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# HOSPITAL ACQUIRED ACUTE KIDNEY INJURY-A STUDY ON ITS INCIDENCE, RISK FACTORS AND ATTRIBUTABLE MORTALITY

**Sreevyshali M S[1], Vaishnavi Venkat[1], Apoorva Dev*[2], Gorakati Pradeep Reddy[3], Hemant H R[4]**

[1]Pharm D Interns, Department of Pharmacy Practice, PES College of Pharmacy, Bengaluru, Karnataka, India-560 050.

[2]Assistant Professor, Department of Pharmacy Practice, PES College of Pharmacy, Bengaluru, Karnataka, India-560 050.

[3]Student, National University of Galway, Ireland.

[4]Senior Consultant and Academic Lead, Department of Critical Care Medicine, Narayana Hrudayalaya, Bengaluru, Karnataka, India.

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**Abstract:**

***Back ground:*** *Hospital-Acquired Acute Kidney Injury (HAAKI) is associated with higher length of stay, morbidity, mortality and cost among hospitalized patients. If managed adequately and in a timely manner, the majority of cases are preventable, treatable and often reversible with simple measures.*

***Objectives:*** *To establish the incidence, risk factors and attributable mortality associated with HAAKI in the patients admitted in MICU using the staging given by KDIGO guidelines.*

***Methodology:*** *A prospective observational study was carried out from October 2018 to March 2019. In a specially designed proforma patient details were collected. AKI was defined and staged according to KDIGO criteria. Results were analysed using logistic regression method, Chi-square test, Z-test, descriptive analysis. SPSS software was used for analysis.*

***Results:*** *Of a total of 200 admissions in MICU, 46 (23%) patients developed HAAKI. The mean time for AKI attack was found to be day 4. Common comorbid risk factors for HAAKI was found to be sepsis (73.9%), diabetes (54.3%), hypertension (52.2%), cardiovascular diseases (50%), pneumonia (34.8%), MODS (32.6%), hypotension (32.6%), CKD (30.4%), ARDS (30.4%). The most common risk factor for the development of HAAKI was administration of nephrotoxic medications (93.5%). Death occurred in 41.3% of the patients who had HAAKI as an attributable risk. MODS and ARDS were found to be the significant risk factor that leads to the mortality in HAAKI patients.*

***Conclusion:*** *Common risk factors of developing HAAKI were older age, male gender, sepsis, pneumonia, cardiovascular diseases, CKD. It is important to develop strategizing approaches for early detection and prevention of HAAKI.*

***Key words:*** *HAAKI (Hospital Acquired Acute Kidney Injury), KDIGO (Kidney Disease Improving Global Outcomes), attributable mortality, incidence.*

**Corresponding author:**

**Mrs. Apoorva Dev,**
Asst. Professor,
Department of Pharmacy Practice,
P.E.S. College of Pharmacy, Hanumanth nagar,
Bengaluru, Karnataka, INDIA - 560 050
E-Mail: apurva.dev22@gmail.com, Mob: +91 78995 33444

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## INTRODUCTION:

The term Acute Kidney Injury (AKI) has replaced old terms such as acute renal failure and acute renal insufficiency, which previously had been used to describe the same clinical condition. AKI is not just failure; it also incorporates the entire spectrum of the syndrome, from minor changes in renal function to the most severe form, where renal replacement therapy (RRT) may be required. A uniform definition for acute kidney injury has existed only since 2004, when the Acute Dialysis Quality Initiative (ADQI) proposed the Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE) criteria for AKI[1,2]. Since then two modifications of the RIFLE: Acute Kidney Injury Network (AKIN) 2007[3] and Kidney Disease: Improving Global Outcomes (KDIGO) 2012[1] has emerged. All of the three modern definitions are based on changes in serum or plasma creatinine (Cr) and urine output (UO).

