A Prospective Study of Acute Kidney Injury According to KDIGO Definition and its Mortality Predictors

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Abstract

**Background:** Acute kidney injury is no longer considered to be an innocent bystander merely reflecting co-existent pathologies but an independent risk factor for mortality in the ICU.

**Aims and Objectives:** To study clinical profile and correlation of patients with acute kidney injury (AKI) according to KDIGO definition with respect to incidence, outcome and different causes of AKI in critical care unit.

**Study Design and Setting:** It is a prospective observational study; and was carried out in the ICU of a tertiary care, teaching, public hospital.

**Material and Methods:** We studied 316 patients developing AKI in ICU over a period of 1 year.

**Results and Conclusion:** Incidence of AKI in our ICU was 37.71% and mortality rate was 51.9%. Tropical Acute febrile illnesses followed by sepsis were the most common causes of AKI in ICU. Most common cause of AKI among tropical acute febrile illnesses (AFI) was malaria and among sepsis group was lung infection. In our study KDIGO staging could not predict outcome because majority of patients had multisystem failure. Pre-existing co-morbidities, multi-organ system failure were associated with high mortality. APACHE II scoring system under-predicted the mortality in patients with AKI.

Introduction

Acute kidney injury (AKI) has now replaced the term acute renal failure and a universal definition and staging system has been proposed to allow earlier detection and management of AKI. The new terminology enables healthcare professionals to consider the disease as a spectrum of injury. This spectrum extends from less severe forms of injury to more advanced injury when acute kidney failure may require renal replacement therapy (RRT). Clinically AKI is characterized by a rapid reduction in kidney function resulting in a failure to maintain fluid, electrolyte and acid-base homeostasis. There have been many different definitions of AKI used in the literature which has made it difficult to determine the epidemiology and outcomes of AKI. Over recent years there has been increasing recognition that relatively small rises in serum creatinine in a variety of clinical settings are associated with worse outcomes. Acute kidney injury is no longer considered to be an innocent bystander merely reflecting co-existent pathologies. It has been demonstrated to be an independent risk factor for mortality. AKI occurs in approximately 7% of all hospitalized patients (pts) and in up to 36% to 67% of critically ill patients depending on the definition used.

Most recently the international guideline group, Kidney Disease: Improving Global Outcomes (KDIGO) has brought together international experts from many different specialties to produce a definition and staging system that harmonizes the previous definitions and staging systems proposed by both ADQI and AKIN.

AKI (by KDIGO group) is

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defined as any of the following (Not Graded): 5

- Increase in Serum Creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours; or
- Increase in Serum Creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 ml/kg/h for 6 hours

It is anticipated that this definition and staging system will be adopted globally. This will enable future comparisons of the incidence, outcomes and efficacy of therapeutic interventions for AKI. Hence we decided to do study acute kidney injury according to KDIGO definition. The aim of the study was to observe clinical profile of patients with AKI according to KDIGO definition with respect to incidence, outcomes and different causes of AKI in critical care unit and also to study correlation between KDIGO stage and outcome.

**Material and Methods**

After obtaining institute’s Ethics committee approval and valid written informed consent or consent from legally acceptable relative / child’s assent in case of a minor aged less than 18 years, patients were enrolled in the study. We studied AKI according to KDIGO definition in the tertiary care teaching public hospital. The following data was collected for each patient: age; gender; date and time of admission, complete physical and general examination; provisional diagnosis; co-morbid conditions such as diabetes mellitus (DM), hypertension (HTN); clinical and laboratory data were collected / noted and necessary cultures were sent. APACHE II scores were calculated from data collected during the first 24 hours following ICU admission. We also noted need for oxygen supplementation, duration of mechanical ventilation, ICU length of stay and mortality.

Renal imaging scans as and when indicated were done. Diagnostic procedures if necessary: kidney biopsy and its preparatory tests like ultrasonography, urinalysis or urine culture, coagulation parameters as and when needed were done. Requirement of RRT was noted. Polysulphone dialyzers were used in current study, as per patient’s bodyweight, and bicarbonate dialysate was used during dialysis. Blood (250-300 ml/min) and dialysate (500-600 ml/min) flow rate were adjusted in haemodynamically unstable patients. Double lumen polycarbonate/polysilicon haemodialysis catheters were used during dialysis. Heparin schedule was adjusted as per coagulation profile in those patients with bleeding predisposition. Patients with severe fluid overload/catabolic state were dialysed daily. All tropical diseases were collectively referred as Tropical acute febrile illnesses (AFI). Multi-organ system failure (MOSF) was defined as per the definitions for sepsis and organ failure published by the Consensus Conference Committee American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) and in current study MOSF was all organ failure excluding AKI.

