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# Risk Factors of Acute Kidney Injury in Patients with Sepsis; A Cross-Sectional Study

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## *Abstract*

**Background and Objective:** Due to the importance of acute kidney injury associated in patients with sepsis and the impact of various factors on mortality and hospital stay of these patients, this study was conducted to investigate the clinical features and risk factors for acute kidney injury in patients with sepsis. In addition, we examined whether the severity of acute kidney injury affected clinical outcomes.

**Methods:** This was a cross-sectional study performed on patients admitted with sepsis in Firoozgar Hospital between 2018 and 2020. Patients were divided into two groups, those with and without acute kidney injury, to compare baseline and laboratory characteristics.

**Results:** In total, 380 patients entered. Acute kidney injury (AKI) occurred in 41.1% of patients with sepsis. Analysis of multivariate logistic regression showed that the risk of acute kidney injury significantly was associated with older age, history of ischemic heart disease, hypertension and diabetes, smoking and drug abuse, use of ACEI and ARB medications, presence of bacteremia, presence of tissue infection as sepsis etiology, low serum albumin, and high AST levels, delayed antibiotic and fluid therapy, and vasopressor administration. Hospital mortality and length of hospital stay were higher in the AKI group.

**Conclusion:** Septic AKI had a negative effect on clinical outcomes. Also, the severity of acute kidney injury was associated with increased short-term mortality, length of hospital stay, and the need for dialysis.

**Keywords:** Acute kidney injury, Sepsis, Risk factors, Mortality

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مقالهٔ پژوهشی

# بررسی عوامل خطر آسیب کلیوی حاد در بیماران مبتلا به سپسیس:یک مطالعه توصیفی مقطعی

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برای دانلود این مقاله، کد زیر را با موبایل خود اسکن کنید.

## چکیده

**زمینه و هدف:** با توجه به اهمیت آسیب حاد کلیه در ارتباط با بیماران مبتلا به سپسیس و تأثیر عوامل مختلف بر مرگ‌ومیر و بستری شدن در این بیماران، این مطالعه با هدف بررسی خصوصیات بالینی و عوامل خطر آسیب حاد کلیه در بیماران مبتلا به سپسیس انجام شد. علاوه بر این، ما بررسی کردیم که آیا شدت آسیب حاد کلیه بر نتایج بالینی تأثیر دارد یا خیر.

**مواد و روش‌ها:** این مطالعه‌ای توصیفی-مقطعی است که بر روی بیماران مراجعه‌کننده با تشخیص سپسیس در بیمارستان فیروزگر بین سال‌های ۱۳۹۶ تا ۱۳۹۸ انجام شده است. بیماران برای مقایسه ویژگی‌های پایه و آزمایشگاه به دو گروه با و بدون آسیب حاد کلیه تقسیم شدند.

**یافته‌ها:** درمجموع ۳۸۰ بیمار وارد مطالعه شدند. آسیب حاد کلیه در ۴۱/۱٪ از بیماران مبتلا به سپسیس رخ داده است. رگرسیون لجستیک نشان داد که خطر آسیب حاد کلیه با سن بالاتر، سابقهٔ بیماری ایسکمیک قلب، فشار خون بالا و دیابت، استعمال سیگار و سوء مصرف مواد مخدر، استفاده از ACEI و ARB، وجود باکتریمی، وجود عفونت بافتی به‌عنوان علت سپسیس، آلبومین سرم پایین و مقادیر بالای AST، تأخیر در درمان آنتی‌بیوتیک و مایعات و تجویز وازوپرسور وابسته است. میزان مرگ و میر بیمارستان و مدت زمان بستری در بیمارستان در گروه AKI بیشتر بود.

**نتیجه‌گیری:** نارسایی حاد کلیه به‌علت سپسیس تأثیر منفی بر نتایج بالینی دارد. به‌علاوه، شدت آسیب حاد کلیه با افزایش مرگ‌ومیر کوتاه مدت، طول مدت بستری در بیمارستان و نیاز به دیالیز همراه بود.

**کلمات کلیدی:** نارسایی حاد کلیه، سپسیس، ریسک فاکتور، مرگ‌ومیر

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## Introduction

Acute kidney damage or acute renal failure is defined as a sudden decrease in renal filtration function. This condition is usually characterized by an increase in serum creatinine or azotemia (an increase in blood urea nitrogen concentration). Acute renal impairment may be classified into three general categories as prerenal, intrinsic or post-renal (1-3).

