Journal of Multidisciplinary Healthcare

Dovepress
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ORIGINAL RESEARCH

Acute Kidney Injury Among Patients with Multi-Drug Resistant Infection: A Study from Jordan

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Background: Acute kidney injury (AKI) is a well-known complication for hospitalized patients. Sepsis and various infections play a significant role in increasing the incidence of AKI. The present study evaluated the risk for Multidrug-resistant (MDR) infections and its effect on the incidence of AKI, hospitalization, need for dialysis, and mortality.

Methods: In a retrospective study design, data were collected from all adult patients with a positive multi-drug resistant culture who were admitted to King Abdullah University Hospital (KAUH). Records of 436 patients were reviewed between January 2017 – December 2018 with at least one year of follow-up.

Results: The mean age was 57.3 years (SD± 23.1), and 58.5% were males. The most common source of positive cultures was sputum, with 50% positive cultures. The incidence of AKI was 59.2%. The most isolated microorganism was *Acinetobacter baumannii* (76.8%), followed by *Pseudomonas aeruginosa* (14.9%).On multivariate analysis, age (OR 1.1, 95% CI 1.1–1.2, P=0.001), HTN (OR 1.8, 95% CI 1.0–3.3, P=0.02), DM (OR 1.1, 95% CI 0.6–1.9, P=0.69) and the use of Foley catheter on chronic bases (OR 4.3, 95% CI 2.6–6.8, P<0.0001) were strong predictors of AKI. Among patients with AKI, 74.4% died compared to 44.4% among non-AKI patients (p<0.001).

Conclusion: In patients with MDR, AKI incidence, hospitalization, and mortality were high. Early detection and addressing the problem may decrease bad outcomes, and health education for reducing antibiotic abuse is needed to lower MDR.

Keywords: infection, multi-drug resistant, mortality, acute kidney injury

Introduction

The rapid emergence of antibiotic resistance in pathogenic microbes is becoming an imminent global public health problem. Wide-spread multidrug-resistant (MDR) infections, especially in hospitalized patients, may complicate the course of the disease and increase the risk of complications. The rise in the incidence of AKI is another serious problem in hospitalized and ICU patients leading to increased hospitalization, the need for renal replacement therapy (RRT), mortality, and long-term morbidity.[1,2]

The main risk for MDR is emerging from the overuse of antibiotics in sick hospitalized patients and healthy people in the community. *Klebsiella pneumonia, Pseudomonas aeruginosa, Escherichia coli, and Acinetobacter baumannii* make up the majority of Gram-negative hospital-acquired infections in the U.S.[3] AKI causes include the virulence of MDR bacteria, the associated development of sepsis, and the antibiotic combinations used for the treatment of AKI, especially in the ICU settings. AKI can be classified through different criteria,[4,5] and the incidence can be as low as 2% to as high as 92% in hospitalized patients.[6] Identifying risk factors and patients at risk for AKI related to MDR infection will help treating physicians develop preventive and treatment protocols for AKI and may lower mortality in those patients. Therefore, in the present study, the risk for Multidrug-resistant (MDR) infections and its effect on the incidence of AKI, hospitalization, need for dialysis, and mortality was evaluated.

Received: 3 August 2022
Accepted: 29 November 2022
Published: 5 December 2022

Methods

Patient Selection and Data Collection

This was a retrospective study where data was collected from all adult patients with a positive multi-drug resistant culture who were admitted to the hospital - King Abdullah University Hospital (KAUH), a 650-bed, 20 medical ICU beds, urban academic tertiary referral hospital that serves five provinces in the north of Jordan. The medical records for all patients admitted to general floors or the intensive care units between January 2017 – December 2018, with at least one-year follow-up, were reviewed. One admission was analyzed, the first admission, if the patient had more than one admission. The study was approved by the institutional review board at Jordan University of Science and Technology and King Abdullah University Hospital. Due to the retrospective study design and the expected high mortality rate among patients enrolled, the IRB agreed to waive informed consent for this study.

