Original Article
Incidence and outcomes of acute kidney injury among patients attending intensive care unit in China

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Abstract: Background: Despite vigorous and substantial measures to combat acute kidney injury (AKI) in intensive care unit (ICU), incidence and mortality of AKI is steadily increasing over time that requires more efforts needed to understand disease condition and course. Current study was aimed to determine incidence and outcomes of patients attending ICU in China. Methodology: Data from patients attending ICU during March 2014 to August 2014 were prospectively collected. AKI was stratified according to AKIN classification system. Patients with and without AKI were compared by appropriate statistical methods. Logistic regressions were used to determine predictors of AKI, longer ICU stay and mortality. Results: Incidence of AKI was 47.1% (769/1633) in total cohort including AKIN-I (8.7%), AKIN-II (15.3%) and AKIN-III (23.1%). Old age (OR 3.4), diabetes (OR 2.8), high SOFA/APACHE II scores (OR 2.2/4.1), sepsis (OR 9.4) and vasopressors (OR 6.2) were significant predictors of AKI. AKIN-III (OR 7.4), multiple organ dysfunctions (OR 3.8), RRT (OR 5.5) and mechanical ventilation (OR 2.7) were strongly associated with longer ICU stay. ICU mortality in our study was 27.4%. Elderly patients (OR 3.3) with AKIN-III (OR 5.6) having high SOFA score (OR 2.5) requiring RRT (OR 7.1) and mechanical ventilation (OR 9.2) had higher odds of death in our study. Conclusions: AKI imposes substantial burden to the health care system and patients in terms of morbidity, mortality and cost of care (hospital stay). Identification of high risk patients and adequate measures in timely manners may go in long run to combat AKI in ICU.

Keywords: Acute kidney injury, intensive care unit, emergency, predictors, mortality

Introduction

Acute Kidney Injury (AKI) is common (especially among patients in intensive care units), increasing in incidence and is associated with considerable morbidity and mortality. AKI affects 1 in 5 hospitalized patients, is associated with high expenditure of resources, and leads to adverse outcomes [1, 2]. Several efforts have been made to unveil the accurate characteristics, mechanisms and consequences of AKI. RIFLE (risk, injury, failure, loss of function, end stage renal disease) classification was first accurate criterion to diagnose AKI that have been followed by AKIN (Acute Kidney Injury Network) and KDIGO (Kidney Disease Improving Global Outcomes) classifications [3, 4]. Furthermore, research on sensitive and accurate biomarkers has opened new pathway for early detection and better outcome prediction of AKI. Additionally, the role of the immune system in pathogenesis of AKI is less elusive now that may help to further categorize AKI and to discover new therapeutic options [5].

Despite these efforts true incidence of AKI in intensive care unit (ICU), accurate characteristics of AKI and influential factors for the development of AKI are not clear. It may be attributed to heterogeneous study population, varying management protocols in ICU, criteria used to define AKI and methodological differences [4]. The incidence of AKI is about 7% among total hospitalized patients and up to 36% to 67% among patients attending ICU, depending upon definition used [6, 7]. About 4% to 25% patients have severe AKI on ICU admission and 5% to 6% patients with AKI require renal replacement therapy (RRT) during their ICU stay [8, 9]. Reported mortality due to AKI in ICU varies considerably between studies depending on definition of AKI and its etiology (e.g. sepsis, trauma,
cardiothoracic surgery or contrast nephropathy). It has been proposed that mortality increases proportionately with increasing severity of AKI where need of RRT in ICU is well recognized independent predictor of mortality accompanied by 50% to 70% fatality rate. Despite adjustment for co-morbidities and severity of disease, AKI with cardiopulmonary bypass, sepsis, major trauma and burn injury have consistently demonstrated significant association with increased risk of death [10]. Few studies have described incidence, characteristics and outcomes of AKI in ICU among Chinese population [11-14]. Current study was aimed to determine incidence and outcomes of AKI among patients attending ICU in China. Our study will be a valuable addition to the literature describing epidemiology and outcomes of ICU induced AKI.