Cardiovascular complications (e.g., heart failure, myocardial infarction, arrhythmia, cardiac arrest) have been reported in 35% of patients with acute renal failure. Fluid overload, secondary to acute oliguric kidney damage, is a particular risk for elderly patients with limited cardiac functional reserve. Conversely acute renal impairment can also be a complication of heart disease such as endocarditis, compensated heart failure, or embolic atrial fibrillation (4-6). Pulmonary complications have been reported in approximately 54% of patients with acute renal impairment and is the most important risk factor for death in patients with acute renal impairment (7-9). Neurological consequences include lethargy, drowsiness, reversal of the

sleep-wake cycle, and cognitive impairment or memory impairment (10, 11).

Acute renal impairment associated with sepsis has a significantly higher mortality rate than patients with acute non-septic renal impairment according to the literature. Acute kidney damage is a recurrent and serious complication of sepsis in patients in the intensive care unit, especially in the elderly group (12-14). Sepsis is the most common cause of acute kidney damage in critically ill patients. Acute renal failure associated with sepsis is associated with worsen disease course and increased risk of death and hospital stay compared to non-sepsis-related acute kidney damage. Sepsis is responsible for 26 to 50 percent of acute kidney injuries in developed countries, compared to 7-10 percent of acute kidney injuries (AKI) caused by primary kidney diseases (15-17).

Although septic shock is one of the main causes of AKI, the exact underlying mechanisms are not entirely clear. Despite extensive research and advances, prevalence and mortality of sepsis associated with AKI have remained unacceptably high (18). The pathophysiology of AKI in sepsis is complex and multifactorial, and includes intra-tubal hemodynamic changes, endothelial dysfunction, infiltration of inflammatory cells in renal parenchyma, intracellular thromboembolism, and blockage of tubules by necrotic cells and debris (19-21).

Interleukin-18 (IL-18) excretion is more in acute septic kidney damage compared to non-septic kidney injury (22, 23). In addition, elevated IL-18 levels predict a worsening of renal function approximately 24 to 48 hours before a significant clinical renal impairment. A new study showed that patients with acute septic renal impairment had higher urine and plasma neutrophil gelatinase–associated lipocalin (NGAL) compared to non-septic renal failure patients (24). The use of these markers and other new biomarkers such as cystatin C, liver fatty acid–binding protein and neutrino-1 is very encouraging for the early detection of acute renal failure caused by sepsis and may have prognostic values.

The aim of this study was to assess the risk factors of developing AKI during sepsis for the treatment and prognosis of such patients.

## Methods & Materials

In this cross-sectional study, patients who were diagnosed with sepsis, were monitored regarding any evidence in favor of acute kidney injury according to the RIFLE criteria (risk (class R), injury (class I) and failure (class F)). Simple convenience sampling was used. Patients' demographic characteristics, laboratory data and sepsis underlying causes were recorded. Also, the time interval from the initiation of antibiotics or fluid therapy to the onset of infection symptoms, receiving vasopressors during, number of hospital days, need for dialysis and whether acute renal impairment has occurred in the first 24 hours were recorded. After that, patients were followed for 1 month and morbidities and mortalities were recorded.

Exclusion criteria were age below 18 years, chronic renal failure, hemodialysis patients, using nephrotoxic medicines, organ transplantation, obstructive nephropathies or those who did not consent for enrolment.

All patients signed a written informed consent. All the study steps were performed in accordance to the declaration of Helsinki. Ethics committee of Iran University of Medical Sciences approved the study.

Data was analyzed using SPSS 16 (SPSS Inc., Chicago, Illinois, USA). For descriptive analysis, percentage and frequency, mean and standard deviation were used. Kolmogorov-Smirnov was used to check data normality. Chi-square, Independent T-test or ANOVA or their non-parametrics counterparts were used. P-value below 0.05 was considered as statistically significant.

## Results

In total, 380 patients entered the study. Of the psamples, 212 (55.8%) were males and 168 females (44.2%). Mean ± SD of body mass index (BMI) was 25.11 ± 3.90 kg/m2. The mean hospital stay was 14.31 ± 4.34 days (minimum and maximum of 7 and 30 days, respectively). Baseline characteristics of participants in the two groups of with and without AKI are presented in Table 1.