Clinical symptoms may be scarce in the early stages of AKI. As the kidney injury progresses and affects the Glomerular Filtration Rate (GFR), Serum Creatinine (SCr) starts to rise. Oliguria or anuria may develop early, but sometimes the UO remains intact for quite long. Later in the course of AKI the severely diminished GFR manifests as electrolyte and acid-base disturbances, most often as elevated potassium and acidosis. The arising consensus suggests that AKI is a syndrome with several different predisposing factors and mechanisms of pathophysiology. A growing amount of data supports the idea that risk for AKI increases with a growing "burden of illness" whether chronic or acute[1]. In the ICU, AKI is usually multifactorial with both chronic conditions and acute events contributing to the development of kidney injury. Sepsis is the most common single underlying cause for AKI[4]. AKI has significant consequences. AKI is associated with increased morbidity, mortality and as a consequence, higher health care costs[5].

Recovery from AKI is not always, as previously thought, complete and many patients progress to develop chronic kidney disease (CKD), end-stage renal disease (ESRD), or worsening of pre-existing CKD later on in life. Treatment of AKI is needed to reduce the high morbidity and mortality and improve recovery of renal function[6]. The multifactorial etiology and the heterogeneous patient population coupled with the complicated clinical course of patients with AKI have created challenges in the search for effective pharmacological therapy. In some scenarios, such as surgery or administration of intravenous contrast, the onset of AKI can be predicted providing a window of opportunity for intervention and prevention. In the majority of cases, however, intervention takes place after the onset of AKI with the aim to shorten the course and enhance recovery of renal function[1].

Acute kidney injury (AKI) is a clinical syndrome generally defined by an abrupt reduction in kidney functions as evidenced by changes in laboratory values, serum creatinine (Scr), blood urea nitrogen (BUN), and urine output[7]. The first consensus criteria for AKI, RIFLE (Risk, Injury, Failure, Loss, and End-stage) were proposed in 2004[2] and supplemented with some changes by the Acute Kidney Injury Network resulting in the AKIN criteria a few years later[3]. In 2012 KDIGO (Kidney Disease: Improving Global Outcomes) released the latest guidelines for diagnosing and staging AKI[1]. With the consensus criteria, the term Acute Kidney Injury (AKI) replaced the formerly used Acute Renal Failure (ARF). Defining unified criteria was a vital improvement in the field of AKI, for over 35 different definitions for ARF were previously used making comparison of studies challenging[8].

SCr concentration and UO are the basis of all the three current criteria. In brief, the AKIN classification supplemented the RIFLE with a small change (≥26.5 μmol/l) in SCr as a criterion for stage 1 AKI, and narrowed the observation period for change in Cr to 48 h. Data from comparison of RIFLE and AKIN, showed, however, that the two classifications partly identified different patients[9]. The KDIGO criteria was then developed aiming to correct this by combining elements from both previous classifications. According to data the SCr criteria seem to identify more patients having AKI than the UO criteria[10].

**Objectives**

- To determine the incidence and contributing risk factors for HAAKI in MICU.
- To find out the incidence associated with each risk factor.
- To determine attributable mortality of HAAKI.

## MATERIALS AND METHODS:

**Study site:**

The study was conducted in MICU of a tertiary care hospital, Bengaluru, Karnataka, India.

**Study design:**

A prospective hospital based observational study.

**Study duration:**

The study was conducted for a period of 6 months.

**Study criteria:**

**Inclusive criteria**

- All adult patients (>18 years) of either gender who developed AKI based on KDIGO criteria of classification (using serum creatinine), 48 hours after hospitalization.
- AKI on CKD (1-3 stage).

**Exclusion criteria**

- Recent use of nephrotoxic drugs before hospitalization.
- Patients that have undergone renal transplant (excluded for first year).
- Nephrectomy.
- Patients admitted in the last 24 h.
- Pregnancy.
- Chronic dialysis.

**Source of data:**

The patient profile form was designed by us in accordance with the required information for the study. The form consisted of: patient information (including gender, age, weight in kg, height in cm, date of admission, date of discharge, Unique Health Identification number (UHID)), subjective and objective details of the patient (current medical diagnosis, medical and medication history , medication history, presence of any co-morbidities such as diabetes mellitus; chronic lung disease; immunosuppressed status; renal insufficiency etc., laboratory data, radiographic data like reports of the tests like ECHO, MRI,USG,CT etc., surgery details (previous and present)), treatment details, and other data related to HAAKI such as (information about the use of contrast media, ventilator support, polypharmacy, known case of PVD, presence of other diseases such as sepsis, cardio-vascular disease etc).