Demographic data, including age, gender, comorbidities, the cause of admission, medications, laboratory data, and length of ICU stay, were extracted from patients' electronic records. The AKIN classification was used to define and stage AKI. The Chronic Kidney Disease Epidemiology (CKD - EPI) equation was used to estimate Glomerular Filtration Rate (eGFR). Chronic kidney disease is an eGFR of less than 60 mL/min. Records of 436 patients with multidrug-resistant were reviewed, and 14 patients were excluded for being on regular hemodialysis.

Statistical Analysis

Data analysis was performed using Stata/SE, version 14.2 (StataCorp, College Station, TX). Patients were divided into two groups: patients with and patients without AKI. For continuous variables, the mean, the standard deviation (± SD), and the minimum and maximum were used, unpaired *t*-test was used to compare differences between normally distributed values. Percentages were used to express categorical variables. Mann–Whitney *U*-test was used to compare nonparametric groups when data were not normally distributed. Pearson Chi-square for categorical variables. To determine the independent predictors of AKI, univariate and multivariate regression analyses were performed based on significant factors in univariate analysis and those considered clinically significant by consultant nephrologist nephrologists. Finally, Kaplan–Meier survival analysis was performed to assess mortality outcomes. A p-value of < 0.05 was considered statistically significant.

Results

The mean age for the patients was 57.3 years (SD± 23.1), where 58.5% were males. Table 1 describes their baseline characteristics. The incidence of AKI was 59.2%, and most were in stage 3 AKI (41%) (Figure 1). The mean arterial pressure (MAP) on admission was 82.5 mmHg (SD± 38.3) for the AKI group and 75.9 mmHg (SD± 38.0) for the group without AKI (P=0.08). Of patients who developed AKI, 3.8% were started on hemodialysis.

The mean eGFR on admission was 115 mL/min (SD±75.3) for all patients and 96.8 mL/min (SD± 66.6) for the AKI group vs 140.9 mL/min (SD±88.2) for the other group (P<0.01). The mean eGFR on the last follow-up was 70.9 mL/min (SD±51.8) for all patients and 50.1 mL/min (SD±43.8) for the AKI group vs 100.5 mL/min (SD±47.8) for the non-AKI group (P< 0.001) (Figure 2). The most common cause for admission was neurological disorders (24.2%), followed by pneumonia (19, infected diabetic foot (6.9%), urinary tract infection (5.7%), and malignancy-related issues (5.9%).

The most common source of positive culture was sputum culture (50%), followed by wound culture (22.2%), urine culture (13.8%), blood culture (10.0%), others (4%; tip of central line 1%, pleural fluid culture 1%, ear culture 1%, peritoneal fluid culture 0.5%, cerebrospinal fluid culture 0.5%). The most commonly isolated microorganism was *Acinetobacter baumannii* (76.8%), followed by *Pseudomonas aeruginosa* (14.9%), *Proteus mirabilis* (2.8%), *Stenotrophomonas maltophilia* (2.4%), *Morganella morganii* (0.95%), *Serratia marcescens* (0.7%), *Enterobacter cloacae* (0.7%), *Achromobacter* species, *Achromobacter xylosoxidans, Acinetobacter anitratus*; 0.24% for each one (Figure 3).

Based on culture results, the commonly prescribed antibiotics were the combination of carbapenem and Colistin (79.5%), aminoglycosides and colistin (4.7%), aminoglycosides, and carbapenems (2.5%). As a monotherapy, piperacillin-tazobactam was the most likely to be used (8.5%), followed by carbapenems alone (3.6%). Using univariate analysis, increased age (P<0.001), hypertension (HTN) (P=0.001), diabetes mellitus (DM) (p=0.08) and being on chronic

