Clinical Analysis of Etiology, Risk Factors and Outcome in Patients with Acute Kidney Injury

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ABSTRACT

Introduction: Acute kidney injury (AKI) is increasingly recognized as a major contributor to adverse outcomes. The sequelae of AKI are severe and characterized by increased risk of short-term and long-term mortality, incident chronic kidney disease (CKD) and accelerated progression to end-stage renal disease (ESRD) (1). The in-hospital mortality rate is approximately 20% to 50%, and may exceed 75% in critically ill patients or patients with sepsis (2).

The rate of renal recovery varies in the literature, possibly because of the lack of a consistent definition for renal recovery (3-7). Some studies (3, 4) reported that recovery rates ranged from 36% to 99%, based on the definition of recovery as dialysis independence at discharge. Furthermore, to reduce the severity and improve recovery from AKI, it is important to identify the underlying cause and risk factors of AKI. Currently, little attention is given to AKI after it resolves in clinical practice throughout the healthcare system. Understanding the impact of AKI on adverse outcomes may identify a segment of patients during hospitalization who are at greater risk of longer-term sequelae.

1. INTRODUCTION

Acute kidney injury (AKI) is increasingly recognized as a major contributor to adverse outcomes. The sequelae of AKI are severe and characterized by increased risk of short-term and long-term mortality, incident chronic kidney disease (CKD) and accelerated progression to end-stage renal disease (ESRD) (1). The in-hospital mortality rate is approximately 20% to 50%, and may exceed 75% in critically ill patients or patients with sepsis (2).

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2. GOAL

The objective of this study was to investigate etiology, clinical characteristics and outcome of AKI patients, as well as to identify risk factors for adverse outcome of renal function and death in these patients hospitalized in tertiary medical centre.

3. MATERIALS AND METHODS

We retrospectively studied a cohort of 84 adult patients with diagnosis of AKI who were admitted to Nephrology Clinic in the University Clinical Centre Sarajevo from July, 2012 to June, 2014. We included all adult patients (>18 years old) with diagnosis of AKI and length of hospital stay more than 24 hours. Patients with ESRD and those who received renal transplantation were excluded from the study. This cohort of survived patients has been followed up for six months after hospital discharge.

All data were collected from medical files of routine patients care in hospital. Demographic informations included age, gender and duration of hospital stay. Relevant laboratory tests were retrieved. Clinical informations included severity, etiology and type of AKI, treatment and outcomes of AKI patients. A
standard algorithm proposed by Quan et al. was used to define the Charlson comorbidity index (CCI) score (5).

AKI was defined as an abrupt (within 48 hours) absolute increase in serum creatinine (SCr) of at least 26.5 μmol/L or by a percentage increase in SCr ≥50% from baseline according to the AKIN criteria (6). The severity of AKI was defined by the AKIN staging criteria. When pre-admission serum creatinine was unavailable, it was estimated by the Modification of Diet in Renal Disease (MDRD) equation, with the assumption of a near lower limit of normal glomerular filtration rate (GFR) of 75 mL/min/1.73 m², as recommended by the Acute Dialysis Quality Initiative (ADQI) Working Group (7). AKI was classified as prerenal, intrinsic and post renal according to the identified etiology. Oliguria was defined as urine output under 400 mL/day, and anuria as urine output under 100 mL/day.

The primary outcome of AKI patients was in-hospital mortality. The outcome of renal function was defined 3 months following discharge by the values of estimated GFR (eGFR) as recovered (eGFR >60 mL/min/1.73 m²) or non-recovered (eGFR <60 mL/min/1.73 m²). This definition of renal function outcome refers only to AKI patients without pre-existing CKD. AKI patients with underlying CKD were considered to have renal function recovery if SCr concentrations fell to the baseline 3 months after discharge. Non-recovery of renal function was defined if SCr remained above the baseline. The secondary outcome was 6 months mortality. The patients alive 6 months after discharge were classified as „survivors”, and those who died as „non-survivors”.

**Statistical analysis**

Normally distributed continuous variables were reported as means with standard deviations and compared by Student’s t-test. Non-normally distributed continuous data were reported as medians with interquartile ranges and compared using Mann-Whitney U-test. When outcome variable was binary or categorical, proportion between two or more groups was assessed by Chi-square test or Fischer’s exact test when there were sparse data. P values less than 0.05 were considered statistically significant.

