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ORIGINAL ARTICLE

# Clinical outcomes of septic patients with diabetic ketoacidosis between 2004 and 2013 in a tertiary hospital in Taiwan

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**KEYWORDS**
Acute kidney injury;
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End-stage kidney disease (RIFLE) classification;
Failure;
Injury;
Loss;
Risk;
Sepsis

*Background:* Infection is the most common predisposing factor for diabetic ketoacidosis (DKA); however, studies are rare that have investigated the clinical outcomes of septic patients with infection-precipitated DKA.
*Methods:* A retrospective cohort study was conducted at a tertiary hospital from 2004 to 2013. Patients with DKA in whom the presence of a predisposing infection was confirmed were enrolled. Characteristics at initial presentation, primary infection sources, and causative microorganisms were compared between the nonacute kidney injury (non-AKI) group and acute kidney injury (AKI) group at each stage. Risk factors for the development of failure-stage AKI and its outcomes were also analyzed.
*Results:* One hundred and sixty DKA episodes were assessed. The most common infection sites were the urinary and respiratory tracts. The leading causative microorganism was *Escherichia coli*, followed by *Klebsiella pneumoniae*. A complicated/severe infection state [odds ratio (OR), 15.27; $p < 0.001$] and a high level of C-reactive protein (OR, 1.012; $p < 0.001$) were independently associated with bacteremia. Corrected sodium (Na; OR, 1.062; $p = 0.039$), initial

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plasma glucose (OR, 1.003; $p = 0.041$), severe grade of DKA (OR, 13.41; $p = 0.045$), and the Acute Physiology and Chronic Health Evaluation (APACHE) II score (OR, 1.08; $p = 0.033$) were identified as independent risk factors for the development of failure-stage AKI among septic patients with infection-precipitated DKA. Patients with failure-stage AKI had a higher frequency of incomplete recovery of renal function (20.4% of patients in failure vs. 5.9% of patients in risk and injury, $p = 0.009$). Bacteremia independently predicted the absence of complete recovery of renal function (OR, 5.86; $p = 0.038$).

*Conclusion:* For patients with infection-precipitated DKA, the clinician should aggressively monitor renal function if a patient presents with risk factors associated with failure-stage AKI. Furthermore, bacteremia predicts a poor renal prognosis.



## Introduction

Infection is the most common predisposing factor for the development of hyperglycemic crises, diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state; it has an estimated range of 32–60%.[1] Among the predisposing factors for hyperglycemic crises, infection is the most common cause of death. However, previous studies are lacking that address in detail the infection source and microbiological characteristics of septic patients with infection-precipitated DKA. Potential complications of diabetic ketoacidosis (DKA) include electrolyte imbalance, dehydration, cerebral and peripheral venous thrombosis, rhabdomyolysis, and acute renal failure.[2] Diabetic ketoacidosis can result in severe fluid depletion that is accompanied by marked metabolic disturbance, although a low incidence of acute renal failure in patients with DKA was reported in a previous study.[3] However, acute kidney injury (AKI) is an independent risk factor for mortality in critically ill patients.[4–7] Furthermore, a more severe stage of AKI—as classified by Risk, Injury, Failure, Loss, End-stage Kidney Disease (RIFLE) criteria or by the Acute Kidney Injury Network (AKIN) criteria—is associated with increased hospital mortality.[4,6,8]

To further our understanding of the relationship between the infection site or the causative microorganism in septic patients with DKA and renal involvement, especially with regard to the severity stage of AKI in which renal replacement therapy may be necessary or a higher mortality is expected, we conducted a retrospective cohort study to investigate the risk factors and clinical outcomes of patients with infection-precipitated DKA that develops into failure-stage AKI.