**Study procedure:**

A prospective observational study was conducted in the MICU of the study site by obtaining permissions from the hospital for a period of 6 months. A specially designed case collection proforma was used to collect the data. The collected data was analysed for the incidence, incidence of each risk factor that caused HAAKI and attributable mortality.

**Statistical study:**

The required data for the study was collected in a restructured proforma till completeness. Descriptive analysis was performed for data containing the continuous variables like age, length of stay, AKI attack day and represented in the form of mean and standard deviation. Categorical data were represented in percentage. Univariate and multivariate analysis was performed to analyze the significant association of factors and attributable mortality. All statistical analysis was performed using Statistical Package for social sciences (SPSS) software version IBM SPSS version 22.

## RESULTS:

During this 6 month study period, 200 individual patients were included in the study. Amidst them, 32 (69.6%) and 14 (30.4%) represented the male and female population respectively.

**Incidence:**

There were 46 (23%) patients who had an episode(s) of Hospital Acquired Acute Kidney Injury during their MICU stay.

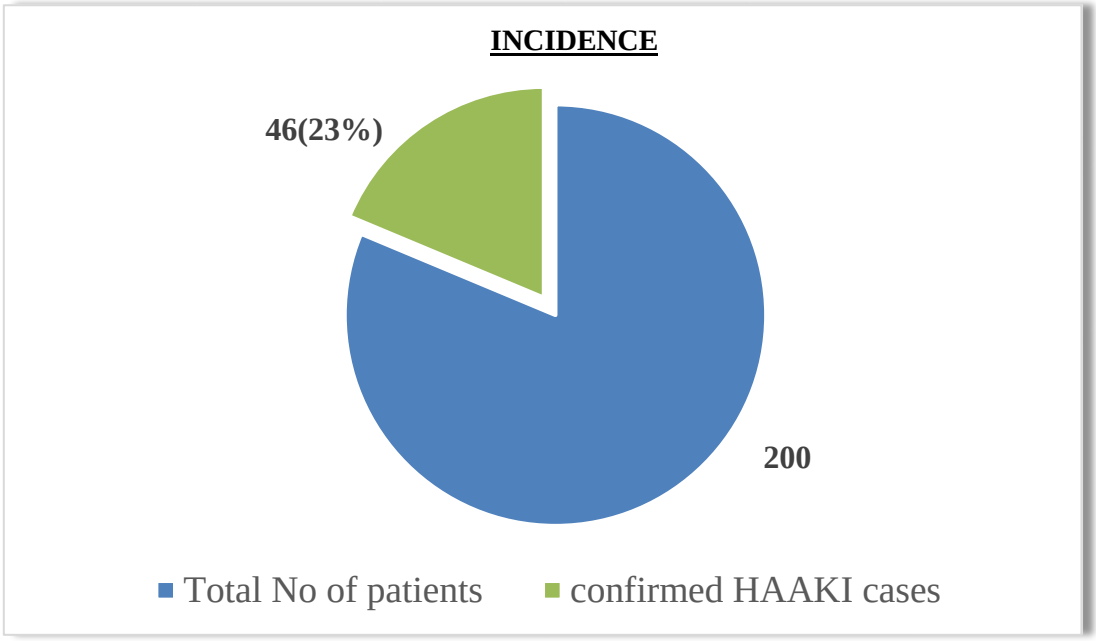


**Figure 1: Incidence of Hospital Acquired Acute Kidney Injury**

The mean age of the HAAKI victims was 58.15±15.8 years.

The staging was performed using KDIGO criteria. Among 46 confirmed HAAKI patients, 41 (89.1%) had stage 1 and 5 (10.86%) had stage 2 injury.

**Risk factors of Hospital Acquired Acute Kidney Injury:**

The risk factors that lead to the cause of one episode of HAAKI at least included nephrotoxic medications (93.5%), sepsis (73.9%), pneumonia (34.8%), and ARDS (30.4%) as principal factors. Major Comorbid diseases found in HAAKI victims were diabetes mellitus, hypertension, and cardiac disorders. AKI on CKD was observed among 14 (30.4%) patients, which led to further deterioration of kidney function in such patients. MODS (32.6%) and hypotension (32.6) induced from sepsis had significant association in causing Hospital acquired acute kidney injury (p value < 5).

