation are a direct predictor of acute kidney injury in the Pakistani local population especially in case of patients undergoing CABG. This is supported by evidence of increased serum creatinine levels with time, low urine output etc. in the patients with elevated CRP levels.

Key words: Acute Kidney Injury, Coronary Artery Bypass Surgery, C-reactive Protein, CRP, Serum Creatinine.

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INTRODUCTION

Following routine cardiac surgery, a frequent and potentially fatal complication known as acute kidney injury (AKI) can develop. Inflammation and renal ischemia are two potential causes of AKI.¹ During a patient's stay in the intensive care unit, it plays a key role in the development of morbidity and death. Patients who have undergone coronary artery bypass grafting have a 30% likelihood of having AKI.² Cardiopulmonary bypass (CPB) usage in CABG surgery has been demonstrated to dramatically increase the risk of postoperative acute kidney injury when compared to the off-pump method. The complex mechanisms that take place during cardiopulmonary bypass usually result in

acute kidney injury (AKI).³ Mechanisms for renal hypoperfusion include hemodilution, hypothermia, and low-flow, low-pressure, non-pulsatile perfusion. Another potential mechanism is an inflammatory reaction, which may maintain afferent arteriolar constriction. Vasopressors, both endogenous and exogenous, both increase afferent arteriolar resistance, which lowers glomerular filtration rate (GFR).⁴ According to studies, inflammation has a significant role in both the onset and development of AKI.⁵ Postoperative acute renal injury leads to higher medical costs, chronic kidney disease and dialysis dependence in addition to lowering long-term survival rates.⁶

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Acute kidney injury (AKI) following cardiac surgery that necessitates renal replacement therapy (RRT), is linked to a mortality incidence up to 25%.⁷ Finding a precise biochemical marker that can predict with accuracy the probability of AKI following surgery is crucial.⁸

According to multiple research studies, acute kidney injury (AKI) has a higher death rate after correcting for baseline factors.^{9,10,11} These results have consistently been verified. But as of yet, the mechanisms for this connection are not well understood. However, even after adjusting for baseline variables, patients with a kidney ailment had a higher death risk than those with normal renal function.^{12,13} Even those with normal renal function who do not have chronic kidney disease experience this.

The plasma biomarker of inflammation C-Reactive Protein, often known as CRP, is commonly regarded as one of the most important ones in clinical practice.¹⁴

Acute kidney injury is more likely to occur in patients with severe conditions who have elevated blood levels of inflammatory markers such as C-Reactive Protein (CRP), D-dimers, ferritin, procalcitonin (PCT), and interleukin-6 (IL-6).¹⁵ It is likely that the underlying cause of the severe renal tubular injury was a hyper-inflammatory response to some procedure or invasion.¹⁶ A thorough knowledge of the relationship between these elevated inflammatory markers and the danger of developing AKI in these individuals can be beneficial in avoiding AKI and may also enhance their general care. This is due to the fact that AKI is avoidable and that a thorough understanding of the relationship between these elevated inflammatory markers and the likelihood of developing AKI exists.

It is a characteristic acute pro-inflammatory process marker that may reliably foretell a wide range of illnesses, from acute infectious diseases to long-term morbidity or death.¹⁷ C-reactive protein, often known as CRP, is a useful marker of inflammatory activation since it is an acute phase reactant and its level can be determined using simple techniques.¹⁸ It contributes significantly to the onset

of atherosclerotic diseases, such as myocardial infarction and stroke.¹⁹ The secret to understanding CRP's predictive capabilities is its ability to represent acute inflammation in clinically important situations.²⁰ It was formerly believed that it just functioned as a marker of vascular inflammation, but current study has revealed that it also actively contributes to the formation of atherosclerosis.²¹ A CRP level between 0 and 5 mg/L is typically regarded as normal. The third postoperative day is often when C-reactive protein levels are at their peak after surgery however, this varies widely from patient to patient.²² Additionally, in post-operative patients who have had percutaneous coronary intervention (PCI) as well as other types of operations, the function of CRP has been researched as a possible predictor of acute kidney damage (AKI).⁹

This study will evaluate if CRP is a reliable indicator of CABG-related AKI in our population. The study's main goal is to achieve that due to the lack of any current pertinent local research. Despite this, there is now a sizable amount of global study and recently uncovered evidence that may be accessed. This research will contribute to the identification of a relationship between AKI and CRP as well as the development of recommendations for the prevention and management of AKI in our patients.