## Materials and methods

### Study design and setting

This retrospective cohort study was conducted at a tertiary hospital in southern Taiwan—Kaohsiung Medical University Hospital (Kaohsiung, Taiwan)—in which medical records were reviewed of patients who developed DKA from January 2004 to December 2013. The protocol for this study was reviewed and approved by the Institutional Review Board of Kaohsiung Medical University Hospital (approval number KMUH-IRB-980057). Diabetic ketoacidosis was diagnosed in accordance with the diagnostic criteria of the American Diabetes Association: hyperglycemia (i.e., plasma glucose $> 250$ mg/dL) and high anion gap metabolic acidosis (i.e., arterial pH $< 7.30$, serum bicarbonate $< 18$ mEq/L, and an anion gap $> 10$) with positive serum or urine ketones.[1] In the event that a patient developed multiple DKA episodes during the study period, each episode was evaluated. Patients under the age of 18 years were excluded. Precipitating factors of DKA were extracted. Two infectious disease specialists confirmed the infection state and the primary infection source with the recovered causative microorganism, based on specific symptoms and signs, imaging study results, and microbiologic results from the appropriate specimen. In the event of a disagreement, a third specialist participated in the adjudication. To further identify a complicated or severe infection state, we defined complicated urinary tract infection in accordance with the guidelines of the Association of Medical Microbiology and Infectious Diseases Canada.[9] We also defined pneumonia with parapneumonic effusion or empyema, severe skin and soft tissue infection with systemic inflammatory response syndrome or deeper infection, and complicated intra-abdominal infection, based on the clinical practice guidelines of the Infectious Diseases Society of America.[10–13] Patients who were confirmed as having infection-precipitated DKA were enrolled and then evaluated for whether AKI developed in the first 48 hours after admission. Patients in the AKI group were further divided into three stages (i.e., "risk", "injury", and "failure") on the basis of the RIFLE classification. Demographic characteristics and physiologic and laboratory data at the initial presentation were compared between the non-AKI and AKI groups at each stage. For investigation of the risk factors associated with the development of severe AKI, for which renal replacement therapy may be necessary or which may have a higher than expected mortality, we compared AKI in the failure stage and other infection-precipitated DKA episodes (non-AKI group and AKI in the risk and injury stages). Also investigated were the clinical outcomes of patients in failure-stage AKI, which included the length of hospital stay, recovery of renal function at discharge, and hospital mortality.

### Definition and classification of AKI and renal outcome

The RIFLE criteria were designed by the Acute Dialysis Quality Initiative (ADQI) Working Group to obtain a general definition of AKI.[14] The definition and classification of AKI were determined by the worst serum creatinine (SCr) level in the first 48 hours after admission. Patients were determined to have developed AKI when they had a decrease in the glomerular filtration rate (GFR) of $\geq$ 25% or an increase in the SCr level of $\geq$ 50% (1.5 times) from the baseline. The baseline renal function was based on the lowest known SCr level during the preceding 3 months.

Patients who had AKI were divided into three stages ("risk", "injury", and "failure"), based on the RIFLE classification. A patient who had a decrease in the GFR of $\geq$ 25% or an increase in the SCr level of $\geq$ 50% (1.5 times) from the baseline level was classified as being in the risk stage. A patient who had a decrease in the GFR of $\geq$ 50% or an increase in the SCr level of $\geq$ 100% (2 times) from baseline level was classified as being in the injury stage. A patient in the failure stage had a decrease in the GFR of $\geq$ 75%, an increase in the SCr level of $\geq$ 200% (3 times) from the baseline, or an absolute SCr level of $\geq$ 4.0 mg/dL or with an acute increase of $\geq$ 0.5 mg/dL.

For patients who developed AKI, the renal outcome at hospital discharge was defined as follows (as previously applied): "complete recovery" if the discharge SCr level was within 120% of the baseline level, "partial recovery" if the discharge SCr level was 121—150% of the baseline level, or "nonrecovery" if the discharge SCr level was $>$ 150% of the baseline level or if the patient was still receiving renal replacement therapy.[15]