**Table 1: Risk factors for the cause of HAAKI**

| S. No. | Risk factors | Frequency | Percentage (%) | Significance |
|---|---|---|---|---|
| 1 | Nephrotoxic medications | 43 | 93.5 | 0.772 |
| 2 | Sepsis | 34 | 73.9 | 0.976 |
| 3 | Diabetes mellitus | 25 | 54.3 | 0.845 |
| 4 | Hypertension | 24 | 52.2 | 0.081 |
| 5 | Cardiac disorders | 23 | 50.0 | 0.134 |
| 6 | Pneumonia | 16 | 34.8 | 0.133 |
| 7 | MODS | 15 | 32.6 | 0.001 |
| 8 | Hypotension | 15 | 32.6 | 0.073 |
| 9 | Neurological disorders | 14 | 30.4 | 0.246 |
| 10 | ARDS | 14 | 30.4 | 0.036 |
| 11 | AKI on CKD | 14 | 30.4 | 0.887 |
| 12 | Cancer | 6 | 13.0 | 0.189 |
| 13 | Gastric disorders | 5 | 10.9 | 0.950 |
| 14 | Contrast induced AKI | 5 | 10.9 | 0.950 |

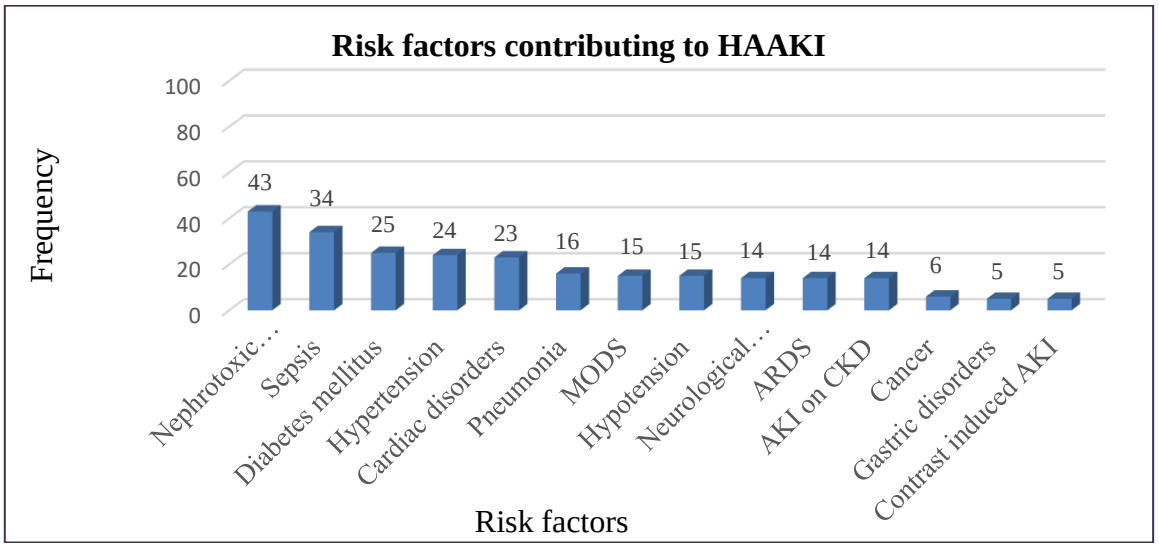


**Figure 2: Frequency of the risk factors of HAAKI**

**Nephrotoxic medications:**

Descriptive analysis is conducted to identify the nephrotoxic medications that drove to hospital-acquired acute kidney injury (HAAKI).It explicated that patients who received NSAIDs (58.69%) had an increased risk for HAAKI.

The progression was followed by medications like vasopressors (45.65%), statins (32.60%), polymixin-B (28.26%), colistin (19.56%), anti-viral (6.52%), mannitol (6.52%). Vancomycin and amphotericin-B which was administered in two patients (4.34%) who had an episode of HAAKI. Medications like aminoglycoside, taxol, heavy metals, vancomycin + piptaz and dextran were used least and accounted for 2.17% cause for HAAKI.