### 4. RESULTS

A total number of 84 AKI patients (41 females and 43 males) with mean age of 73.5 years met inclusion criteria. Demographic, laboratory and clinical characteristics of patients have been shown in Table 1. Great proportion of AKI patients were non-oliguric (79.8%), while anuria and oliguria were present in 7.1% and 13.1% of AKI patients, respectively. Among the cohort of 84 AKI patients, 6% cases were classified as Stage I, 15.5% cases as Stage II, and 78.5% cases as Stage III. Prerenal and intrinsic type of AKI were similarly represented (45.2% and 42.8%, respectively), while post renal type of AKI proved to be less frequent (12%).

Prevalence of comorbid diseases was 77.4%. The most common comorbid conditions were hypertension (35.7%), diabetes mellitus (28.6%), congestive heart failure (16.6%), chronic liver disease (13.1%) and cancer (11.9%), with average CCI values 6.4±3.05. Pre-existing CKD was present in 45.2% of AKI patients. Conservative treatment was far more frequent than renal replacement therapy.

**Table 1. Characteristics of patients with acute kidney injury.** Data are presented as median and interquartile range or as means and standard deviation (SD); n – number; SCr–serum creatinine; eGFR–estimated glomerular filtration rate; AKIN–Acute Kidney International Network; AKI–acute kidney injury; CKD–chronic kidney disease; CCI–Charlson comorbidity index; RRT – renal replacement therapy

| Characteristics | Values |
|-----------------|--------|
| Male (n, %)     | 43 (51.2) |
| Age (years)     | 73.5 (64-82) |
| Length of hospital stay (days) | 16.5 (10-23) |
| SCR levels (μmol/L) at admission and at discharge | 446 (304-616)/139.5 (99.5-227) |
| eGFR 3 months after discharge | 42 (20.5-60.4) |
| Diuresis | Anuria (n, %) 6 (7.1) |
| Oliguria (n, %) | 11 (13.1) |
| Diuresis >400 mL (n, %) | 67 (79.8) |
| AKIN Stage | Stage I (n, %) 5 (6) |
| Stage II (n, %) | 13 (15.5) |
| Stage III (n, %) | 66 (78.5) |
| Type of AKI | Prerenal (n, %) 38 (45.2) |
| Intrinsic (n, %) | 36 (42.8) |
| Postrenal (n, %) | 10 (12) |
| Pre-existing CKD | Yes/No (n, %) 38 (45.2)/46 (54.8) |
| Hypertension | Yes/No (n, %) 30 (35.7%)/54 (64.3%) |
| Diabetes mellitus | Yes/No (n, %) 24 (28.6%)/60 (71.4%) |
| CCI score | 6.4±3.05 |
| Treatment | RRT/Conservative (n, %) 18 (21.4)/66 (78.6) |
| Renal function recovery | Yes/No (n, %) 41 (48.8%)/43 (51.2%) |
| Intra-hospital mortality | Yes/No (n, %) 9 (10.7%)/75 (89.3%) |
| 6-month mortality | Yes/No (n, %) 28 (37.3%)/47 (62.7%) |
| Total mortality | Yes/No (n, %) 38 (45.2%)/46 (54.8%) |

**Figure 1. Etiology of acute kidney injury**
rejection of replacement therapy (RRT) (78.6% vs. 21.4%). Renal function recovery was present in 48.8% of AKI patients 3 months after discharge. Total mortality rate was 45.2%, with presence of 10.7% of inhospital deaths and 37.3% of deaths 6 months after discharge.

Etiology of AKI in cohort of 84 patients has been presented in Figure 1. The most common causes of AKI were acute interstitial nephritis (AIN) in 16.7%, acute decompensated heart failure (ADHF) in 15.5%, acute gastroenterocolitis (13.1%), and sepsis (12%), while the remaining etiologies participated with less than 10.5%.

The comparison between prevalence of the most common AKI causes according renal function outcome and survival is shown in Table 2. Only septic etiology of AKI has demonstrated statistically significant higher prevalence in deaths compared to survivors (p=0.004).

Greater proportion of AKI patients without pre-existing CKD has recovered renal function (Figure 2) in comparison to those AKI patients who had presumed CKD (60.53% vs. 43.48%; p=0.120). The presence of presumed CKD in AKI patients seemed to have influence on mortality since greater proportion of AKI patients without CKD survived in comparison to those who had underlying CKD (60.87% vs 47.37%), but without statistically significant difference (p=0.216).