### Data extraction

Demographic information and baseline laboratory data were extracted and included age, sex, body mass index (BMI), type of diabetes, hypertension, glycated hemoglobin (HbA1c) level, baseline SCr level, and uric acid level. Physiologic and laboratory data at the initial presentation were recorded and included body temperature, pulse rate, respiratory rate, mean arterial pressure, white blood cell count, the levels of C-reactive protein, lactate, blood urea nitrogen (BUN), SCr, serum sodium, potassium, chloride, bicarbonate, pH value, and initial plasma glucose level. Detected serum sodium and initial plasma glucose were used to calculate the corrected sodium level:

$$\text{corrected sodium} = \text{detected sodium} + (\text{plasma glucose} - 100) \times 0.024$$

and to calculate the effective blood osmolarity:

$$\text{calculated blood osmolarity} = (\text{detected sodium} \times 2) + (\text{plasma glucose} \div 18).$$

The anion gap was calculated by the following formula:

$$\text{anion gap} = \text{detected serum sodium} - (\text{serum chloride} + \text{serum bicarbonate}).$$

Severity of illness was further evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score, DKA severity, shock with vasopressor use, complicated or severe infection state, and bacteremia. The DKA severity (i.e., mild, moderate, severe) was stratified by the pH value and the serum bicarbonate level in accordance with the American Diabetes Association.[1] A mild grade of DKA is defined as an arterial pH value of 7.25—7.30 or serum bicarbonate ($HCO_3^-$) level of 15—18 mEq/L; the moderate grade is defined as a pH of value 7.00—7.24 or $HCO_3^-$ level of 10—14 mEq/L; and the severe grade is defined as a pH $<$ 7.00 or $HCO_3^-$ $<$ 10 mEq/L. Data on the initial antimicrobial therapy were also extracted. Therapy was considered inappropriate if a patient did not receive within 24 hours from the diagnosis of sepsis at least one antimicrobial agent that was active *in vitro* to the causative microorganism, based on the Clinical and Laboratory Standards Institute (CLSI) guidelines.[16] Primary infection sources and recovered causative microorganisms, as confirmed by the infectious disease specialists, were also recorded.

### Statistical analysis

Categorical variables, expressed by proportions, were compared using Pearson's Chi-square test or Fisher's exact test. Continuous variables were expressed as the mean $\pm$ the standard deviation. The means were compared between the two groups using the Student *t* test. An analysis of variance was used for the means of more than three groups. Multivariable logistic regression analysis was used to assess the associated risk factors of developing failure-stage AKI and assess the independent predictors for the poor clinical outcome of AKI. Variables were included in the regression analysis if they demonstrated a statistically significant association with the outcomes of interest in the univariable analyses or if previous studies suggested that the variables were potential confounders or effect modifiers. Data analyses were performed using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA). All tests were two-tailed. A $p$ value $<$ 0.05 was considered statistically significant.

## Results

We evaluated 403 DKA episodes that presented to our hospital during the study period. Fifty-two episodes occurred in patients under the age of 18 years; these patients were excluded. One hundred and sixty (39.7%) DKA episodes, which involved 144 patients, were precipitated by infectious diseases and were entered in the study. The leading cause of noninfection-precipitated DKA was noncompliance with treatment. Newly diagnosed diabetes was also a common associated factor. Acute kidney injury developed in 139 (86.9%) episodes of infection-precipitated DKA, which included 27 (19.4%) episodes in the risk stage, 58 (41.7%) episodes in the injury stage, and 54 (38.8%) episodes in the failure stage (Fig. 1).

Baseline demographic characteristics and physiologic and laboratory data at initial presentation are shown in Table 1. Patients who had infection-precipitated DKA had a mean age of 45.1 years, and only 11.9% patients were elderly (i.e., older than 65 years). Furthermore, 73.8% of