**Study Design and Setting**

It is a prospective, observational study; and was carried out in the intensive care unit (ICU) of a tertiary care, teaching, public hospital in India over a period of 1 year. Consecutive patients of ICU fulfilling KDIGO definition of AKI (> 12 years old) admitted to ICU in a tertiary care hospital were recruited, with an ICU stay for more than 24 hours. Patients with known case of CKD (chronic kidney disease) on maintenance haemodialysis were excluded from the study; however, those with AKI on CKD were included.

**Statistical Analysis**

Outcome of each patient was classified as either discharged or expired. Data thus obtained was tabulated and statistically analyzed; all values were presented as mean values ± SD (standard deviation) or as median with Inter Quartile Range (IQR) as appropriate. The mean values of the different groups were compared using two-sided t-test, the occurrence rates by the chi-square test. A forward stepwise binary logistic regression (BLR) analysis (conditional) was performed to determine the independent risk factors for AKI and mortality. The included variables were: age, Co-morbidities, AKI stages, APACHE II and Multiple Organ System Failure (MOSF). Co-linearity was analysed between the co-variates. Statistical analysis was performed by the SPSS statistical software package 18.0.

**Results**

During study period, 838 critically ill patients were admitted to the ICUs for more than 24hrs. Among these patients, 316 patients had AKI sometime during their ICU stay as defined by the study criteria. The overall incidence was 37.71% and the incidence of AKI that developed in ICU was 9.19%. The median length of stay in the ICU was 6.5 days and the median length of hospitalization was 10 days. General characteristics of study population are noted in (Table 1). Mean urine output in those who survived was 128.18 ml/hr (IQR – 150) and 84.44 ml/hr (IQR-140) in those who expired. Mean central venous pressure and mean arterial pressure (MAP) in those who survived was 4.17 mmHg (IQR-4) and 81.65 mmHg (IQR-24.33) and 4.19 (IQR-4) and 75.74 (IQR-23.33) in those who expired, respectively. Tropical AFI was the most common cause of AKI. Malaria (52%), followed by undifferentiated fever (24%) (Where the cause of fever couldn’t be found in spite of standard battery of tests) and in the decreasing order, leptospirosis...
Table 1: General characteristics of the study population based on parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=316</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>211</td>
<td>96</td>
</tr>
<tr>
<td>Female</td>
<td>105</td>
<td>56</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>21–40 years</td>
<td>120</td>
<td>65</td>
</tr>
<tr>
<td>41–60 years</td>
<td>94</td>
<td>42</td>
</tr>
<tr>
<td>&gt;61 years</td>
<td>62</td>
<td>23</td>
</tr>
<tr>
<td>No. of organs failure</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>101</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>05</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>00</td>
</tr>
<tr>
<td>Timing of AKI</td>
<td>No AKI</td>
<td>522</td>
</tr>
<tr>
<td>AKI after ICU admn</td>
<td>77</td>
<td>38</td>
</tr>
<tr>
<td>AKI prior to ICU admn</td>
<td>239</td>
<td>114</td>
</tr>
<tr>
<td>Stage of AKI</td>
<td>No</td>
<td>27</td>
</tr>
<tr>
<td>AKI as per KIDGO</td>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>225</td>
<td>102</td>
</tr>
<tr>
<td>RRT and outcome</td>
<td>Yes</td>
<td>93</td>
</tr>
<tr>
<td>No</td>
<td>223</td>
<td>117</td>
</tr>
</tbody>
</table>

Admn: Admission, MOSF: Multi-organ system failure, RRT: Renal replacement therapy, AKI: Acute kidney injury; *Out of total 838 patients admitted in ICU during the study period

<table>
<thead>
<tr>
<th>Causes of AKI</th>
<th>Outcome</th>
<th>Total</th>
<th>Chi-Square Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present (n=316)</td>
<td>Expired</td>
<td>Disch.</td>
<td>Value</td>
</tr>
<tr>
<td>HEELP syndrome</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nephrototoxic Medications</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Sepsis/SIRS</td>
<td>70</td>
<td>31</td>
<td>101</td>
</tr>
<tr>
<td>Cardiogenic Causes</td>
<td>13</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>10</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Obstructive Uropathy</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tropical AFI</td>
<td>57</td>
<td>86</td>
<td>143</td>
</tr>
<tr>
<td>Post-Surgery</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