Table 1. Baseline characteristics of participants in the two groups of with and without AKI

| Variable | All participants | AKI group | Non-AKI group | P-value |
|---|---|---|---|---|
| BMI, kg/m2 | 25.11 ± 3.90 | 4.12 ± 25.06 | 3.74 ± 25.15 | 638.0 |
| **Age group (yr), Percentage** | | | | |
| 18-29 | 16 (4.2%) | 0 | 16 (7.1%) | <001.0 |
| 30-49 | 44 (11.6%) | 8 (5.1%) | 36 (16.1%) | |
| 50-59 | 60 (15.8%) | 28 (17.9%) | 32 (14.3%) | |
| 60-69 | 156 (41.1%) | 60 (38.5%) | 96 (42.9%) | |
| 70-80 | 104 (27.4%) | 60 (38.5%) | 44 (19.6%) | |

| | | | | |
|---|---|---|---|---|
| Gender | | | | |
| Male | 168 (44.2%) | 72 (46.2%) | 96 (42.9%) | 524.0 |
| Female | 212 (55.8%) | 84 (35.9%) | 128 (57.1%) | |
| Smoking, percentage | 96 (25.3%) | 35.9 (56%) | 40 (17.9%) | <001.0 |
| Alcohol consumption, percentage | 12 (3.2%) | 8 (5.1%) | 4 (1.8%) | 067.0 |
| Past medical history | | | | |
| IHD | 104 (27.4%) | 64 (41%) | 40 (17.9%) | <001.0 |
| HTN | 168 (44.2%) | 88 (56.4%) | 80 (35.7%) | <001.0 |
| Diabetes | 92 (24.2%) | 48 (30.8%) | 44 (19.6%) | <001.0 |
| Asthma and COPD | 76 (20%) | 36 (23.1%) | 70 (17.9%) | 211.0 |
| Malignancy | 36 (9.5%) | 12 (7.7%) | 26 (10.7%) | 322.0 |
| Connective tissue disease | 32 (8.4%) | 16 (10.3%) | 16 (7.1%) | 282.0 |
| CHF | 28 (7.4%) | 16 (10.3%) | 12 (5.4%) | 072.0 |
| Neurologic disorders | 88 (23.2%) | 24 (15.4%) | 64 (28.6%) | <001.0 |
| Drug history | | | | |
| NSAIDs | 112 (29.5%) | 52 (33.3%) | 60 (26.8%) | 0.168 |
| ACEs or ARBs | 116 (30.5%) | 72 (46.2%) | 44 (19.6%) | 0.001< |
| Aminoglycosides | 4 (1.1%) | 0 | 4 (1.8%) | 0.119 |
| Radiologic contrasts | 40 (10.5%) | 12 (7.7%) | 28 (12.5%) | 0.133 |
| Herbal medicines | 20 (5.3%) | 8 (5.1%) | 12 (5.4%) | 0.922 |

Of 380 patients, 156 patients (41.1%) developed AKI. Based on the RIFLE criterion, 51.3% (80 patients) developed AKI stage 1, 30.8% (48) stage 2 and 17.9% (28) stage 3. The mortality rate in this study was 11.6% (44).

A study of the correlation between age groups and the incidence of AKI showed a significant statistical relationship (*P*=0.001), so that in older age groups, the incidence of AKI was higher than younger ones. Those aged 70 years or older had the greatest risk for developing AKI following sepsis. In the age groups over 60 years, the incidence of stage III AKI was higher than expected, and the incidence of stage II AKI was higher in those older than 70 years, with a statistically significant difference (*P*=0.001). Figure 1 shows the association between the grade of AKI and the age groups.

No statistical significant difference was found between gender and developing AKI (*P*=0.524), however, higher stages of AKI were more seen in men, and vice versa in women, AKI was more in lower stages (*P*=0.001). Body mass index had no difference between patients with and without AKI (*P*=0.638).

There was a significant association between the history of ischemic heart disease, hypertension, diabetes, neurological diseases, smoking and drug use with the incidence of AKI (*P*=0.001). However, there was no significant associations between pulmonary diseases (*P*=0.211), malignancy history (*P*=0.322), connective tissue diseases (*P*=0.282), congestive heart disease (*P*=0.072) and alcohol consumption (*P*=0.067) and the incidence of AKI.

There was a significant association between the use of ACE and ARB inhibitors with the occurrence of AKI, so that this rate was higher in the group of users of these drugs (*P*=0.001). On the other hand, no significant association was found between the use of NSAIDs (*P*=0.168), aminoglycosides (*P*=0.119), radiopharmaceuticals (*P*=0.133), herbal drugs (*P*=0.922) and developing AKI. However, there was no significant association between ACE and ARB inhibitors and AKI severity (*P* =0.122). However, there was no significant association between the use of ACE and ARB inhibitors and AKI stage (*P*=0.122). A summary of laboratory and clinical findings in patients with and without developing AKI is depicted in Table 2.