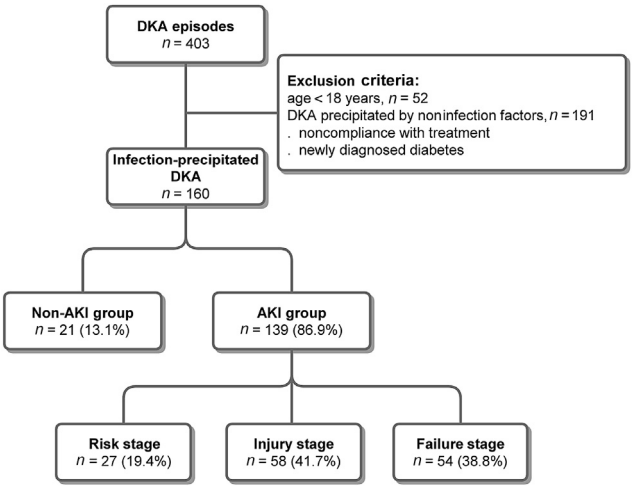


**Figure 1.** Study design. AKI = acute kidney injury; DKA = diabetic ketoacidosis.

episodes occurred in patients with type 2 diabetes, and a mean HbA1c level of 12.4% ± 2.8% was evidence of poor recent glucose control. In the analysis of variance in each stage between the non-AKI (NA) group and AKI group at the initial presentation, patients with failure-stage AKI (F) had a significantly lower BMI [F < NA, $p = 0.042$; F < risk (R), $p = 0.009$; F < injury (I), $p = 0.387$], higher corrected sodium (F > NA, $p < 0.001$; F > R, $p = 0.002$; F > I, $p < 0.001$), higher serum potassium (F > R, $p = 0.005$; F > I, $p = 0.007$), higher initial plasma glucose (F > NA, $p < 0.001$; F > R, $p < 0.001$; F > I, $p < 0.001$), and higher calculated blood osmolarity (F > NA, $p < 0.001$; F > R, $p = 0.002$; F > I, $p < 0.001$). In addition, the APACHE II score had a positive relevance with severity of AKI at each stage (F > I, $p = 0.002$; F > R, $p < 0.001$; I > R, $p = 0.01$).

Table 2 and Table 3 show the primary infection sources and recovered causative microorganisms, respectively. The most common primary infection site for infection-precipitated DKA was a urinary tract infection ($n = 42$, 26.2%), followed by a respiratory tract infection ($n = 41$, 25.7%) and skin and soft tissue infection ($n = 22$, 13.8%); an uncertain infection source represented 4.4%. The overall