#: Fisher’s Exact Test applied. ^: Continuity Correction applied. AFI: Acute febrile illness, HEELP: Haemolysis elevated enzymes and lowered platelets syndrome of pregnancy, No: Number; Disch: Discharged

Discussion

We conducted a single-centre study with 316 ICU patients to characterize AKI, defined by KDIGO classification. We studied AKI according to KDIGO definition with respect to incidence, different causes of AKI and outcome in ICU. Factors such as prospective inclusion of consecutive patients, use of uniform standardized clinical observations, laboratory investigations, standard criteria for diagnosis of acute febrile illness including analysis of convalescent sera wherever necessary, and a study period extending for a full year annulling the possible seasonal variations strengthen the reliability and validity of the observed incidence of the various causes.

AKI is one of the most serious complications in critically ill patients and additionally is an independent mortality risk factor. Various authors have reported the incidence of AKI in ICU patients ranging from 3% to 67%; this marked variability may be due to difference in definition of AKI.
Table 3: Binary logistic regression between ‘outcome’ as dependent variable and a set of independent (predictor) variables

<table>
<thead>
<tr>
<th>Step</th>
<th>Variables</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Constant</td>
<td>-4.705</td>
<td>0.849</td>
<td>30.73</td>
<td>1</td>
<td>0.000</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>MOSF</td>
<td>1.362</td>
<td>0.163</td>
<td>69.51</td>
<td>1</td>
<td>0.000</td>
<td>3.905</td>
</tr>
<tr>
<td></td>
<td>Comorbidity</td>
<td>0.416</td>
<td>0.170</td>
<td>5.96</td>
<td>1</td>
<td>0.014</td>
<td>1.516</td>
</tr>
<tr>
<td></td>
<td>Stage of AKI</td>
<td>0.381</td>
<td>0.233</td>
<td>1.46</td>
<td>1</td>
<td>0.230</td>
<td>1.013</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>0.013</td>
<td>0.009</td>
<td>2.27</td>
<td>1</td>
<td>0.132</td>
<td>1.013</td>
</tr>
</tbody>
</table>

MOSF: Multiple organ system failure, B – Coefficient for the constant in the null model (also called “Intercept”), S.E. – Standard error around the coefficient for the constant, df – degree of freedom, Exp (B) – Exponentiation of the B coefficient, Sig. – significance, Wald-statistical test.

Table 4: Outcome among the cases between-AFI, Sepsis status and stage of AKI

<table>
<thead>
<tr>
<th>Stage of AKI</th>
<th>AFI and Sepsis status</th>
<th>Outcome</th>
<th>Expired</th>
<th>Discharged</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sepsis/SIRS</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Sepsis/SIRS</td>
<td>14</td>
<td>9</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Sepsis/SIRS</td>
<td>50</td>
<td>21</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tropical AFI</td>
<td>8</td>
<td>19</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>7</td>
<td>7</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tropical AFI</td>
<td>46</td>
<td>64</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>27</td>
<td>17</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

Chi-Square Tests

<table>
<thead>
<tr>
<th>Value</th>
<th>df</th>
<th>p-value</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.570</td>
<td>2</td>
<td>3.410E-05</td>
<td></td>
</tr>
</tbody>
</table>

No.: Number; AFI: Acute febrile illness, None: Causes of AKI other than Sepsis/tropical AFI.

used, type of tertiary care facility available and basic underlying disease causing AKI.8-14 There is a progressive change in the demographic profile of patients being admitted to ICU.5,6,15 The mean age of study population was 42.64 years in concordance with similar study done in India where mean age was 39.7 years.13 Majority of patients admitted to ICU with AKI were in age group of 21-40 years, as one of the commonest indications for transfer of the patient to ICU was febrile illnesses which were commonly seen in this working population, which also explains high mortality seen in this age group.