METHODS

It was a prospective comparative study conducted in cardiac surgery department, Faisalabad Institute of Cardiology Faisalabad which is a well equipped tertiary care cardiac centre. After approval from ethical review committee (Letter No. 24/DME/FIC/FSD dated 23/12/2020) and informed written consent, patients who underwent CABG surgery from January 2023 to December 2023 were included in the study using purposive sampling technique. The sample size of 190 patients (95 in each group) was calculated at 5% level of significance with 80% power of study and by taking expected percentage of AKI 25.6% in patients with normal CRP and 42.7% in patients with raised CRP. Both male and female, diabetic & non-diabetic patients between 30 to 70 years of age undergoing isolated elective CABG were included. Patients having elevated liver enzymes, history of liver or muscle disease, anemia and inflammatory diseases using

steroids, left ventricular ejection fraction less than 30%, cardiopulmonary bypass time more than 140 minutes and any intra-operative complication were excluded from the study.

Patients were interviewed, explained and counseled about the procedure of the study. They were admitted in cardiac surgery ward. Routine Investigations including CRP level were performed.

The patients were divided into two groups

Group A: With Raised CRP (More than 5.0mg/L)

Group B: With Normal CRP (Less than 5.0mg/L)

Surgery was performed utilizing standard techniques of median sternotomy, arterial and venous grafts harvesting, pericardiotomy, heparinization, cannulation, cardiopulmonary bypass, hypothermia, aortic cross clamping (20 min to 140 min) and antegrade cold blood cardioplegia. Required number of grafts were anastomosed, rewarming, removal of cross clamp, restoration of normal sinus rhythm, weaning off CPB, protamine administration, placements of pacing wires and drains, hemostasis and chest closure. Patients were shifted to ICU.

Postoperative outcomes in term of AKI, length of ICU stay (Hours), Length of hospital stay (Days), and mortality in early postoperative period were recorded.

RESULTS

190 patients were recruited for this study and were divided into two groups based on whether the CRP values were higher (greater than 5.0mg/dl) in Group A or normal/lower range (less than 5 mg/dl) in Group B. Both groups contained 95 patients thus a total of 190 patients. Several statistical studies of the research population are required to better comprehend the patient population in terms of age, gender, baseline serum creatinine values and postoperative outcomes.

Among the recruited patients, mean age was determined as 56.01 ± 7.07 years in Group A and 54.66 ± 7.3 ($p < 0.001$) in Group B. The population is further divided into multiple age groups as shown in Table-I. According to Table-I, 43.6% of the population was between 50-59 years of age

followed by 26.3% in 60-69 years of age group. Afterwards, patients were also grouped based on their gender distribution. 68.9% of the population was male while 31.1% were females. Mean values were then determined via one-sample t-test for the determination of quantitative variables. Mean CRP of the population at the time of admission was determined as 6.8 ± 0.97 mg/L in Group A and 2.78 ± 0.97 ($p < 0.001$) in Group B as shown in Table-II. Mean of Baseline SCr was determined as 1.107 ± 0.04 in Group A as compared to 1.19 ± 0.03 in Group B ($p < 0.001$) as shown in Table-II. Post op creatinine values on the first day of surgery were determined as 1.39 ± 0.028 in Group A and 1.31 ± 0.030 in Group B as shown in Table-III. Table-III also shows the mean values at the seventh day of surgery in both groups. Group A had a 1.32 ± 0.01 mean post-op creatinine value as compared to 1.27 ± 0.025 in Group B ($p < 0.001$). Afterwards the mean of peak serum creatinine was observed which were same as the values on the first day i.e. 1.39 ± 0.028 in Group A and 1.31 ± 0.030 in Group B as shown in Table-IV. Urine output was noted on ml/kg/hr and the mean of urine output in Group A was 0.470 ± 0.05 in Group A and 0.81 ± 0.38 in Group B as shown in Table-IV. The mean hospital stay in days was observed as 6.1 ± 1.90 in case of Group A and 5.2 ± 2.18 in case of Group B, Table-V. The mean ICU stay in days was 3.4 ± 1.24 in case of Group A and 3.9 ± 1.34 in case of Group B, Table-VI. Post stratification results were done via Chi-square test to determine the correlation between qualitative variables. Firstly, the correlation was calculated between AKI and CRP at the time of admission. As shown in Table-VII, a significant correlation ($p < 0.001$) was found in higher CRP levels and higher incidence of AKI in Group A and AKI was lower in case of group B.