**Table 1** Demographic and clinical characteristics for infection-precipitated diabetic ketoacidosis

| Infection-precipitated DKA | Total episodes | Non-AKI | AKI ($n = 139$) | | | $p$ |
|---|---|---|---|---|---|---|
| | ($n = 160$) | ($n = 21$) | Risk ($n = 27$) | Injury ($n = 58$) | Failure ($n = 54$) | |
| **Demographic characteristics** | | | | | | |
| Age (y) | 45.1 ± 16.1 | 47.2 ± 16.4 | 38.3 ± 13.3 | 45.2 ± 15.7 | 47.5 ± 17.3 | 0.092 |
| Elderly > 65 y | 19 (11.9) | 4 (19.0) | 1 (3.7) | 4 (6.9) | 10 (18.5) | 0.093 |
| Sex, male | 73 (45.6) | 11 (52.4) | 13 (48.1) | 30 (51.7) | 33 (61.1) | 0.658 |
| BMI | 22.2 ± 4.6 | 23.6 ± 3.7 | 24.0 ± 5.4 | 21.8 ± 4.8 | 21.1 ± 3.8 | 0.03* |
| Type 2 diabetes | 118 (73.8) | 17 (81.0) | 19 (70.4) | 42 (72.4) | 40 (74.1) | 0.855 |
| Hypertension | 20 (12.5) | 4 (19.0) | 2 (7.4) | 7 (12.1) | 7 (13.0) | 0.686 |
| **Baseline laboratory data** | | | | | | |
| HbA1C (%) | 12.4 ± 2.8 | 11.3 ± 3.4 | 13.0 ± 2.6 | 12.5 ± 2.4 | 12.3 ± 3.0 | 0.208 |
| Baseline serum Cr (mg/dL) | 0.88 ± 1.03 | 1.77 ± 1.95 | 0.77 ± 0.24 | 0.67 ± 0.25 | 0.81 ± 1.14 | < 0.001* |
| Uric acid (mg/dL) | 6.4 ± 3.1 | 8.6 ± 5.0 | 6.4 ± 2.0 | 5.4 ± 2.8 | 6.8 ± 2.8 | 0.063 |
| **Presenting physiologic and laboratory data** | | | | | | |
| Body temperature >38.3°C or <36.0°C | 45 (28.1) | 6 (28.6) | 7 (25.9) | 14 (24.1) | 18 (34.0) | 0.704 |
| Pulse rate >90/min | 133 (83.1) | 18 (85.7) | 22 (81.5) | 46 (79.3) | 47 (88.7) | 0.586 |
| Respiratory rate >20/min | 82 (51.2) | 14 (66.7) | 12 (44.4) | 27 (46.6) | 29 (54.7) | 0.353 |
| Mean arterial pressure (mmHg) | 95.5 ± 20.4 | 106.3 ± 17.2 | 95.6 ± 18.7 | 94.0 ± 22.8 | 96.5 ± 20.6 | 0.947 |
| WBC count (× 103/μL) | 16.7 ± 6.7 | 14.3 ± 6.6 | 16.4 ± 6.7 | 17.2 ± 7.0 | 17.1 ± 6.5 | 0.344 |
| C-reactive protein (mg/L) | 103.2 ± 128.0 | 76.7 ± 109.4 | 74.0 ± 110.0 | 125.5 ± 143.7 | 103.6 ± 123.3 | 0.261 |
| BUN (mg/dL) | 33.0 ± 32.0 | 27.1 ± 26.0 | 19.3 ± 18.2 | 25.7 ± 15.2 | 49.9 ± 43.9 | < 0.001* |
| Serum Cr (mg/dL) | 1.96 ± 1.62 | 1.86 ± 1.82 | 1.36 ± 0.40 | 1.61 ± 0.60 | 2.66 ± 2.32 | 0.001* |
| Corrected Na (mmol/L) | 142.9 ± 8.8 | 138.9 ± 7.6 | 140.9 ± 6.5 | 141.1 ± 6.1 | 147.2 ± 11.0 | < 0.001* |
| K (mmol/L) | 4.8 ± 1.0 | 4.7 ± 0.8 | 4.5 ± 0.8 | 4.7 ± 0.9 | 5.2 ± 1.2 | 0.012* |
| Cl (mmol/L) | 100.0 ± 8.5 | 98.3 ± 8.8 | 100.5 ± 7.5 | 100.2 ± 7.9 | 100.0 ± 9.6 | 0.834 |
| Initial plasma glucose (mg/dL) | 569.5 ± 227.1 | 435.2 ± 145.6 | 509.7 ± 171.8 | 509.7 ± 167.7 | 712.9 ± 259.9 | < 0.001* |
| Serum pH | 7.127 ± 0.140 | 7.136 ± 0.122 | 7.143 ± 0.129 | 7.143 ± 0.152 | 7.100 ± 0.137 | 0.375 |
| Serum bicarbonate (mEq/L) | 8.6 ± 4.4 | 9.4 ± 5.0 | 9.9 ± 5.0 | 8.6 ± 4.6 | 7.5 ± 3.4 | 0.094 |
| Anion gap | 23.2 ± 6.7 | 23.7 ± 7.9 | 20.8 ± 6.0 | 22.7 ± 6.6 | 25.0 ± 6.5 | 0.076 |
| Blood osmolarity (mOsm/kg) | 300.8 ± 23.8 | 286.4 ± 15.7 | 296.9 ± 17.5 | 295.9 ± 18.2 | 313.4 ± 28.5 | < 0.001* |
| Lactate (mmol/L) | 3.8 ± 4.9 | 7.8 ± 9.5 | 2.0 ± 1.3 | 2.2 ± 1.4 | 4.2 ± 4.5 | 0.002* |

*$p < 0.05$ among the four subgroups: non-AKI, AKI in risk stage, injury stage, failure stage.
AKI = acute kidney injury; BMI = body-mass index; BUN = blood urea nitrogen; Cl = chlorine; Cr = creatinine; DKA = diabetic ketoacidosis; HbA1c = glycated hemoglobin; K = potassium; Na = sodium; WBC = white blood cell.