However, there was a significant statistical association between soft tissue infection as the source of sepsis and developing AKI (*P*=0.001). The results showed that the incidence of AKI was higher than expected if antibiotics and fluid therapy were started with a delay or vasopressors were prescribed (*P*=0.001). Mortality rate was significantly higher in patients who developed AKI (*P*=0.001). Multivariate logistic regression analysis was performed to determine the risk factors for septic AKI. A summary of risk factors with their odd ratio and confidence intervals is presented in Table 3.

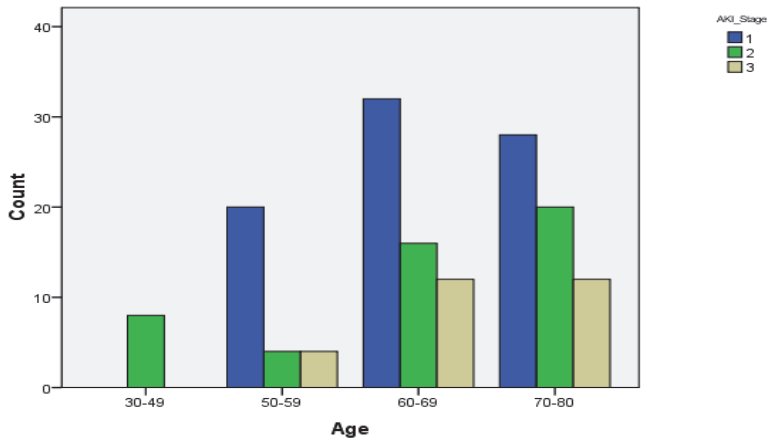


Figure 1. The association between the grade of AKI and the age groups

Table 2. A summary of laboratory and clinical findings in patients with or without developing AKI

| Variable | All participants | AKI group | Non-AKI group | P-value |
|---|---|---|---|---|
| Hospital stay, days | 14.31 ± 4.34 | 16.28 ± 4.30 | 12.93 ± 3.82 | 0.001< |
| Serum albumin, (g/dl) | 3.29 ± 0.52 | 0.35 ± 2.98 | 0.51 ± 3.51 | 0.001< |
| Hemoglobin, (g/dl) | 11.45 ± 2.12 | 11.22 ± 2.43 | 1.86 ± 11.62 | 0.001< |
| WBC, (cells/m3) | 13500 ± 32.13 | 5662.45 ± 137000 | 4921.39 ± 135000 | 0.970 |
| Platelet count, (cells/m3×$10^3$) | 236.82 ± 110.94 | 111.76 ± 236.64 | 110.61 ± 236.95 | 0.796 |
| Serum BUN, (mg/dl) | 28.47 ± 21.03 | 23.04 ± 46.15 | 3.46 ± 16.16 | 0.001< |
| Creatinine at admission, (mg/dl) | 0.95 ± 0.20 | 0.22 ± 1.04 | 0.16 ± 0.89 | 0.001< |
| Creatinine after 48 hours, (mg/dl) | 1.54 ± 0.94 | 0.99 ± 2.36 | 0.17 ± 0.98 | 0.001< |
| Creatinine one month after discharge or at death, (mg/dl) | 1.26 ± 0.64 | 0.83 ± 1.66 | 0.17 ± 0.98 | 0.001< |
| Plasma Na level, (meq/L) | 137.58 ± 5.94 | 5.78 ± 136.79 | 5.99 ± 138.12 | 0.001< |
| Plasma K level, (meq/L) | 4.21 ± 0.72 | 0.84 ± 4.30 | 0.62 ± 4.15 | 0.001< |
| Bacteremia, % | 92 (24.2%) | 52 (33.2%) | 40 (17.9%) | 0.001< |
| Sepsis etiology | | | | |
| Endocarditis | 32 (8.4%) | 16 (10.3%) | 16 (7.1%) | 0.282 |
| Pneumonia | 168 (44.2%) | 68 (43.6%) | 100 (44.6%) | 0.839 |
| Cholangitis | 88 (23.2%) | 36 (23.1%) | 52 (23.2%) | 0.975 |
| UTI | 60 (15.8%) | 24 (15.4%) | 36 (16.1%) | 0.857 |
| Meningitis | 28 (7.4%) | 8 (5.1%) | 20 (8.9%) | 0.163 |
| Soft tissue infection | 80 (21.1%) | 44 (28.2%) | 36 (16.1%) | 0.001< |
| pancreatitis | 12 (3.2%) | 8 (5.1%) | 4 (1.8%) | 0.068 |
| Antibiotics initiation | | | | |
| First 24 hours | 112 (29.5%) | 12 (7.7%) | 100 (44.6%) | 0.001< |
| 24-48 hours of admission | 136 (35.8%) | 56 (35.9%) | 76 (33.9%) | |
| After 48 hours of admission | 132 (34.7%) | 80 (51.3%) | 36 (16.1%) | |
| Hydration therapy initiation | | | | |
| First 24 hours | 128 (33.7%) | 16 (10.3%) | 112 (50%) | 0.001< |
| 24-48 hours of admission | 136 (35.8%) | 60 (38.5%) | 76 (33.9%) | |
| After 48 hours of admission | 116 (30.5%) | 80 (51.3%) | 36 (16.1 %) | |
| Vasopressor receiving, % | 76 (20%) | 44 (30.8%) | 28 (12.5%) | 0.001< |
| Mortality rate, % | 44 (11.6%) | 28 (17.9%) | 16 (7.1%) | 0.001< |