**Table 2: Frequency of nephrotoxic medications that caused HAAKI**

| S. No. | Drugs | Frequency | Percentage (%) |
|---|---|---|---|
| 1 | NSAIDs | 27 | 58.69 |
| 2 | Vasopressors | 21 | 45.65 |
| 3 | Statins | 15 | 32.60 |
| 4 | Polymixin-B | 13 | 28.26 |
| 5 | Colistin | 9 | 19.56 |
| 6 | Anti-viral | 3 | 6.52 |
| 7 | Mannitol | 3 | 6.52 |
| 8 | Vancomycin | 2 | 4.34 |
| 9 | Amphotericin-B | 2 | 4.34 |
| 10 | Aminoglycoside | 1 | 2.17 |
| 11 | Taxol | 1 | 2.17 |
| 12 | Heavy Metals | 1 | 2.17 |
| 13 | Vancomycin + Piptaz | 1 | 2.17 |
| 14 | Dextran | 1 | 2.17 |

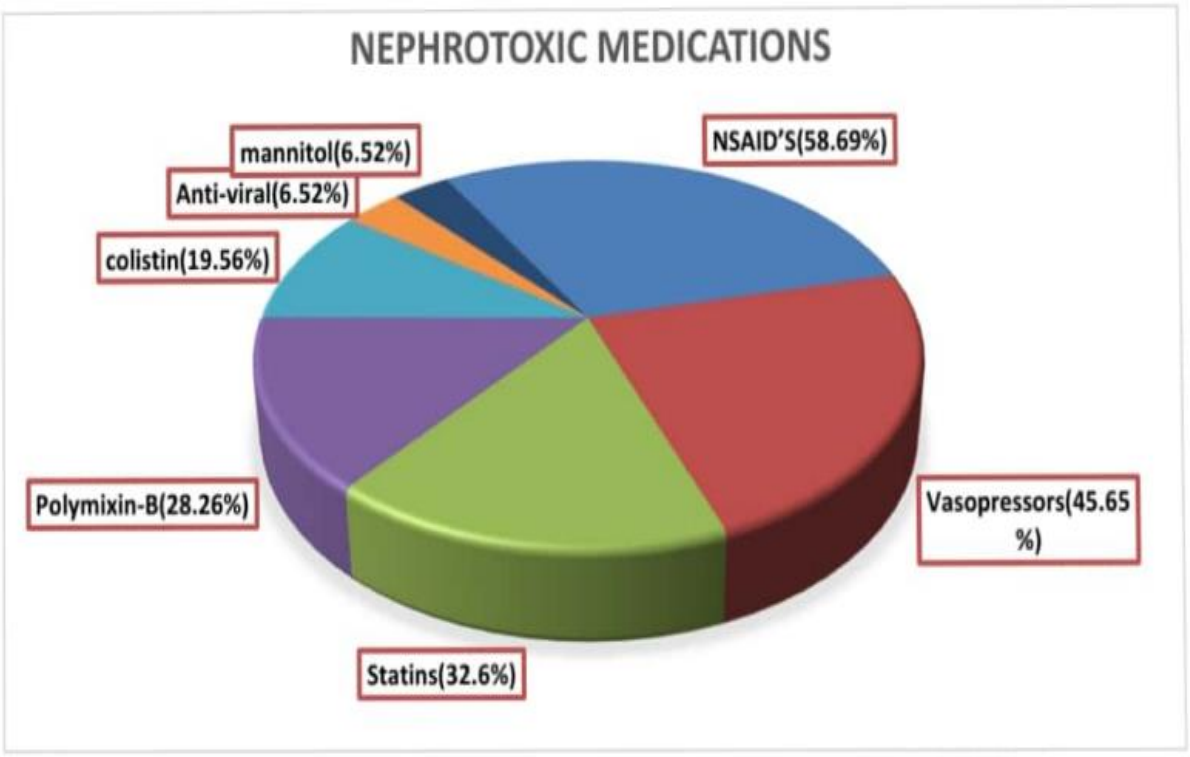


**Figure 3: Frequency of nephrotoxic medications that caused HAAKI**

**Outcomes:**

**Attributable mortality:**

Attributable mortality is defined as the total mortality minus the mortality correlated with the underlying disease process. Univariate analysis is conducted to recognize the significant association between the risk factors accountable for Hospital-acquired acute kidney injury and attributable mortality. Univariate analysis revealed that risk factors such as MODS ($\varkappa 2$=18.89, p=0.001) and ARDS ($\varkappa 2$=4.384, p=0.036) were significantly associated with Mortality.