Methodology

Study location and participants

A single center prospective observational study was performed among patients attending intensive care unit (ICU) of the Second affiliated hospital of Harbin Medical University, China. After taking ethical approval from concerned body, a total 8953 patients were selected for the study purpose during the period of six months (March 2014 to August 2014). Patients with chronic renal insufficiencies, severe hypovolemia, incomplete data or having stay less than 48 hours or on renal replacement therapy were excluded from the study. A total 1633 patients were included in final analysis and were followed up until discharge or death, whichever occurred first.

Classification of acute kidney injury

The values of serum creatinine (Scr) were recorded daily and urine output was taken on hourly basis. AKI was defined by Acute Kidney Injury Network (AKIN) classification and staged into AKIN-I, AKIN-II and AKIN-III on the basis of severity. Patients were referred to AKI if increase in Scr ≥26.2 μmol/L or increase to ≥150-199% (1.5- to 1.9-fold) from baseline or urine output <0.5 mL/kg/h for ≥6 h. Severity classes of AKIN criterion were defined as; AKIN-I (increase in serum creatinine ≥26.2 μmol/L or increase to ≥150-199% (1.5- to 1.9-fold) from baseline or urine output <0.5 mL/kg/h for ≥6 h), AKIN-II (increase in serum creatinine to 200-299% (>2-2.9 fold) from baseline or urine output <0.5 mL/kg/h for ≥12 h) and AKIN-III (increase in serum creatinine to ≥300% (≥3-fold) from baseline or serum creatinine ≥354 μmol/L with an acute rise of at least 44 μmol/L or initiation of RRT or urine output <0.3 mL/kg/h ≥24 h or anuria ≥12 h). Patients without baseline SCR and having no history of chronic renal insufficiency (CRI), baseline SCR was estimated with Modification of Diet in Renal Disease (MDRD) equation by assuming glomerular filtration rate as 75 ml/min/1.73 m² [1]. All the patients were stratified into AKI and non-AKI groups on the basis of Scr and urine output (UO) values, whichever led to worst classification of AKI. For example, if a patient had AKIN-II stage according to Scr criterion and had AKIN-III stage with UO criterion, then worst classification i.e. AKIN-III was considered as final severity stage of the patient. By the similar way if patients progressed to severe stage of AKI during ICU stay then severe stage was recorded as final stage. If patient recovered from severe to less severe stage of AKI during AKI stay then severe stage was recorded as final AKI stage in this patient. Baseline Scr values were calculated in approximately 38% of studied population.

Data collection

The data collected for each participant included demographics, co-morbidities, diagnosis in ICU, surgical and non-surgical procedures, clinical and laboratory parameters, discharge outcomes and renal replacement therapy modalities. Patients with missing data required for the purpose of analysis were excluded from the study. Data was collected by using structured data collection form by trained medical officers and house officers. All the collected data were screened for missing values, incomplete details or any further queries before inclusion into statistical analysis.

Statistical analysis

All the data were presented as mean ± standard deviation or as median with inter quartile range (IQR) as appropriate for continuous variables and as proportion for categorical variables. Groups were compared by student t test, Kolmogorov-Smirnov test, Chi-Square test or Mann-Whitney U test, where appropriate. Stepwise (forward) logistic regression was applied
to determine independent risk factors of AKI and mortality. The variables with \( P \) values
<0.25 in univariate analysis were subjected to multivariate regression analysis [15]. Variables with \( p \) values <0.05 were considered final predictors of AKI and mortality in current study. All the variables were deemed to be significant if \( p \) values were less than 0.05. The statistical package SPSS (version 20.0) was used for all statistical analyses.

### Ethical consideration

Current study was approved by ethical review committee (CRC) of Harbin Medical University (HMU) after reviewing protocol and data collection procedures (Reference: CRCHMU-48-973/2011). Identity of all patients was not disclosed in current study. All the patients were anonymized during statistical analysis.

### Results

A total 1633 patients (mean age: 57.6 ± 11.3 year, males: 57%) were included into the study. Baseline clinical and laboratory characteristics of patients are demonstrated in Table 1. According to AKIN criterion, AKI was observed in 47.1% (769/1633) patients including AKIN-I in 142/769 (18.5%), AKIN-II in 250/769 (32.5%) and AKIN-III in 377/769 (49%). Overall incidence of AKIN-I, AKIN-II and AKIN-III in total study sample was 8.7%, 15.3% and 23.1%, respectively. Most of the patients (566/1633, 34.7%) developed AKI within 48 hours of ICU admission while only 12.4% (203/1633) patients developed AKI after 48 hours. Out of the total AKI cases, renal replacement therapy was initiated in 143 (18.6%, 8.8% of entire cohort) patients. About 30% (233/769) patients with AKI progressed to severe stages of AKIN clasi-
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AKI was found to be more common in some comorbid diseases e.g. congestive heart failure (CHF), cardiac arrhythmia, hypertension, diabetes mellitus and psychiatric disorders. Patients with AKI posed a heavy burden to health care system in terms of length of hospital stay (LOS), use of vasopressors and mortality (Table 1).