By univariate analysis (Table 3), risk factors for poor outcome of renal function in AKI patients were older age (p=0.009) and higher CCI (p=0.000). Protective factor for renal function recovery was higher diuresis (p=0.010). However, risk factors for mortality were increasing age (p=0.0001), higher CCI (p=0.000) and diagnosis of sepsis (p=0.015), while higher diuresis (p=0.047) proved to be a protective factor for mortality.

5. DISCUSSION

Of the 84 AKI patients in our study group, majority of patients were over 70 years of age (mean age 73.5 years) and the most of them were males (51.2%). This is not unexpected since epidemiological data confirm that the median age of patients suffering from AKI is increasing. Male gender is also known to be associated with AKI probably due to more frequent vascular diseases (8).

Majority of patients in our study were classified as Stage III (78.5%) according to AKIN criteria. Cases of AKI in our referral center were mainly associated with CKD (45.2%) with rapid decline in kidney function, which could be explanation for the high prevalence of Stage III in our study. This is consistent with findings of other authors who found a higher prevalence of Stage III in Division of Nephrology in comparison with other Departments of Internal Medicine (2). In our study group prerenal and intrinsic type were detected in 45.2% and 42.8% of AKI patients, respectively, while post renal type of AKI was recognized only in 12% of patients. The prevalence of intrinsic causes was similar to the occurrence of renal causes in the study of Yang et al. (2) while post renal AKI was less frequent.

The main etiological factors of AKI in the present study were AIN (16.7%), ADHF (15.5%), acute gastroenterocolitis (13.1%), and sepsis (12%), followed by severe dehydration (8%), obstructive nephropathy due to the genitourinary cancer (6%) and ATN (6%), with other etiologies prevalence less than 5%. In the PICARD study and BEST Kidney study (9, 10) heart failure and sepsis were among four most common AKI causes which is consistent to our findings. Some authors used extended definitions of renal hypoperfusion (11). Similarly, if we use an extended definition of renal hypoperfusion that includes heart failure and volume depletion due to the gastroenterocolicis and dehydration, prevalence of renal hypoperfusion in our study increases to 36%, which is consistent with the results of Nash et al. (11).

Presence of preexisting CKD was rather high in our study group (45.2%). High proportion of AKI patients suffered from CKD (51%) was found in the study of Pereira et al. too (12). Almost 77.4% of our patients had some kind of comorbid condition. In accordance with recent reports (12), our results confirmed that the most common comorbidities were hypertension (35.7%) and diabetes mellitus (28.6%), followed by congestive heart failure (16.6%), chronic liver disease (13.1%) and cancer (11.9%).

Dialysis was carried out in 21.4% of our AKI patients, which is consistent with the proportion of AKI patients who received RRT (22.5%) in the study of Yang et al. (2). Dialysis requirement in different studies ranged from 12% to 71% (2,13,14).

Recognition that AKI survivors are at high risk of progres-
sive CKD spurred the Kidney Disease Improving Global Outcomes (KDIGO) AKI guidelines to recommend that the kidney function should be evaluated 3 months after an AKI episode to establish the presence and extent of CKD (15), which was done in our study. Renal function recovery was established in 48.8% of cases, which is similar to proportion of patients with renal function recovery in the studies of Pereira and Yang with their associates (50% and 58.6%, respectively) (2, 12). Nevertheless, evaluation of kidney function in these studies was done at hospital discharge that might be too soon due to mentioned KDIGO AKI guidelines (15). Furthermore, definition of renal function recovery was different in all three mentioned studies (included ours), indicating a need for standardization of this definition.

AKI is associated with short and long-term mortality. Undoubtedly, this patient population has a poor short-term outcome with excessive in-hospital mortality rates (40-60%) (16). Total mortality in our cohort group of patients increased from 10.7% at discharge to 45.2% after 6 months of follow up. In-hospital mortality in the study of Schiff et al. (16) increased from 47% at discharge to 65% after 1 year of follow up. All AKI patients included in the study of Schiff et al. had ATN as cause of AKI, RIFLE class Failure and they all underwent RRT. This might be the reason why the in-hospital mortality rate is higher compared to our results. A large Danish study (17) has shown that mortality was the most important during the first 50 days after admission to ICU. Our results have also shown great increase of mortality for AKI survivors after 6 months of follow up, which can be related to great severity of AKI with high burden of comorbid conditions and rather older age of study group.