Table 1 Baseline Characteristics Based on AKI Status

Variable	AKI		P value
	YES	NO	
Age, mean (± SD)	61.0 (±SD 20.6)	50.9 (±SD 25.4)	0.0001
Gender n (%)			
Male	148 (59.2%)	102 (40.8%)	0.98
Female	102 (59.3%)	70 (40.7%)	
Comorbidities n (%)			
Diabetes mellitus	101 (63.9%)	57 (36.1%)	0.084
Hypertension	131 (68.2%)	61 (31.8%)	0.001
Renal disease	37 (16.7%)	16 (10.3%)	0.27
Cancer	17 (26.6%)	47 (73.4%)	0.83
Drugs n (%)			
Angiotensin converting enzyme inhibitors/ Angiotensin II receptor blockers	43 (62.3%)	26 (37.7%)	0.47
Chemotherapy	12 (50%)	12 (50%)	0.48

use of Foley's catheter (P <0.001) were predictors for AKI. On multivariate analysis, age (OR 1.1, 95% CI 1.1–1.2, P=0.001), HTN (OR 1.8, 95% CI 1.0–3.3, P=0.02), DM (OR 1.1, 95% CI 0.6–1.9, P=0.69), and the use of Foley catheter on chronic bases (OR 4.3, 95% CI 2.6–6.8, P<0.0001) were strong predictors for AKI. The overall mean time to discharge was 44.7 days (SD± 24); 40.6 days (SD± 46.2) for AKI vs 50.5 days (SD± 7184.8) for non-AKI patients (p<0.42). Of the discharged patients, 44.5% were re-admitted to the hospital with another infection, where the overall mean time for re-admission was 143.6 days (SD± 206.9); 102 days (SD± 123.5) for the AKI group and 178.3 days (SD± 252.8) for the non-AKI group (P=0.08). The overall average admissions were 1.1 (SD± 3.3); 0.7 (SD± 2) admissions for

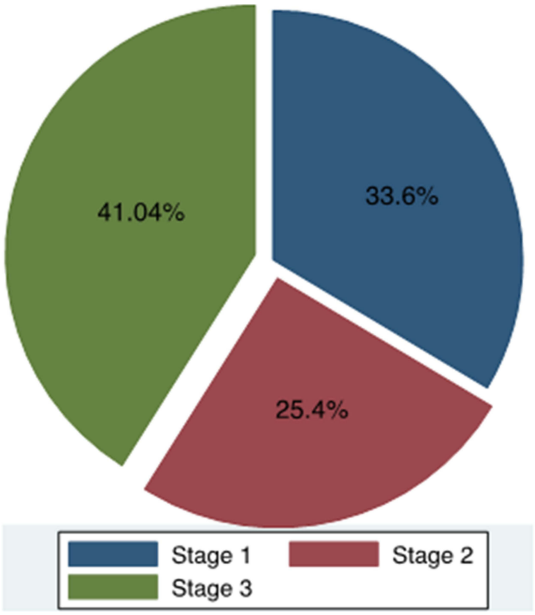

Figure 1 Acute kidney injury (AKI) stage based on Acute Kidney Injury Network (AKIN) classification.

