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Research Article

LONG TERM RISK OF CARDIOVASCULAR EVENTS AFTER ACUTE KIDNEY INJURY (AKI)

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Here we evaluate the association of AKI with a higher risk of cardiovascular outcomes on follow up of 1 year

A B S T R A C T

Background- AKI leads to elevation in inflammatory cytokines, dysregulation of mineral metabolism, endothelial dysfunction which leads to adverse effects on the cardiovascular system such as structural cardiac damage, cardiac inflammation, cellular apoptosis and necrosis. It can thus predispose a patient to a higher risk of cardiovascular events in the long term. Here we evaluate the association of AKI with a higher risk of cardiovascular outcomes on follow up of 1 year .

Materials And Methods- This retrospective observational study was performed in Department of Medicine at SRMSIMS, Bareilly for duration of 12 months (1st august 2018 to 1st august 2019). A total of 218 patients out of the total patients of AKI who were admitted in the Department of Medicine and Nephrology within the study period were taken and followed up for a year. 72 patients out of 218 had cardiovascular outcomes, were taken in to this study. Patients who had confirmed consent and were fit to the inclusion criteria were recruited for this study.

Results- The present study revealed that the majority of the patients with cardiovascular outcomes were above the age of 50 and had presented in stage 2 and 3 of AKI earlier. Many of these patients had associated co morbidities, were on medications and had various risk factors which could predispose them to the development of cardiovascular related events. It was observed that CHF occurred in 31 out of the 218 patients taken into account; ischemic heart disease occurred in 19 patients, stroke occurred in 8 patients, while 2 of them had progressed to chronic kidney disease. 10 patients had developed atrial fibrillation and 2 of the patients had died.

Conclusion- AKI induces structural cardiac damage, cardiac inflammation and cellular apoptosis and necrosis. Other possible cellular mechanisms of cardiac injury AKI include local inflammation, cellular energy regulation through altered mitochondrial function, fibrosis and immune responses.

In conclusion, an episode of AKI was independently associated with a higher risk of cardiovascular events on follow up.

INTRODUCTION

Acute kidney injury leads to elevation in inflammatory cytokines, dysregulation of mineral metabolism, endothelial dysfunction which leads to adverse effects on the cardiovascular mechanisms thus becoming a leading cause of morbidity and mortality. It is associated with an increased risk of end stage renal disease and also has various adverse effects on the other organs .There are different interactions between the cardiac and kidney diseases that have been hypothesized . Various studies have been conducted to decipher the role of AKI and various cardiovascular outcomes.

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AIMS AND OBJECTIVES

1. To evaluate the association of AKI with a higher risk of cardiovascular outcomes on follow up.
2. To analyze the risk factors and the associated major cardiovascular outcomes

Study Setting

This study was conducted in the Department of Medicine, Sri Ram Murti Medical Institute of Medical Sciences, Bareilly

Period of Study

The period of study was from 1st August 2018 to 1st August 2019, for a time period of 12 months.

Sample Size

A total of 218 patients out of the total patients of AKI who were admitted in the Department of Medicine and Nephrology within the study period were taken and followed up for a year. 72 patients out of 218 had cardiovascular outcomes, were taken in to this study. They were taken randomly and were the patients who fulfilled the inclusion and exclusion criteria.

Study Design

Retrospective observational study.

Methodology

The patients of Acute Kidney Injury (AKI) were diagnosed using the KDIGO criteria:

1. Increase in Sr. Creatinine by 0.3mg/dl or more within 48 hours or
2. Increase in Sr. Creatinine to 1.5 times baseline or more within the last 7 days or
3. Urine output less than 0.5ml/kg/hour for 6 hours.

Complete history and physical examination was done in all the patients and all the necessary investigations were done. A written and informed consent was obtained from these patients. Follow up of the patients was done after a year with censoring due to disenrollment , end of follow up .The primary outcome was composite of heart failure , acute coronary syndromes , cerebro vascular accident , chronic kidney disease , atrial fibrillation , death .The hospitalization and treatments were ascertained from the hospital records and follow up records .

Inclusion Criteria

1. The patients with AKI (as per the KDIGO criteria)
2. Patients who were willing.
3. Age > 18 years.

Exclusion Criteria

1. Patients with any pre-existing Kidney diseases.
2. Patients who were unwilling.
3. Patients who had a known prior history of cardiovascular events such as heart failure, acute coronary syndromes, cerebro vascular accident, chronic kidney disease, atrial fibrillation before the onset of AKI.