**Table 2** Primary infection sources in infection-precipitated diabetic ketoacidosis

| Primary infection sources | Total episodes $n = 160$ |
|---|---|
| Urinary tract infection | 33 (20.6) |
| Complicated urinary tract infection | 9 (5.6) |
| Respiratory tract infection | 35 (21.9) |
| Pneumonia with parapneumonic effusion | 6 (3.8) |
| Skin and soft tissue infection | 12 (7.5) |
| Severe SSTI with SIRS | 10 (6.3) |
| Intra-abdominal infection | 13 (8.1) |
| Complicated intra-abdominal infection | 8 (5.0) |
| Bone and joint infection | 2 (1.3) |
| Severe BJI with SIRS | 1 (0.6) |
| Catheter-related bloodstream infection | 2 (1.3) |
| CNS infection | 1 (0.6) |
| Multifocal | 11 (6.9) |
| Uncertained | 7 (4.4) |

All data are presented as *n* (%).
BJI = bone and joint infection; CNS = central nervous system; DKA = diabetic ketoacidosis; SIRS = systemic inflammatory response syndrome; SSTI = skin and soft tissue infection.

complicated or severe infection states accounted for 21.3% of cases. Ninety-three causative microorganisms were obtained from 29 blood specimens, 26 urine specimens, 18 pus specimens, 13 sputum specimens, and four other specimens. The leading causative microorganism was *Escherichia coli* ($n = 26$, 30.0%), followed by *Klebsiella pneumoniae* ($n = 25$, 26.9%) and *Staphylococcus aureus* ($n = 14$, 15.1%). No significant relationship between either primary infection sources or causative microorganisms and the development of failure-stage AKI or mortality was noted in this study. However, a complicated or severe infection state (adjusted OR, 15.27; $p < 0.001$) and a higher C-reactive protein level (adjusted OR, 1.012; $p < 0.001$) were independently associated with bacteremia.

**Table 3** Causative microorganism in infection-precipitated diabetic ketoacidosis

| Causative microorganisms | | Total ($n = 93$) | |
|---|---|---|---|
| Bacteria | | Fungus | |
| **Gram-negative cocci** | 64 (68.8) | *Candida albicans* | 2 (2.2) |
| *Escherichia coli* | 26 (30.0) | | |
| *Klebsiella pneumoniae* | 25 (26.9) | | |
| *Pseudomonas aeruginosa* | 5 (5.4) | | |
| *Proteus mirabilis* | 4 (4.3) | | |
| *Serratia marcescens* | 1 (1.1) | | |
| *Enterobacter spp.* | 1 (1.1) | | |
| *Acinetobacter spp.* | 1 (1.1) | | |
| *Burkholderia pseudomallei* | 1 (1.1) | | |
| **Gram-positive cocci** | 24 (25.8) | | |
| *Staphylococcus aureus* | 14 (15.1) | | |
| *Group B Streptococcus* | 5 (5.4) | | |
| *Coagulase-negative Staphylococcus* | 3 (3.2) | | |
| *Enterococcus spp.* | 2 (2.2) | | |
| **Others** | | | |
| *Mycobacterium tuberculosis complex* | 3 (3.2) | | |

All data are presented as *n* (%).

At initial presentation, patients with infection-precipitated DKA who developed failure-stage AKI—compared to the non-AKI group and patients with AKI at the risk and injury stages—had a significantly higher corrected sodium (Na) level (147.2 ± 11 mmol/L vs. 140.6 ± 6.5 mmol/L; $p < 0.001$), higher initial plasma glucose level (712.9 ± 259.9 mg/dL vs. 495.1 ± 165.8 mg/dL, $p < 0.001$), greater severity of DKA ($p = 0.003$), and higher APACHE II score (21.3 ± 7.2 vs. 16.7 ± 5.3, $p < 0.001$) (Table 4). In multivariable analysis, corrected Na level (adjusted OR, 1.062; $p = 0.039$), initial plasma glucose level (adjusted OR, 1.003; $p = 0.041$), severe grade of DKA (adjusted OR, 13.41; $p = 0.045$), and APACHE II score (adjusted OR, 1.08; $p = 0.033$) were independent risk factors for developing failure-stage AKI among the septic patients with DKA.