**Table 2. A summary of laboratory and clinical findings in patients with or without developing AKI**

| Variable | Odds ratio (OR) | 95% CI | P-value |
|---|---|---|---|
| Age over 60 years | 1.619 | 2.595 – 1.010 | 0.045 |
| Smoking | 2.576 | 4.135 – 1.605 | 0.001< |
| Addiction | 1.654 | 2.607 – 1.049 | 0.030 |
| IHD | 3.20 | 5.108 – 2.005 | 0.001< |
| HTN | 2.329 | 3529 – 1.533 | 0.001< |
| DM | 1.818 | 2.919 – 1.132 | 0.013 |
| Neurologic diseases | 0.455 | 0.767 – 0.270 | 0.003 |
| ACEIs or ARBs consumption | 6.506 | 5.531 – 2.223 | 0.001< |
| Mean arterial pressure (mm/hg) | 0.991 | 1.003 – 0.979 | 0.144 |
| Heart rate | 1.012 | 1.030 – 0.994 | 0.194 |
| Serum hemoglobin, | 0.914 | 1.010 – 0.828 | 0.77 |
| Serum Albumin | 0.90 | 0.155 – 0.052 | 0.282 |
| Serum BUN | 1.512 | 1.762 – 1.368 | 0.001< |
| Serum HCO3 | 0.808 | 0.860 – 0.759 | 0.001< |
| Serum AST | 1.006 | 1.010 – 1.001 | 0.014 |
| Serum Na | 0.962 | 0.997 – 0.928 | 0.033 |
| Serum K | 1.340 | 1.783 – 1.007 | 0.045 |
| Creatinine at admission | 59.216 | 192.393 – 18.174 | 0.001< |
| Creatinine 48 hours after admission | 1091000 | 8317000 – 14320 | 0.001< |
| Creatinine one month after discharge or before death | 933.951 | 4413 – 197.670 | 0.001< |
| Bacteremia | 2.30 | 3.707 – 1.427 | 0.001 |
| Soft tissue infection as the etiology of sepsis | 2.052 | 3.378 – 1.246 | 0.005 |
| Antibiotics therapy initiation at 24 hours of admission | 0.60 | 0.121 – 0.30 | 0.001< |
| Antibiotics therapy initiation at 24-48 hours of admission | 0.350 | 0.576 – 0.213 | 0.001< |
| Hydration therapy initiation at first 24 hours | 0.64 | 0.124 – 0.33 | 0.001< |
| Hydration therapy initiation at first 24-48 hours | 0.355 | 0.579 – 0.211 | 0.001< |
| Vasopressor | 3.11 | 5.243 – 1.846 | 0.001< |
| Hospital stay | 1.232 | 1.311 – 1.160 | 0.001< |

## Discussion

In our study more than 40% of patients eventually developed AKI based on the RIFLE criteria. The overall mortality rate in this study was 11.6%. Risk factors of developing AKI during sepsis in our study were older age, smoking and drug use, ischemic heart disease, hypertension and diabetes, and the use of ACE and ARB inhibitors. Besides, low levels of albumin, bicarbonate and serum sodium and high levels of BUN, AST, potassium and serum creatinine were associated with an increased risk of AKI. Other risk factors for AKI were bacteremia, soft tissue infection as the source of sepsis, delayed initiation (more than 48 hours) of antibiotic and fluid therapy, and administration of vasopressors. Also, in patients who ultimately needed dialysis, the mortality rate was up to 22 times higher than those with AKI who did not require dialysis.