Most of the patients (60.6%, 989/1633) were admitted to ICU due to surgical causes and among them gastrointestinal surgery was more profound. Medical causes of ICU admission accounted 39.4% (644/1633). All the causes of ICU admission among patients with and without AKI are given in Table 2. Patients admitted due to gastrointestinal problems, malignancies and infections were found to be associated with AKI in our study. In incidence of severe stage of AKI (AKIN-III) was higher in gastrointestinal and cardiovascular reasons of ICU admission (9% versus 11%).

Out of 769 AKI cases, 41% patients had AKI as a result of septic shock while second most contributing factor was hypovolemia (30%). About 17% AKI cases were associated with cardiogenic shock and 8% AKI cases with major surgery. Approximately 1% AKI was potentially drug induced (Figure 1).

Underlying factors causing AKI were determined by logistic regression analysis. All the statistically tested and previously known variables were subjected to univariate analysis. Factors with p values <0.25 were considered as candidate for multivariate analysis. Out of total 8 variables (Old age, GFR <60 mL/min/1.73 m², hypertension, diabetes mellitus, APACHE-II score, SOFA non-renal score, GCS, Sepsis and vasopressor need) tested in univariate analysis, only hypertension had P>0.25 and excluded from multivariate analysis. Factors with p values <0.05 in adjusted analysis were considered as significant predictors of AKI (Table 3).

A total six risk factors of AKI were determined by logistic regression. GFR <60 mL/min/1.73 m² was failed to demonstrate any association in multivariate analysis. Similar risk factors were also tested for its association with severe AKI (AKIN-III). Subgroup analysis revealed that patients with old age (OR: 2.9, P = 0.001), diabetes mellitus (OR: 1.8, P = 0.042), High SOFA (OR: 2.2, P = 0.023) and APACHE (OR: 3.4, P<0.001) scores and sepsis (OR: 5.5, P<0.001) were found to be more associated with AKI. Out of total 377 patients with AKIN-III, 156 (41.4%) patients required renal replacement therapy (RRT). Patients with AKIN-III having old age (OR: 2.9, P = 0.001), diabetes mellitus (OR: 1.8, P = 0.042), High SOFA (OR: 2.2, P = 0.023) and APACHE (OR: 3.4, P<0.001) were found to be more associated with AKI. Out of total 377 patients with AKIN-III, 156 (41.4%) patients required renal replacement therapy (RRT). Patients with AKIN-III having old age (OR:

Table 2. Primary Intensive care Unit (ICU) admission diagnosis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Overall patients N = 1633</th>
<th>Patients with AKI N = 769</th>
<th>Patients without AKI N = 864</th>
<th>P values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>989 (60.6%)</td>
<td>366 (47.6%)</td>
<td>623 (72.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical</td>
<td>644 (39.4%)</td>
<td>389 (50.6%)</td>
<td>255 (29.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>364 (22.3%)</td>
<td>204 (26.7%)</td>
<td>159 (18.4%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>297 (18.2%)</td>
<td>148 (19.2%)</td>
<td>149 (17.2%)</td>
<td>0.381</td>
</tr>
<tr>
<td>Respiratory</td>
<td>241 (14.8%)</td>
<td>128 (16.3%)</td>
<td>113 (13.1%)</td>
<td>0.062</td>
</tr>
<tr>
<td>Neurological</td>
<td>366 (22.4%)</td>
<td>178 (23.1%)</td>
<td>188 (21.8%)</td>
<td>0.075</td>
</tr>
<tr>
<td>Malignancies</td>
<td>387 (23.7%)</td>
<td>276 (35.9%)</td>
<td>111 (12.8%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Renal^</td>
<td>27 (1.7%)</td>
<td>13 (1.7%)</td>
<td>14 (1.6%)</td>
<td>0.811</td>
</tr>
<tr>
<td>Infectious</td>
<td>489 (29.9%)</td>
<td>294 (38.2%)</td>
<td>195 (22.6%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Others†</td>
<td>181 (11.1%)</td>
<td>83 (10.8%)</td>
<td>98 (11.3%)</td>
<td>0.332</td>
</tr>
</tbody>
</table>