The incidence of AKI was greater in males in both groups as compared to females, but the results were not statistically significant ($p > 0.05$). Moreover, patients were distributed based on the follow-up treatments and outcomes, they received, and it was observed that majority of patients suffered AKI followed by medication, dialysis and death respectively in case of both Groups A and B, Table-VIII.

TABLE-I

Age groups distribution of patients

Age Groups

		Frequency	Percent
Valid	30-39	3	1.6
	40-49	22	11.6
	50-59	83	43.6
	60-69	50	26.3
	70+	32	16.8
	Total	190	100.0

TABLE-II

One-sample t-test to determine the mean of Pre-operative CRP and baseline CRP levels in Group A and B

Case Type		N	Mean	Std. Deviation	P-Value
Group A (CRP >5.0 mg/L)	Pre-Operative CRP	95	6.8558	0.97049	<0.001
Group B (CRP<5.0 mg/L)		95	2.7811	0.97482	
Group A (CRP >5.0 mg/L)	Baseline SCr	95	1.1075	0.04342	<0.001
Group B (CRP<5.0 mg/L)		95	1.1990	0.03252	

TABLE-III

Determination of mean of Post op creatinine values on 1st and 7th days of surgery in Group A and B

Case Type		N	Mean	Std. Deviation	P-Value
Group A (CRP>5.0 mg/L)	Post Op Creatinine (1st Day)	95	1.3961	0.02811	<0.001
Group B (CRP<5.0 mg/L)		95	1.3173	0.03012	
Group A (CRP >5.0 mg/L)	Post Op Creatinine (7th Day)	95	1.3253	0.01050	<0.001
Group B (CRP<5.0 mg/L)		95	1.2702	0.02564	

TABLE-IV

Determination of mean values of Peak serum creatinine and urine output in Group A and B

Case Type		N	Mean	Std. Deviation	P-Value
Group A (CRP >5.0 mg/L)	Peak Serum Creatinine (mg/dl)	95	1.3961	.02811	<0.001
Group B (CRP<5.0 mg/L)		95	1.3173	.03012	
Group A (CRP >5.0 mg/L)	Urine Output (ml/kg/hr)	95	0.4706	0.05634	<0.001
Group B (CRP<5.0 mg/L)		95	0.8160	0.38080	

TABLE-V

One-sample t-test to determine the mean of hospital stay (days) in Group A and B

Case Type		N	Mean	Std. Deviation	P-Value
Group A (CRP >5.0 mg/L)	Hospital Stay (days)	95	6.1	1.90332	<0.001
Group B (CRP<5.0 mg/L)	Hospital Stay (days)	95	5.2	2.18249	

TABLE-VI

Mean of ICU stay in days in Group A and B

Case Type		N	Mean	Std. Deviation	P-Value
Group A (CRP >5.0 mg/L)	ICU Stay (days)	95	3.457	1.24609	<0.001
Group B (CRP<5.0 mg/L)	ICU Stay (days)	95	3.963	1.34172	

TABLE-VII

Chi-square test to determine the correlation between Acute Kidney Injury and Group A and B (Case Type)

		Acute Kidney Injury		Total	P-Value
		Yes	No		
Case Type	Group A (CRP >5.0 mg/L)	46	49	95	<0.001
	Group B (CRP <5.0 mg/L)	15	80	95	<0.001
Total		61	129	190	

TABLE-VIII

Distribution of AKI patients in terms of follow-up treatments

		AKI	Dialysis	Medication	Death
Case Type	Group A (CRP >5.0 mg/L)	46	6	37	3
	Group B (CRP <5.0 mg/L)	15	4	10	1
Total		61	9	51	4

DISCUSSION

In this study, we recruited 190 patients who presented for Coronary Acute Bypass Grafting (CABG) and divided them into 2 groups based on their CRP values. The main post operative outcome (development of AKI) was to be correlated with the CRP values observed at the time of admission. After receiving their informed consent to participate, participants' information was gathered in compliance with ethical norms. Patients provided their informed consent for the collecting of their data, but only the researchers involved in the study were given access to either their names or the data. After getting clearance from the Ethical Committee, the department of cardiac surgery at the Faisalabad Institute of Cardiology (FIC) in Faisalabad granted us access to every research subject.