## Clinical outcomes

Nine patients died in hospital, thereby contributing to a hospital mortality rate of 5.6% in septic patients with DKA (Table 5). No significant difference was evident in hospital mortality between the non-AKI group and AKI group at each stage. In addition, no significant difference was observed in the length of hospital stay and hospital mortality in septic patients with infection-precipitated DKA who developed failure-stage AKI (Table 6). For renal outcome at discharge, 123 (88.5%) of 139 AKI episodes showed complete recovery of renal function, 6 (4.3%) episodes showed partial renal recovery, whereas 10 (8.1%) episodes did not show recovery of renal function (Table 5). Patients who developed failure-stage AKI had incomplete recovery of renal function at discharge more frequently than patients with AKI who were in the risk or injury stages (20.4% vs. 5.9%, respectively; $p = 0.009$; Table 6). Bacteremia (adjusted OR, 5.86; 95% CI, 1.10—31.1; multivariable $p = 0.038$) was identified as an independent predictor for incomplete recovery of renal function at discharge, after adjusting for the covariates of lactate ($p = 0.026$), shock with vasopressor use ($p < 0.001$), failure-stage AKI ($p = 0.009$), bacteremia ($p = 0.031$), and for the suspected confounder of an age older than 65 years (Table 7).

## Discussion

Diabetic ketoacidosis can result in severe fluid depletion, accompanied by marked metabolic disturbance; it is surprisingly rare for it to be complicated by acute renal failure.[3] To our knowledge, only a few case reports have demonstrated complicated DKA with rhabdomyolysis or thrombotic thrombocytopenic purpura contributing to acute renal failure.[2,17,18] The present study was conducted retrospectively to increase our comprehension of the relationship between DKA (specifically DKA that is precipitated by an infectious disease) and AKI. The pathophysiology of DKA illustrates that stress, infection, or insufficient insulin

**Table 4** Multivariate analysis of factors associated with the development of failure-stage acute kidney injury in infection-precipitated diabetic ketoacidosis

| | Non-AKI, risk, injury, ($n$ = 106 ) | AKI in failure stage, ($n$ = 54) | Univariate $p$ value | Adjusted odds ratio | 95% CI | Multivariate $p$ value |
|---|---|---|---|---|---|---|
| Corrected Na (mmol/L) | 140.6 ± 6.5 | 147.2 ± 11.0 | < 0.001 | 1.062 | 1.003–1.124 | 0.039* |
| Initial plasma glucose (mg/dL) | 495.1 ± 165.8 | 712.9 ± 259.9 | < 0.001 | 1.003 | 1.000–1.005 | 0.041* |
| DKA severity | | | 0.003 | | | |
| Mild grade | 13 (12.3) | 1 (1.9) | | 1 (reference) | | |
| Moderate grade | 35 (33.0) | 9 (16.7) | | 4.91 | 0.37–65.78 | 0.23 |
| Severe grade | 54 (54.7) | 44 (81.5) | | 13.41 | 1.07–168.83 | 0.045* |
| APACHE II score | 16.7 ± 5.3 | 21.3 ± 7.2 | < 0.001 | 1.08 | 1.006–1.160 | 0.033* |

*Multivariate $p < 0.05$.
The data are presented as $n$ (%) or as the mean + the standard deviation.
AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; DKA = diabetic ketoacidosis; $HCO_3^-$ = bicarbonate; Na = sodium.

therapy reduces effective insulin and increases the concentrations of counter-regulatory hormones (e.g., catecholamines, cortisol, glucagon, and growth hormone), which further contributes to hyperglycemia and ketoacidosis.[1] Hyperglycemia will facilitate osmotic diuresis, loss of water and electrolytes, dehydration, and impaired renal function. Furthermore, increasing evidence indicates that hyperglycemic crises are associated with a severe inflammatory state that is characterized by an elevated level of proinflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-β, -6, and -8) even in the absence of obvious infection.[19] All of these parameters return to near-normal values with insulin therapy and hydration within 24 hours. In addition, patients with DKA presented with an elevated body temperature, tachycardia, tachypnea, or leukocytosis for which a predisposing infection state was documented. This indicated that these patients met the criteria of sepsis.