**Table 3: Univariate analysis showing significant association between risk factors responsible for HAAKI and attributable mortality**

| | | Death | | $\varkappa^2$ | P-Value |
|---|---|---|---|---|---|
| | | No | Yes | | |
| | | Count | Count | | |
| Diabetes Mellitus | No | 12 | 9 | | |
| | Yes | 15 | 10 | 0.038 | 0.845 |
| Hypertension | No | 10 | 12 | | |
| | Yes | 17 | 7 | 3.049 | 0.081 |
| Cardiac disorders | No | 16 | 7 | | |
| | Yes | 11 | 12 | 2.242 | 0.134 |
| AKI on CKD | No | 19 | 13 | | |
| | Yes | 8 | 6 | 0.020 | 0.881 |
| Contrast induced | No | 24 | 17 | | |
| | Yes | 3 | 2 | 0.004 | 0.995 |
| Hypotension | No | 21 | 10 | | |
| | Yes | 6 | 9 | 3.209 | 0.071 |
| Sepsis | No | 7 | 5 | | |
| | Yes | 20 | 14 | 0.001 | 0.976 |
| MODS | No | 25 | 6 | | |
| | Yes | 2 | 13 | 18.892 | <0.001*** |
| Pneumonia | No | 20 | 10 | | |
| | Yes | 7 | 9 | 2.260 | 0.133 |
| ARDS | No | 22 | 10 | | |
| | Yes | 5 | 9 | 4.384 | 0.036** |
| Neurological disorders | No | 17 | 15 | | |
| | Yes | 10 | 4 | 1.346 | 0.246 |
| Gastric disorders | No | 24 | 17 | | |
| | Yes | 3 | 2 | 0.004 | 0.950 |
| Cancer | No | 22 | 18 | | |
| | Yes | 5 | 1 | 1.728 | 0.189 |
| Nephrotoxic drugs | No | 2 | 1 | | |
| | Yes | 25 | 18 | 0.084 | 0.772 |

Mechanical ventilation was provided to 89.1 % of the patients who developed HAAKI as one of the comorbidities. The mean AKI attack day in this study was witnessed to be day 4 which guided to the increased length of stay in HAAKI patients to 11.7 ± 8.05 days.

Out of 46 patients, 16 patients underwent Renal Replacement Therapy i.e., 14 patients from stage 1 and 2 patients from stage 2 had to undergo RRT to improve their renal function. The death ensued in 41.6% of the sufferers. 16 victims with stage 1 and 3 victims with stage 2 had death.

## DISCUSSION:

The main purpose of our study was to have an overall view of the incidence of HAAKI and mortality associated with it. We also emphasized the risk factors contributing to the malady. Several studies confirmed the increasing incidence of HAAKI; this study serves as a proof of the same. In this study, we found that the HAAKI incidence increased steadily in a decade. This poses a significant burden on the patients both economically as well as on the quality of life.

In this study, we used KDIGO criteria for detecting AKI in hospitalized patients. This criterion is a very refined and accurate criterion for the early detection of AKI in hospitalized patients thus; further complications can be prevented upon giving proper therapy and withdrawal of the causative agent. KDIGO in 2012 has defined AKI as an absolute increase of SCr of >0.3mg/dl in 48 h after the patient's admission. This criterion is better when compared to the previous counterparts AKIN and RIFLE as it uses elements from both the criteria which broaden the inclusion criteria for the patients, thus helping in the early detection.

This study was conducted in the MICU unit of a tertiary care hospital where we assessed 200 adult patients over 6 months. Using KDIGO criteria we confirmed the presence of HAAKI in 46 patients. Thus, confirming the incidence at 23%. A study conducted in central India[4] from January 2014 to December 2015, 9800 patients were admitted among which the incidence was found to be 2.1% for AKI. This when compared to our study where the incidence accounts to 23%, a huge hike can be seen in the incidence rate which raises an alarming situation to incorporate measures for early detection and prevention of AKI.