*Others includes trauma, metabolic, hematological, orthopedic; †Renal disorders refer to renal dysfunctions other than chronic insufficiencies; *P values are calculated between AKI and non-AKI group.

Figure 1. Contributing factors of AKI in ICU (percentages were calculated out of total AKI cases).
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Table 3. Stepwise logistic regression (Multivariate analysis) to determine predictors of AKI

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odds ratio</th>
<th>P value</th>
<th>95% confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 years</td>
<td>3.4</td>
<td>0.001</td>
<td>1.8 - 7.3</td>
</tr>
<tr>
<td>GFR &lt;60 mL/min/1.73 m²</td>
<td>1.7</td>
<td>0.082</td>
<td>1.1 - 4.7</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>2.8</td>
<td>0.004</td>
<td>1.6 - 6.2</td>
</tr>
<tr>
<td>High SOFA non-renal score</td>
<td>2.2</td>
<td>0.010</td>
<td>0.9 - 3.5</td>
</tr>
<tr>
<td>High APACHE-II score</td>
<td>4.1</td>
<td>0.001</td>
<td>2.3 - 7.9</td>
</tr>
<tr>
<td>Need to vasopressors</td>
<td>6.2</td>
<td>&lt;0.001</td>
<td>2.1 - 11.5</td>
</tr>
<tr>
<td>Sepsis</td>
<td>9.4</td>
<td>&lt;0.001</td>
<td>4.8 - 15.3</td>
</tr>
</tbody>
</table>

SOFa: sepsis related organ failure assessment score, APACHE-II: acute physiology and chronic health evaluation, OR: odds ratio, CI: confidence interval. Selection of variables for multivariate analysis was performed by forward selection method.

with mortality in our study. Neurological disorders and need of vasoactive drugs were found as risk factors of overall hospital morality (mortality in ICU and after discharge from ICU in hospital) in addition to risk factors associated with ICU mortality.

Discussion

This study advances the current understanding of clinical and laboratory characteristics of AKI among patients attending ICU. Despite vigorous efforts to combat AKI in hospital, its incidence is steadily rising every year, especially in ICU. The incidence of AKI in ICU is much higher (6%-25%) than hospital acquired or community acquired acute kidney injury [16, 17]. Several studies have described a wide range of AKI ranging from 5.2% to 67.2% depending upon setting of ICU and admission diagnosis [18-21]. In current study, incidence of AKI was 47.1% and most of the cases were belonged to severe stage of AKI i.e. AKIN-III (377/769). The high incidence of AKI in our study is might be due to presence of patients with old age (about 40%), comorbid conditions and surgical procedures. Mendelbaum and co-workers performed a large single center study on ICU patients and AKI was observed in 57% population by using AKIN criterion [22]. These findings are consistent with our study using same criterion to define AKI. The incidence reported by Park and his co-workers (41.3%) by using RIFLE criterion is also comparable with our findings [23]. Similarly, the incidence reported in recent investigation by Peres et al by using RIFLE criterion (53.2%) is comparable to incidence reported in our study by using AKIN criterion [24]. Several studies have described the sensitivity advantage of AKIN criterion over RIFLE [4, 25] but still the available evidences are not sufficient to draw firm conclusion that which criterion is superior to stratify AKI in ICU setting. A great disparity in reported incidences of AKI in published literature might be contribute to differences in ICU settings, protocol used in ICU, heterogeneity of studied population, criterion used to stratify AKI and selection of serum creatinine versus urine output criterion. In previously published literature about 35 definition of
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AKI were used causing wide variation in incidence and mortality in these studies [26]. These findings suggest the need of multicenter, prospective and controlled trials in order to clearly understand epidemiology and outcomes of AKI.