Statistical Analysis

The data collected was analyzed in terms of descriptive statistics with the help of SPSS version 17 software .Continuous variables were presented as mean ± SD and categorical variables were expressed as frequencies and percentages.

RESULTS AND OBSERVATIONS

Table 1

Aki patients followed up after 1 year	218(100%)
Aki patients followed up after 1 year with cardiovascular events	72(33%)

Patients with Cardiovascular Events on Follow Up

A total of 72 patients with cardiovascular outcomes , who had been previously diagnosed with AKI were analyzed between August 2018 and august 2019.

Table 2

	Males	Females	Total
18-49	6	11	17
50-59	13	7	20
60-69	8	9	17
>70	16	2	18
TOTAL	43	29	72

Age and Sex of the Study Group

Out of the total 72 patients, 43 were males and 29 were females. 17 patients fell in the age group of 18-49 years, 20 were in the age group of 50-59 years, 17 were in the age group of 60 – 69 years and 18 were above the age group of 70. It was observed that the majority of the patients with cardiovascular outcomes were above the age of 50.

Table 3

Staging of aki (kdigo)	Male patients	Female patients	Total
STAGE1	11	6	17
STAGE 2	13	15	28
STAGE 3	19	8	27

Kdigo Staging Opf Study Group

The patients were divided into three groups according to the stage of KDIGO classification of AKI. 17 patients fell in the stage 1 of KDIGO classification for AKI,28 patients fell in the stage 2 and 27 patients fell in the stage 3 .it was observed that the majority of the patients who had cardiovascular outcomes had presented in stage 2 and 3 of AKI earlier .

Table 4

Stages of aki	Previous comorbid conditions	Risk factors	Drug history	Outcome of renal function at previous discharge
STAGE 1	9	12	9	Normal
STAGE 2	14	17	7	Normal
STAGE 2	15	11	11	Normal

Comorbid Conditions and Risk Factors of Study Group

It was noticed that the patients had various co morbidities such as diabetes, hypertension and various risk factors such as alcohol, smoking, and dyslipidemia. Many of the patients were on drugs such as beta blockers, antihypertensive medication, antidiabetic medications, dyslipidemic drugs etc. They had been discharged in a normal condition with satisfactory investigations after the initial episode of AKI earlier.

Table 5

Previous co morbid conditions	HTN	DM	DYSLIPIDEMIA	Drug history	ANEMIA
18-49	7	4	8	8	5
50-59	5	7	6	7	9
60-69	8	7	7	5	7
>70	7	5	9	7	7

Drug History and Comorbid Conditions Of Study Group

The patients had various co morbid conditions such as diabetes, dyslipidemia, drug history and anemia which could

predispose the patient to develop cardiovascular events at an earlier pace.

Table 6

Cause of aki on 1st visit	Pre- renal	Renal	Post renal	Total
18-49	5	11	1	17
50-59	13	6	1	20
60-69	5	12	0	17
>70	15	3	0	18

Cause of Aki in Study Group

It was observed that the major cause of AKI had been renal and pre – renal causes for which the patients had been admitted earlier.

Table 7

Stages of aki	CHF	IHD	STROKE	CKD	AF	DEATH
STAGE 1	7	4	2	0	4	0
STAGE 2	11	8	4	0	5	0
STAGE 3	13	7	2	2	1	2
TOTAL	31	19	8	2	10	2

Cardiovascular Events on Follow Up

After taking into account various investigations and hospital records , it was observed that CHF occurred in 31 out of the 218 patients taken into account , ischemic heart disease occurred in 19 patients , stroke occurred in 8 patients , while 2 of them had progressed to chronic kidney disease . 10 patients had developed atrial fibrillation and 2 of the patients had died. It is note worthy that the majority of patients with cardiovascular events had initially been in stage 2/3 of AKI and majority of them being in the older age groups had multiple co morbidities initially.

DISCUSSION

Acute kidney injury is associated with an increased risk of chronic kidney disease and has adverse cardiovascular sequelae as seen in various studies.[1,2]

In our study, we observed that the majority of the patients with cardiovascular outcomes were above the age of 50 and had presented in stage 2 and 3 of AKI earlier. Many of these patients had associated co morbidities such as diabetes, hypertension and various risk factors such as alcohol, smoking, dyslipidemia and anemia which could predispose them to the development of cardiovascular related events. Many of the patients were on drugs such as beta blockers, antihypertensive medication, antidiabetic medications, and dyslipidemic drugs. It was observed that CHF occurred in 31 out of the 218 patients taken into account; ischemic heart disease occurred in 19 patients, stroke occurred in 8 patients, while 2 of them had progressed to chronic kidney disease. 10 patients had developed atrial fibrillation and 2 of the patients had died. These findings are in agreement with the various cardiovascular outcome mentions in other studies conducted throughout the world, although we did not take many other factors which needed to be considered.