The risk profiling of our study demonstrates nephrotoxic medications (93.5%), sepsis (73.9%), pneumonia (34.8%) and ARDS (30.4%) as the major contributors of AKI. It was also common among patients with predisposing factors like diabetes mellitus, hypertension, cardiovascular diseases, ARDS, neurological disorders, cancer, gastric disorders. MODS and hypotension induced from sepsis also had a significant association with HAAKI (p value<5). Polypharmacy is a key factor that puts the health at stake for hospitalized patients. The most frequently administered nephrotoxic medications were NSAID'S (58.69%), vasopressors (45.65%), statins (32.60%), polymyxin-B (28.26%), and colistin (19.59%).

Anaemia and hypoalbuminemia were often observed and had a causal relationship with HAAKI. RRT was initiated in 34.7% of the HAAKI patients including both stage 1 and stage 2 patients to improve their renal function. Mechanical ventilation was provided to most of the patients having HAAKI as one of the comorbidities.

Pre-existing chronic kidney disease plays a crucial role in the development of HAAKI which is called ''AKI on CKD''. In our study, 30.4% of such patients developed HAAKI. Therefore, the dosage of nephrotoxic medications must be administered according to patient demographics.

Hospitalized patients with AKI had a 14 times higher mortality rate when compared with hospitalized patients without AKI. In this study, we calculated the attributable mortality using the univariate analysis to identify the significant association between the risk factor contributing to the mortality of the patients. Our study demonstrated that the major risk factors contributing to this are the presence of ARDS and MODS in the patients. In our study death occurred in 41.3% of the patients which when compared to the study conducted by Sara Nisula et al. on incidence, risk factors and mortality of the patients with acute kidney injury in Finnish Intensive care units for 5 months, which stated that hospital mortality in AKI patients was 25.6%. This increase in mortality alarms the seriousness of the malady whereby the death rate increased by up to 15% in 6 years.

Contrast-induced nephropathy is another serious factor which is a leading cause of AKI in many studies. It leads to a 25% increase in s.cr value from baseline within 48-72hrs after IV contrast administration. Propitiously, IV contrast was not much used in our hospitalized patients. Only 10.9% of the patients developed HAAKI.

The main strength of our study is the availability of SCr laboratory results which was done on daily basis to all the patients, which allowed us to use the up to date consensus KDIGO criteria, to detect HAAKI and to know the stage of HAAKI. KDIGO definition of AKI also includes urine criteria and this is not used in our study as it is not recorded much reliably. It is hard to carry out the study using this criterion as the data is sparsely recorded in the medical setting.

## CONCLUSION:

There is a heightened need to understand the incidence and rising consequences of hospital-acquired acute kidney injury as it is correlated with progressed morbidity, mortality and length of stay. The extended length of stay affects patients both economically and psychologically. As the mortality prevails unacceptably high despite the care provided in critical care with globally escalating incidence. These show that we require high clinical vigilance and therapeutic intervention to tackle this emerging yet a serious issue. The use of nephrotoxic medications and sepsis emerge as leading risk factors of Hospital-Acquired Acute Kidney Injury. More emphasis is required on medications leading to AKI in ICU. Engendering of risk prediction models and pioneering nephrologist intervention and enhanced monitoring may limit the further deterioration of kidney function in injured patients. Though death can be multi-factorial, its risk due to AKI can be depreciated.

**Limitations of this study**

- The study period was six months which was very limited to carryout observations in a wider aspect.
- This study could not emphasize more on biomarkers as a prevention measure as biomarkers were not used much.

**Future perspectives**

- → Establishing knowledge of a biomarker sensitive to predict AKI early on could lead to a clinical practice to measure this marker together with risk stratification models to guide admission to an ICU or treatment in general e.g. use of contrast media, antibiotics, or other potential AKI risk factors. Identifying early markers for AKI would also be crucial for planning randomised control trails concerning factors preventing AKI.
- → Doppler- and micro-vesicle contrast-enhanced ultrasonographies are relatively new methods that may provide more information on renal perfusion in the future341-343.
- → Constructing AKI risk stratification models on the basis of existing data and implementing the models to clinical use could still increase awareness of AKI risk factors and help to further reduce the incidence of AKI.

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**CONFLICTS OF INTEREST:**

The author declares that there is no conflict of interest to disclose.

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