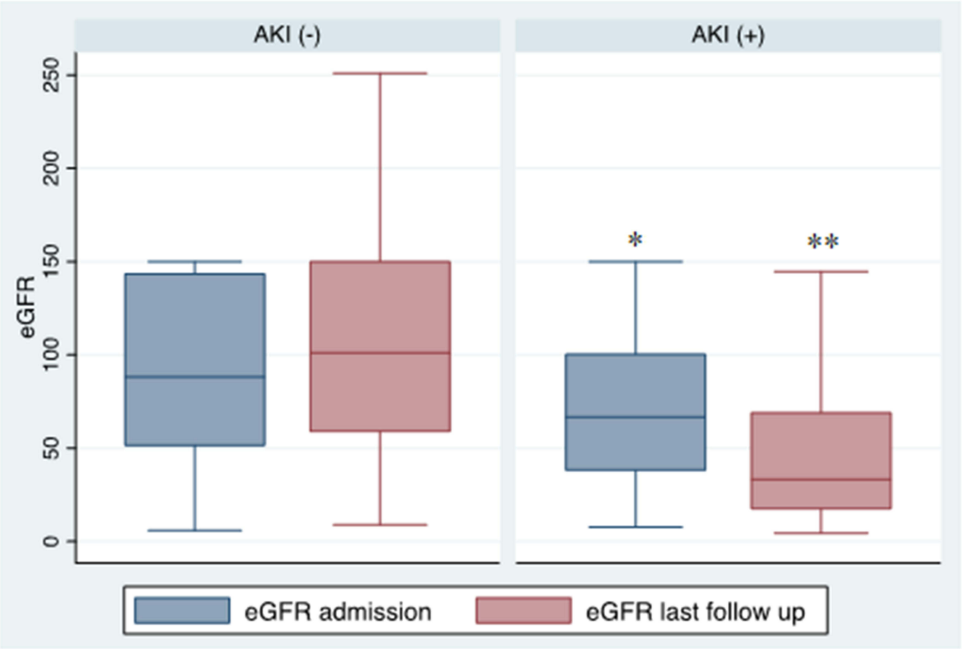

Figure 2 eGFR based on AKI status on admission and at the last follow-up time.

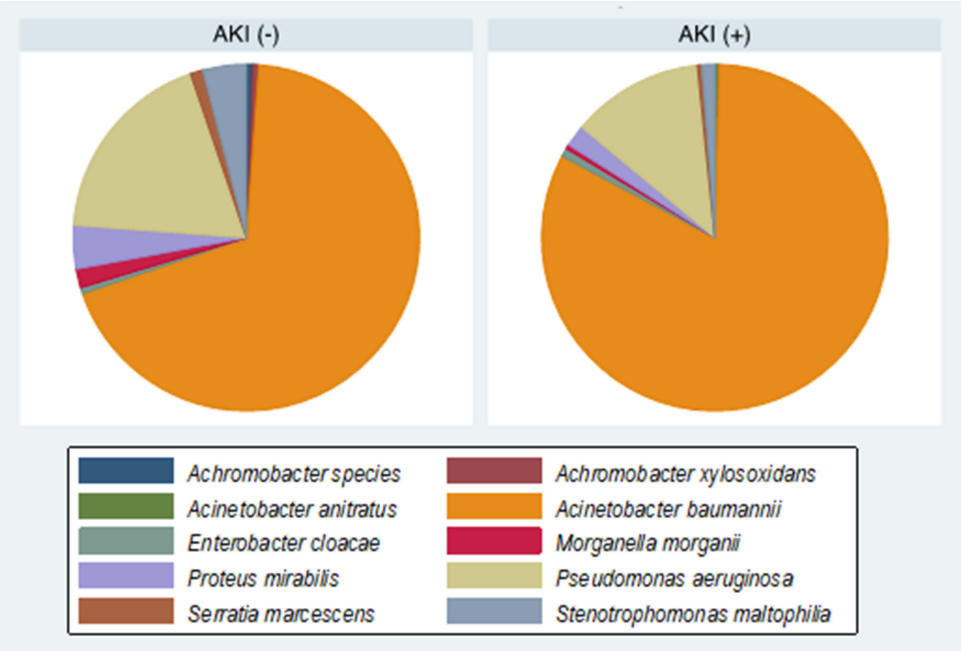

Figure 3 Pie chart showing isolated microorganisms based on AKI status.

the AKI group vs 1.7 (SD± 4.4) for the non-AKI group (P=0.004). The overall mean time to ICU transfer was 3.6 days (SD± 9.9), 3.8 days (SD± 10) for the AKI group vs 3.3 (SD± 9.8) for the non-AKI group (p=0.066). Of patients with AKI, 75.2% were transferred to ICU compared to 54.6% of the other group (P=0.001).