In 2018, Go *et al*. observed the association between acute kidney injury and the risk of cardiovascular outcomes in a cohort of 430,159 hospitalized adults (39,153 had acute kidney injury). On follow after a year of discharge, he observed that the risk of hospitalization for heart failure was higher by 44% in the group with acute kidney injury as compared with the group that did not have AKI.[3]

A 2017 meta-analysis of 25 studies having 254,408 patients, including 55,150 with AKI, showed that it was associated with 86% increase in the risk of death from cardiovascular causes during a follow-up of 1.4 years. There was a 58% increase in risk of chronic heart failure during 2.9 years of follow up, a 40% increase in risk of acute myocardial infarction during 2.3 years of follow up and a 15% increase in the risk of stroke over a period of 2.7 years on follow up.[4]

Bansal *et al*. observed that among patients without any history of heart failure, the incidence of acute kidney injury was associated with a 23% increase in risk of incident heart failure. In another study that excluded patients with cardiovascular risk factors, the risk associated with AKI was 38%.[5]In a Canadian study involving 156,690 patients who survived a hospitalization associated with acute kidney injury, 1 in 5 patients had to be readmitted within 30 days, mostly with heart failure.[6]Another retrospective study from Taiwan between 1999 and 2008 which analyzed 4869 patients who recovered from dialysis requiring AKI, it was seen that on follow-up of 3.4 years, dialysis-requiring AKI was associated with a higher rate of a composite of "coronary events" defined as coronary bypass surgery, nonfatal myocardial infarction, and diagnostic coronary angiography[7]

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Chronic hypertension, sepsis and heart failure are risk factors for acute kidney injury and can hamper recovery from kidney injury.[i] Another study shows that patients with AKI are more vulnerable than patients without such injury to have hypertension. Hypertension thus appears likely to be associated with unfortunate cardiovascular and renal outcomes of AKI.[8]

Another Veterans Affairs-based analyzed AKI in the presence of myocardial infarction and observed that compared with those who had myocardial infarction alone, patients with AKI and myocardial infarction had a higher subsequent rate of composite cardiovascular end point.[9]In another study including 146,941 hospitalized adults, 31,245 of whom had AKI. At 365 days post discharge, AKI was seen to be independently associated with higher rates of the composite outcome of hospitalization for heart failure and other atherosclerotic events[10]

The most significant causes of cardiovascular damage are cardiac fibrosis, cardiac inflammation, neurohormonal activation, and electrolyte disturbances which increases plasma levels of certain circulating inflammatory mediators which have direct cardio depressant effects.

Many biomarkers that are up-regulated after AKI have been found to be associated with increase in cardiovascular events and it is further postulated that the underlying pathways of these biomarkers plays a significant role in the development of cardiovascular damage. Biomarkers such as neutrophil gelatinase–associated lipocalin (NGAL) were reported to be associated with development of cardiac fibrosis after mineralocorticoid-receptor activation.[11] Acute kidney injury also induces structural cardiac damage, cellular apoptosis and necrosis, with cardiac inflammation which develops within days after an event which is followed by the development of cardiac fibrosis in the long run.

Induction of renin–angiotensin–aldosterone system is characteristic of the cardiovascular response to AKI and it triggers a cardiac immune response leading to fibrosis.[12]The activation of the renal sympathetic nervous system also contributes to cardiac injury after AKI, increasing the chances of endothelial dysfunction, cardiac fibrosis and ventricular dysfunction.[13]Electrolyte disturbances such as Hyperkalemia and metabolic acidosis also contribute to cardiac manifestations after AKI.

SUMMARY

The cause for which AKI was more strongly associated with subsequent heart failure than atherosclerotic events is unclear , it can be postulated to be related to increase in inflammatory markers , endothelial dysfunction, and other mechanisms associated with AKI or possible drug therapy (use or dosage of renin-angiotensin system inhibitors or diuretics) after AKI.
AKI induces structural cardiac damage, cardiac inflammation and cellular apoptosis and necrosis. Other possible cellular mechanisms of cardiac injury AKI include local inflammation, cellular energy regulation through altered mitochondrial function, fibrosis and immune responses.

In conclusion, an episode of AKI was independently associated with a higher risk of cardiovascular events on follow up.

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