Acute renal impairment is more common in patients with sepsis and septic shock. The present study showed that among 380 patients with sepsis or septic shock, 156 (41.1%) developed AKI according to the RIFLE criteria. A cohort study of 390 patients with septic shock in the intensive care unit reported that approximately two thirds of patients experienced AKI (25). In a multicenter retrospective study of 4,532 patients with septic shock, 64.4% developed AKI as well (26). These rates are a bit

higher than our study which might be due to case selections, ethnicity differences or smaller sample size in our trial.

Septic AKI pathophysiology is not yet fully elucidated (27, 28). AKI in sepsis is attributed to hemodynamic and inflammatory, immune or apoptotic mechanisms, most of which can be corrected by adequate resuscitation and antibiotic administration (29, 30). This was highlighted in our study as well.

In a study by Begshaw *et al.*, prolonged hypotension and delayed initiation of antimicrobial therapy were associated with an increased risk of developing AKI (26). In our study, early initiation of fluid therapy and antibiotic therapy, especially in the first 24 to 48 hours after hospitalization, was associated with a significant reduction in the risk of AKI, which indicates the importance of hydration and antibiotics treatment. However, in our study, the mean arterial pressure was not significantly associated with the risk of developing AKI.

The higher prevalence of AKI in patients with sepsis, but without hypotensive shock, cannot be explained by reduced renal blood flow alone. In an experimental animal study, Langenberg *et al.* found that AKI in septic shock is mainly affected by impaired renal vascular function to systemic hypotension or decreased renal blood flow (31). In their study, fluid resuscitation did not prevent GFR deterioration. It can be assumed that uncontrolled infection leads to more severe immunological responses, resulting in impaired renal function.

In other studies, in contrast to our study, higher body mass index has been associated with renal failure (32) and shown to be an independent risk factor for AKI in ICU patients (33) or specific subgroups such as liver transplant patients (34). This needs further evaluations in larger sample size trials to clearly elucidate the role of body mass index in developing AKI.

In our study, the history of ACEIs and ARB use was identified as an independent risk factor for predicting AKI. In case of shock and decreased renal perfusion, these drugs further reduce the pressure inside the glomerulus (35, 36), which justifies the association of developing AKI and these medicines.

In agreement with the findings of Begshaw *et al.*, in our study there was a significant association between the progression of AKI disease and pre-existing chronic diseases including ischemic heart disease, hypertension, diabetes and neurological diseases.

Current evidences suggest that the association between AKI and the source of infection is not well elucidated. We found no association between AKI and endocarditis, pneumonia, cholangitis, pancreatitis, genital tract infections and CNS as the primary source of sepsis. However, soft tissue infection as a source of infection was an independent risk factor for AKI based on logistic regression model. There is paucity of data regarding the association of sepsis source and AKI development, and further larger trials are necessary to confirm our finding regarding higher probability of AKI in case of soft tissue infection as the source of sepsis. The findings of our study further confirmed the hypothesis that septic AKI is not only affected by hemodynamic instability and controlling the source of infection, especially soft tissues abscess or collections promptly is of great importance. However, there was no possible link between blood hemoglobin levels and septic AKI in previous studies based on our data, although in the study of multivariate logistic regression, this relationship was not significant, indicating the need for further research in this area.

As the development of septic AKI is associated with an increased mortality rate, patients at risk for septic AKI should be carefully monitored for nephrotoxic factors in the early stages of infection management. We failed to examine the effect of septic AKI on long-term survival of patients. Despite the fact, our study had some advantages. There were a relatively large number of medical records of patients reviewed in this study. Second, we assessed various risk factors associated with septic AKI, some of which were new.

## Conclusion

Older age, smoking, drug abuse, previous history of ischemic heart disease, hypertension and diabetes, positive blood culture results, use of ACEI and ARB drugs, lower albumin levels, higher AST, soft tissue infection as septic etiology, delayed antibiotics and fluid therapy and vasopressor administration were associated with an increased risk of septic AKI. In addition, the severity of AKI was associated with increased short-term mortality, length of hospital stay and the need for hemodialysis.

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