When evaluating the overall mortality, 62.2% died during their admission to the hospital (Figure 4). Among patients with AKI, 74.4% died compared to 44.4% (p<0.001). For the overall ICU mortality, 79% of ICU admissions died; 86.7% for the AKI group vs 63.4% for the other group (p<0.001). The mortality rate among patients who started on

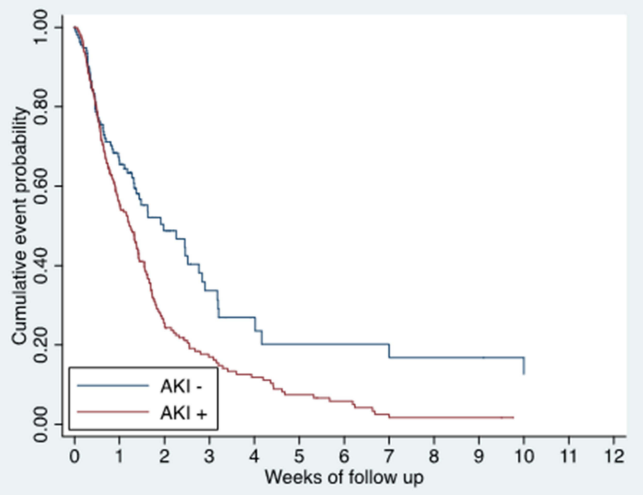

Figure 4 KM survival curve based on AKI status.

hemodialysis was 77.8%. The overall mean time to death was 48.8 days (SD± 128.4), 44.4 (SD± 46.5) for the group with AKI vs 55 days (SD±192.2) for the group without AKI (p= 0.42).

Discussion

AKI is a known health problem, with the incidence in hospitalized patients from 7% to 30% and even more in ICU patients. Different classifications are found based on the rise in serum creatinine or change in urine output, such as Acute Kidney Injury Network (AKIN), risk, injury, failure, loss, end-stage kidney disease (RIFLE), Kidney Disease: Improving Global Outcomes (KDIGO).[4,5] Both direct effects of infection in the body and the broad spectrum antibiotics to cover primary virulent organisms in septic patients will contribute to the patient's outcome. The present study investigated the effect of infection with MDR organisms on hospitalized patients' outcomes, such as AKI, hospitalization time, need for dialysis, and mortality. All patients were included after having a multidrug-resistant positive culture from sputum, wound, or urine cultures.

The age difference between the two groups (AKI vs non-AKI) was at least 10 years, which is clinically and statistically significant. Increased age is one of the known risk factors for AKI. This can be in part due to physiological changes in the kidneys.[7] In addition, the burden of co-morbidities and exposure to nephrotoxic medications increases with age.[8,9] The risk for AKI was shown to be higher among octogenarians and nonagenarians.[10,11]

Gender is suggested to increase the risk for AKI regardless of other co-morbidities, where males are at higher risk to get AKI as per Loutradis et al group,[12] In the present study, the number of males with AKI males' number was slightly higher than females. In addition, patients with hypertension were more likely to have AKI than others. Hypertension is a risk factor for the progression of renal dysfunction, especially in the presence of nephrotoxic substances like the contrast.[13] Other risk factors, including cardiovascular disease, chronic liver disease, nephrotoxic drugs such as antibiotics, sepsis, and being an ICU patient, increase AKI and 28 days mortality.[14] Also, chronic use of Foley's catheter mainly due to chronic bladder outlet obstruction increases the chance for AKI.[15,16]

A more severe disease course is expected with AKI, which can contribute to ICU admissions and transfers. The incidence of AKI in the ICU varies between 2.5% and 92%. In the Jordanian population, it reached up to 31.6%.[6] Factors that affect the outcome of these patients with AKI in ICU settings include volume overload, sepsis, and the need for RRT. All of which can increase the hospital stay, the recurrence of AKI, the development of chronic kidney disease (CKD), and the rate of in-hospital mortality.[17–20]

In the present cohort, more than 75% of patients with AKI were transferred to the ICU, and 79% of these patients died, whereas 86% of dead patients suffered from AKI. Using RRT contributed to the death of 77.8% of patients with AKI admitted to the ICU. Sepsis and AKI combined with ICU admission not only increased in-hospital mortality but also increased the risk for 28 and 90 days mortality.[21] This was obvious in the present study when comparing the time to death in the AKI group vs the

Non-AKI group (44.4 vs 55 days). The severity of AKI impacts the rate of renal recovery, future development of CKD, and a drop in eGFR.[22] Most patients in the present study had severe AKI (41% stage 3), which resulted in a difference in the eGFR on follow-up between AKI vs non-AKI group (Figure 2).