The previous conventional opinion that survivors of AKI tend to do well and fully recover renal function appears to be flawed. AKI can cause ESRD directly, and increase the risk of developing incident CKD and worsening of underlying CKD (18). In accordance with previous reports (19,20), we have also found that greater proportion of AKI patients with pre-existing CKD had impaired recovery of renal function in comparison to the patients with “pure” AKI (56.52% vs. 39.47%), but without statistically importance. Presence of CKD is also known to be a significant risk factor for the development of cardiovascular diseases from which this CKD population of patients often dies (12). However, our results showed that presence of pre-sumed CKD was similar in the survivors and non-survivors groups (47.36% vs. 52.63%) which is consistent with published researches (12, 20).

Our findings revealed that risk factors for non-recovery of renal function were advanced age and higher CCI, while protective factor for renal function outcome was higher diuresis. Other authors identified older age, the presence of diabetes mellitus, decreased baseline eGFR (21), or higher CCI score (22) as risk factors for the progression to advanced-stage CKD in AKI survivors which is similar to our results. The risk factors for mortality in present study were diagnosis of sepsis as well as increasing age and higher CCI score, while protective factor was higher diuresis. In the previously published studies (8,14) sepsis and oliguria were found to be associated with mortality which is in accordance with our findings. Similarly to our findings, Harel et al. (22), found that increasing age and higher CCI were predictive of post-AKI mortality.

Sepsis is the most common cause of AKI in ICU (14). Recent evidence suggests that AKI in patients with sepsis may have different pathophysiology including hyperemia, vasodilatation, and acute tubular apoptosis instead of ischemia, vasoconstriction, or acute tubular necrosis (23). The mortality of sepsis induced AKI is more than 70% (14). Our findings suggest that septic cause of AKI is statistically significantly more common in non-survivors compared to survivors, as well as that sepsis is risk factor for death in AKI patients.

6. CONCLUSION

Elderly patients with high burden of comorbidities who experience severe AKI episode and especially those with sepsis as AKI etiology are with high risk for adverse outcome of renal function and death. These observations highlight the importance of close monitoring high-risk hospital AKI patients. The CCI score is a validated method for estimating the risk of death from comorbid disease but it also seemed to be a good tool in predicting adverse renal function outcome.

CONFLICT OF INTEREST: NONE DECLARED.

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Association of Nephrology, Dialysis and Transplantation of Bosnia and Herzegovina has precipitants of acute kidney injury such as sepsis, congestive heart failure, higher age and disease. Contributors to the growth of acute kidney injury include increases in the known mortality, incident chronic kidney disease and accelerated progression to end-stage renal international participation that will be held in Sarajevo from 22nd to 25th April 2015. The should be an important health strategy for the patient and the community. but preventable and treatable syndrome. Protecting the kidneys from acute kidney injury is needed in order to reduce the severity and improve recovery of this harmful, as well as many distinguished international speakers will certainly contribute to the chronic kidney disease, cardiovascular diseases, hypertension, diabetes mellitus, dialysis and many other diseases. This scientific meeting covers the most recent discoveries in the fields of acute kidney injury, nephrology (ISN), dialysis and transplantation association (ERA-EDTA) and the international society of nephrology (NEFROINT). Distributions of pre-existing comorbidities on long-term mortality after acute kidney injury, PLoS One. 2012; 7(10): e47746.

Rapid increases in the incidence of acute kidney injury have been reported, highlighting a key cause of death and disability. Since the prevalence of chronic kidney disease is higher in older people, the health impact of population aging will depend in part on how the kidney comorbidity burden of patients. Identification of the underlying cause and risk factors of acute kidney injury is needed in order to reduce the severity and improve recovery of this harmful, as well as many distinguished international speakers will certainly contribute to the chronic kidney disease, cardiovascular diseases, hypertension, diabetes mellitus, dialysis and many other diseases. This scientific meeting covers the most recent discoveries in the fields of acute kidney injury, nephrology (ISN), dialysis and transplantation association (ERA-EDTA) and the international society of nephrology (NEFROINT). Distributions of pre-existing comorbidities on long-term mortality after acute kidney injury, PLoS One. 2012; 7(10): e47746.

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