We observed a trend towards an increasing number of AKI cases among male patients compared to female patients [66.8% (211) and 33.2 % (105), respectively]. Compared with all ICU admissions, patients with AKI were found to be older and of male gender.13,16 It is also possible that still unknown genetic aspects may have influenced the incidence of AKI in the male population.5-11,16,17

The morbidity and mortality depends upon the underlying disease causing AKI. Tropical AFI (45%) was the leading cause of AKI in this study. This is because in contrast to trauma, industrial accidents, drugs, cardiogenic shock and renal transplantation rejection in the developed world, whereas, acute tubular necrosis (ATN) due to community-acquired infections remains the commonest cause of AKI in the tropics.12-14,16,17 Acute gastroenteritis, a rare entity in developed nations, still poses a challenge in developing countries like India due to poor hygienic conditions, overcrowding and late referral to tertiary hospitals. In study by Basu and colleagues the incidence of AKI was highest with falciparum malaria followed by mixed malaria, leptospirosis and least with enteric fever.13 AKI was observed at an average rate of 35-40% among other acute febrile illnesses. This can explain high incidence malaria as a cause of AKI in tropical AFI group in present study. Through this study we report 2nd case of hepatitis E causing non oliguric AKI; first one was reported by Verschuuren et al.18 Sepsis and septic shock were the second important risk factors for the development of AKI in the present study, contributing to 32% of the cases. In majority of studies the most common contributing factor to AKI was sepsis which is in discordance with our study, the prevalence of AKI in sepsis ranges from 9 to 40%.1,13,15,17,19,20 Like current study, a study done on AKI in sepsis patients in ICU, demonstrated the most common cause as lung infection.21 Cardiogenic shock associated renal hypoperfusion is strongly associated with AKI. The incidence of acute cardio-renal syndrome in patients with AKI is estimated to be between 19% and 45%.13 In current study 5.7% of AKI was related to cardiogenic shock which is much lower than that in other studies as the percentage of incidence is skewed because of tropical AFI.13,21

Ten percent of AKI were associated with major surgery in current study, which is comparable to other studies.21-23 We found only 2% of AKI potentially drug-related whose incidence in other studies varies from 2-22%.13,15 In our study KDIGO staging could not predict outcome because majority of patients had multisystem failure.

Co-morbidities similar to current study were observed in other studies too.12,13,19,24 Patients with HTN, DM, COPD and neurological disease as co-morbid conditions had higher mortality in comparison to those without these conditions (p<0.05). Patients with chronic diseases such as liver cirrhosis, cardiovascular disease and previous renal insufficiency have also been found to be the risk factors for high mortality.10,21
RRT was required by 29.43% of the patients in our study, similar to the study done by Cruz DN et al where 30.3% needed RRT.16,25 Other studies however report varied percentage of RRT use.13,16,25,26 This difference possibly denotes the difference in initial criteria used to diagnose AKI. The need for dialysis treatment has been associated with a higher mortality rate (50-70%) than among patients with AKI who did not require RRT.25-27 In our study, the mortality among patients on dialysis (50.5%) was identical to non-dialysis patients (52.5%). This was probably because; we had less percentage of septicemic patients as compared to other studies and more patients with tropical AFI.

Recent reviews suggest that the overall prognosis of AKI has changed little since 1960s and the mortality is significantly higher in ICU patients (70–80%) compared to non ICU patients (30–50%).25,28,29 The mortality in our study was 51.9%, whereas APACHE II predicted mortality was 40%. The outcome of patients in various studies varies from 37% to 63% reflecting differences in the severity of patients and possibly in therapies.28,29 Our findings showed a high mortality rate among patients with AKI associated with sepsis and vasoactive drugs. The patients with sepsis (n = 101) presented a higher mortality rate 70%, in comparison with the patients without sepsis (n = 215), whose mortality rate was 43.51% (p < 0.0001). This observation was similar to study by Prakash et al and Silva Júnior et al who also observed a higher mortality rate among AKI patients with sepsis.28,29

For patients admitted with AKI, the median length of stay in ICU increased by upto 120% and the median length of hospitalization by 35% as compared to patient without AKI, which was comparable to our study.13,28,29 We attempted to identify clinical predictors of death on the day of AKI diagnosis, a clinically relevant time point if early interventions are to be initiated. In present study, the mortality due to MOSF was high and there was progressive increase in mortality as the number of organ system failures increased. In current study, MOSF, respiratory involvement, sepsis, cardiovascular and Neurologic affection along with AKI had statistically significant chances of poor outcome (p<0.05) this finding was also seen in other studies.25,26,28,29 The mean APACHE II score was 20.61 which is concordant with a study by Han SS using KDIGO criteria for AKI.9 There was a difference between predicted (40%) and real mortality (55.6%) suggesting that this index is not appropriate for AKI assessment. This finding has been reported previously by Mataloun et al.8 We observed much higher APACHE-II score (22.62) in patients who died in comparison to lower scores (18.45) in surviving patients (p<0.001).