The mean age of the patients was determined as 56.01 ± 7.07 years in Group A and 54.66 ± 7.3 ($p < 0.001$) in Group B. A further distribution of patients in age groups showed that majority of the patients lied in the 50-59 and 60-69 years of age groups. This particular distribution is in line with other studies of Pakistan which shows that the majority of the patients undergoing cardiac issues are in their fifties and sixties.²³ A gender wise distribution showed that the patients presenting with CABG were mostly men as compared to women and this trend is also seen in other studies of Pakistan due to social factor²⁴, prevalence of increased smoking in men as compared to women²⁵ etc. These social factors put men at more risk of cardiac issues as

compared to women in Pakistan.^{26,27,28}

After demographic analyses of the population, multiple factors at presentation were noted and their mean values were computed in both groups. Since the groups were made on the basis of pre-operative CRP values, therefore the Group A had a mean of 6.8 ± 0.97 whereas Group B had a mean of 2.78 ± 0.97 . Elevated CRP has been linked with renal function disorders in multiple studies.^{18,29} In our study however, there was not a marked difference in serum Creatinine levels at presentation between patients with elevated CRP and non-elevated. According to a study¹⁸, there is direct increase in serum Creatinine levels in patients presenting with elevated CRP. In their study, they developed mouse models with elevated CRP levels to understand the effect of increased CRP and serum Creatinine and the models with increased CRP levels were more prone to developing renal injury within 24 hours as compared to normal CRP levels.¹⁸

After the procedure, Creatinine values were observed on the 1st and 7th day of surgery. The increase in Creatinine levels were observed as the mean in Group A was 1.396 ± 0.28 as compared to 1.317 ± 0.030 ($p < 0.001$) in Group B. This difference in post op Creatinine indicates renal complexities arising in higher CRP patients. The difference was further increased on the 7th day when the mean serum Creatinine value was 1.325 ± 0.010 in Group A as compared to 1.27 ± 0.02 in Group B ($p < 0.001$). This increasing Creatinine value in Group

A can be correlated with increased CRP levels as has been shown in previous studies^{30,31}, therefore indicating increased risk of renal complexities leading to AKI.^{30,18} This also indicated that serum creatinine increased over time since the peak serum Creatinine values were the same as the values on the seventh day of procedure.

Increased serum creatinine levels are associated with lower urine outputs and increased chances of Acute Kidney Injury.^{32,33} In order to assess this relationship in our study participants, the urine outputs in ml/kg/hr were noted. It was observed that the urine output was low in case of Group-A patients as compared to Group-B. This decrease in urine output in high serum Creatinine level patients is consistent with previous observations.^{32,33} and also signals an increased risk of acute kidney injury in Group A patients. The increased complications due to renal injury possibilities also led to an increased hospital and ICU stay of the patients. The mean of hospital stay in days was observed as 6.1 ± 1.90 in case of Group A and 5.2 ± 2.18 in case of Group B and mean of ICU stay in days was 3.4 ± 1.24 in case of Group A and 3.9 ± 1.34 in case of Group B.

The incidence of AKI was greater in males in both groups as compared to females, but the results were not statistically significant ($p > 0.05$). Moreover, patients were distributed based on the follow-up treatments and outcomes, they received, and it was observed that majority of patients suffered AKI followed by medication, dialysis and death respectively in case of both Groups A and B.

These findings are direct evidence of already reported results which show that increased CRP is linked with increased AKI incidences especially in patients undergoing CABG¹⁷ in the local population of Pakistan. Moreover, it has been proposed that CRP promotes AKI incidence by the impairment of G1/S-dependent tubular epithelium cell regeneration.¹⁸ This direct relationship has also been used to establish CRP as a predictive biomarker for the occurrence of Acute Kidney Injury in multiple studies.^{9,17}

CONCLUSION

CRP levels at presentation are a direct predictor of

acute kidney injury in the Pakistani local population especially in case of patients undergoing CABG. This is supported by evidence of increased serum creatinine levels with time, low urine output etc. in the patients with elevated CRP levels. These results reinforce previous research indicating that CRP plays a role in AKI development, possibly by impairing renal recovery mechanisms. Therefore, pre-operative CRP levels may serve as a useful predictive biomarker for AKI risk stratification in CABG patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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