Most patients with MDR in the current cohort had infections with Gram-negative Bacilli. This is similar to another study done in the middle east area.[23] Certain factors increase the risk of bacteremia with Gram-negative bacteria, such as hemodialysis, intravascular devices, extended-spectrum β-lactamase, and carbapenemase-producing organism.[24,25] Other risk factors for having MDR include previous use of antibiotics and comorbidities such as chronic obstructive lung disease, chronic liver disease, cerebral vascular accidents, and encephalopathy. Prior infection with MDR, hospitalization within the last few months, number of admissions, interventions during admissions, transfer to ICU, and being a kidney transplant patient all increase the risk for MDR.[26–29] Different stages of chronic kidney disease (CKD), as shown by Guobin et al, will increase the risk for MDR.[30] Lastly, emerging resistant genes in bacteria contributed to increased incidence of MDR.[31–33] Additionally, using new antibiotics and combinations of antibiotics in MDR will increase AKI and nephrotoxicity.[34–38] It is worth mentioning that the abuse of antibiotics in healthy individuals can increase the risk of MDR in the community.[39,40] Many other risk factors were identified to increase the incidence of MDR even in people as carriers, such as travel history to areas endemic with MDR, health occupations, comorbidities including DM and inflammatory bowel disease, immunosuppressive drugs and chemotherapy, AIDS, cystic fibrosis and extreme of ages.[41–44] Nowadays, worldwide measures are taken to decrease the risk for MDR.[45,46]

In the present study, most of the isolates with MDR were *Acinetobacter baumannii*, which can present into three distinct clinical entities.[47] Most isolates of *Acinetobacter baumannii* have MDR, as showed in a large study including 1861 isolates and showed more than 70% chance of MDR in these isolations.[48] This kind of infection has a high risk of mortality, as was found in a cohort of 102 patients from china, in this cohort mortality was around 29%.[49] The mortality in the present study was above 60%, mainly in the AKI group. Other organisms, including *Pseudomonas aeruginosa, Klebsiella, Enterobacter, Enterococcus*, and coagulase-negative *staphylococcus*, are common microorganisms, especially in the ICU admitted patients.[50]

Limitations

This was a single-center study with a short period and a retrospective design; we hope to do a new study with a prospective design including more centers from northern, middle, and southern Jordan to get data that can be universal to our country and compare this data with neighboring countries and the rest of the word. We also would like to include more transplant patients and have the chance to compare between patients with AKI, CKD and renal transplant regarding outcomes after having MDR and get our recommendations to the most common MRD infections in Jordan accordingly.

Conclusion

MDR is a serious health problem in both healthy and hospitalized patients. Risk for re-hospitalization and mortality increased with MDR, especially in ICU-admitted patients.

Identifying risk factors for MDR will decrease both morbidity and mortality. Further health education to prevent antibiotic abuse may reduce the community carrying of MDR bacteria and improve the survival and outcome of patients.

We would advise our colleagues, especially those who are taking care of ICU patients, to have a lower threshold to identify patients with MDR as soon as possible, which will decrease the chance for AKI, and mortality and prevent future pandemic clusters in hospitalized patients and patients in ICU through initiating solid protocols to avoid and reduce MRD.

Ethics and Patient Consent

Institutional approval was obtained from the Institutional Review Board at King Abdullah University Hospital, Internal IRB number 489/2020. This study was conducted by the Declaration of Helsinki and all its amendments. Patients' data confidentiality was ensured as per international standards. Due to the retrospective study design and the expected high mortality rate among patients enrolled, the IRB agreed to waive informed consent for this study.

Acknowledgment

We would like to thank Jordan University of Science and Technology / Deanship of Research for their continuous support.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors report no competing interests in this work.

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