The laboratory analysis showed significantly higher levels of AST, ALT, total bilirubin and Serum creatinine at admission to the hospital in patients who did not survive. This group also presented with lower levels of haemoglobin, platelet count and pH, which reflected the poorer condition of these patients. It is not surprising that non-survivors presented worse laboratory tests. In the present study, there were some significant factors which were associated with death, such as age, haemoglobin, pulse rate, systolic blood pressure, arterial pH, APACHE II and total bilirubin. This suggests that the occurrence of hematological disorders (thrombotic events, anemia or hemorrhage), hypotension and metabolic acidosis is associated with a higher risk of death. There is concordance for above factors with the study by Silva Júnior and co-workers.29

There are many studies in which attempts have been made to identify prognostic factors for AKI in critically ill patients.10,11,15,16 Liaño et al showed that oliguria, hypotension, mechanical ventilation and jaundice were associated with higher mortality.30 Metnitz et al observed that some medical interventions were associated with higher incidence of death among AKI patients from an ICU (mechanical ventilation, vasoactive medication, cardiopulmonary resuscitation and treatment of metabolic acidosis/alkalosis).25 The presence of chronic cardiac failure at admission, late onset of RRT and presence of chronic respiratory failure at admission were also associated with higher mortality.31 In one of the studies on this subject, the presence of liver and biliary tract diseases, respiratory dysfunction, need for vasoactive drugs and sepsis were found to be prognostic factors.10 Mehta et al studied 605 cases of AKI in an ICU, showed that advanced age, male gender, respiratory, liver and hematological failure, oliguria, high levels of creatinine and elevated heart rate were factors associated with high mortality.32 Sural et al in an Indian study showed that the presence of sepsis, associated organ dysfunction, severe renal failure requiring dialysis and prolonged stay in the ICU were associated with increased risk of death.33 The likelihood of survival was found to be associated with the absence of oliguria, absence of dialysis and absence of ischemic acute tubular necrosis.

The limitation of our study was that we did not include long-term follow-up and thus the outcomes for patients following hospital discharge was unknown. For this reason, we chose not to analyze data using survival rates (e.g. Cox proportional hazards) because we would have had to assume that survival post discharge resembled in-hospital survival rates and this seems unlikely. Assessing baseline creatinine values by the Modification of Diet in Renal
Disease (MDRD) may have exposed our study methodology to the risk of inclusion. We relied on serum creatinine as a surrogate marker for the GFR, particularly given its dependence on muscle mass and the numerous non-glomerular factors that affect accumulation of creatinine in the intravascular space. However, in clinical practice, serum creatinine remains the gold standard for monitoring kidney function, notwithstanding its limitations. In our study KDIGO staging could not predict outcome because majority of patients had multisystem failure so further studies are required to validate this new classification of AKI.

Conclusions

From the experience of the present study, we put forth the following:

Current study has established the incidence of AKI using the KDIGO criteria in Indian ICUs. Incidence of AKI in our ICU is 37.71% and the mortality rate is 51.9%. Tropical AFI illnesses are still a big challenge in our country being the most common cause of AKI in ICU in our study. There are significant chances of mortality in patients with AKI due to sepsis and tropical AFI. These findings call for early detection and aggressive management of sepsis and its associated complications so as to bring down the mortality in patients admitted to intensive care unit. Most common cause of AKI among tropical AFI illnesses was malaria and among sepsis group was lung infection. Pre-existing co-morbidities like HTN, DM, COPD and neurological illness have high chances of mortality. As number of organs failed increased, mortality increased significantly. Low hemoglobin, platelet count, pH, systolic blood pressure and high Serum creatinine and total bilirubin on admission significantly affect outcome. However, more prospective studies are necessary to confirm the identified risk factors associated with unfavourable outcomes in AKI, which would in turn allow for the development of prophylactic measures for early diagnosis. Use of RRT did not improve outcome significantly. Further investigations focusing on the potential confusing role of RRT are warranted to better characterize the prognosis of AKI. APACHE II score under predicted the mortality for AKI. This information may be helpful in the design of future international interventional trials, which would apply to worldwide practice, in regard to the statistical power and choice of appropriate outcome measures. Thus, Early recognition of the patient going downhill before one or multiple systems start failing is important as is the importance of good intensive care once this does occur.

References

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