Acute Kidney Injury has become a major issue with rising incidence causing more than 4 million deaths per year across globe. Therefore, early recognition of AKI in ICU setting is very crucial. Identification of patients having high risks of developing AKI may provide sufficient time to clinicians to make corrective measures and in long run may cause reduction in morbidity and mortality associated with AKI in ICU. We identified seven risk factors of AKI by using stepwise (forward) logistic regression. Elderly and diabetic patients with high SOFA/APACHE II scores and sepsis requiring vasopressors were found to associate with AKI in our study. Such patients should be monitored vigilantly and special attention and care must be taken into consideration. Cartin-Ceba and co-workers conducted a meta-analysis of observational studies describing risk factors of AKI among critically ill patients [26]. The results of this meta-analysis demonstrated the association of risk factors identified in our study with AKI except hypertension. These findings are consistent with our study as hypertension was not found as a significant predictor of AKI.

The high occurrence rate of AKI among elderly population in our study might be explained by increased susceptible of such patients towards drug toxicities, altered pharmacokinetics and dynamics, polypharmacy including nephrotoxic drugs and compromised renal functions [1]. It might be possible reasons that older patients in our study had high severity scores (SOFA & APACHE II).

About 60% patients in our study were admitted to ICU due to surgical causes and among them abdominal surgery accounts 28.9% (222/769) of AKI. These findings are consistent with previous literature [27, 28]. Usually complicated abdominal surgery leads to inadequate renal perfusion pressures (intra-abdominal pressure-IAP) and it has been documented that change in IAP has great impact on renal function and urine output [28]. Similarly patients with AKI also had high prevalence of malignancies demonstrating their contributing role in the development of AKI [29]. Infections also present a wide impact on renal functions and may lead to AKI with varying severity [3]. Infectious AKI accounted 38.2% of total AKI cases in our study. Sepsis was leading etiological factor of AKI in current study and these findings are in concordance with previous literature [9, 23, 24].

We found that patients with AKI posed heavy burden to patients and health care system not only due to morbidity but also longer ICU and hospital stay. Patients with AKI had about twice longer ICU stay than patients without AKI resulted in a significant burden in terms of cost of care and this is of particular concern in resource limited settings where ICU beds are limited and in great demand. Patients with severe AKI and MODs requiring RRT and mechanical ventilation had longer ICU as well hospital stay in our study. Such patients should be carefully monitored from day one in order to reduce their stay in ICU and ward that will be beneficial for both health care system and patients to reduce their expenditures.

It has been documented that a mild increase in serum creatinine is associated with mortality [30, 31]. Overall mortality in our study was 27.4% and patients having AKI had about twice mortality rate than patients without AKI. These findings are in concordance with previous studies [23, 24]. As demonstrated in previous studies [19, 28], we also observed higher mortality rate in patients with AKIN-III followed by AKIN-II and AKIN-I. Out of total 377 patients with AKIN-III, 156 (41.4%) patients were on RRT and among them about 80% (125/156) patients died at the end of this study. Need of RRT was also found to be a significant risk factor of mortality along with AKIN-III stage. Other risk factors associated with mortality were elderly patients with severe disease scores. Patients with AKI in our study also had higher in-hospital mortality (mortality in ICU and ward) than patients having no AKI. Need of vasopressors and neurological disturbances were factors significantly associated with in-hospital mortality addition to the factors associated with ICU mortality. It has been documented that onset of AKI along with MODs is associated with mortality ranging from 50-70% [20, 33]. About one quarter patients in our study died in ICU while overall in-hospital mortality was observed in more than one third of study population. The high mortality in our study might be due to presence
Acute kidney injury (AKI) imposed significant burden to the patients attending intensive care unit in terms of morbidity and mortality. AKI doubles the length of ICU as well as overall hospital stay. Elderly patients (>60 years) with sepsis having diabetes mellitus and severe disease scores and requiring vasopressors were found to be strongly associated with AKI. AKIN-III patients with multiple organ dysfunctions requiring RRT and mechanical ventilation had higher odds of longer ICU as well overall hospital stay in our cohort. Patients with severe AKI (AKIN-III), on RRT or mechanical ventilation have higher odds of death than patients without these conditions. Early identification of factors related to development of AKI, longer hospital stay and mortality along with adequate and vigorous management in timely manners will provide significant benefits to both health care system and patients.

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Disclosure of conflict of interest

None.

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