In the pathogenesis of septic AKI, inflammation and acute tubular apoptosis have been implicated in septic patients with hyperdynamic circulation.[20,21] In this study,

**Table 5** Severity of illness and clinical outcomes for infection-precipitated diabetic ketoacidosis

| Infection-precipitated DKA | Total episodes ($n$ = 160) | Non-AKI ($n$ = 21) | AKI ($n$ = 139) | | | $p$ |
|---|---|---|---|---|---|---|
| | | | Risk ($n$ = 27) | Injury ($n$ = 58) | Failure ($n$ = 54) | |
| **Severity of illness** | | | | | | |
| DKA severity | | | | | | |
| Mild grade | 14 (8.8) | 2 (9.5) | 5 (18.5) | 6 (10.3) | 1 (1.9) | 0.02* |
| Moderate grade | 44 (27.5) | 9 (42.9) | 7 (25.9) | 19 (32.8) | 9 (16.7) | |
| Severe grade | 102 (63.7) | 10 (47.6) | 15 (55.6) | 33 (56.9) | 44 (81.5) | |
| APACHE II score | 18.2 ± 6.4 | 18.3 ± 4.9 | 13.8 ± 5.7 | 17.4 ± 4.8 | 21.3 ± 7.2 | < 0.001* |
| Shock with vasopressor use | 17 (10.6) | 5 (26.3) | 0 | 3 (5.7) | 9 (18) | 0.014* |
| Complicated or severe infection state | 46 (28.7) | 4 (19.0) | 9 (33.3) | 16 (27.6) | 17 (31.5) | 0.688 |
| Bacteremia | 29 (18.1) | 4 (19.0) | 4 (14.8) | 12 (20.7) | 9 (16.7) | 0.909 |
| Inappropriate initial antimicrobial therapy | 37 (23.1) | 3 (15.0) | 6 (24.0) | 14 (24.6) | 14 (26.9) | 0.767 |
| **Clinical outcomes** | | | | | | |
| Length of hospital stay (d) | 13.5 ± 12.6 | 12.2 ± 9.4 | 13.2 ± 11.1 | 11.1 ± 6.9 | 16.6 ± 17.7 | 0.134 |
| Recovery of renal function at discharge | | | | | | 0.073 |
| Complete recovery | 123 (88.5)[a] | — | 26 (96.3) | 54 (93.1) | 43 (79.6) | |
| Partial recovery | 6 (4.3)[b] | — | 1 (3.7) | 2 (3.4) | 3 (5.6) | |
| Non-recovery | 10 (8.1)[c] | — | 0 | 2 (3.4) | 8 (14.8) | |
| Hospital mortality | 9 (5.6) | 3 (14.3) | 0 | 1 (1.7) | 5 (9.3) | 0.055 |

[a] 123 of 139 episodes of AKI had complete recovery of renal function.
[b] 6 of 139 episodes of AKI had partial recovery of renal function.
[c] 10 of 139 episodes of AKI had non-recovery of renal function.
*$p < 0.05$ among the four subgroups: non-AKI, AKI in risk stage, injury stage, failure stage.
The data are presented as $n$ (%) or as the mean ± the standard deviation.
AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; DKA = diabetic ketoacidosis.

**Table 6** Clinical outcomes of failure-stage acute kidney injury in infection-precipitated diabetic ketoacidosis

| Clinical outcomes | Non-AKI, risk, injury, ($n$ = 106) | AKI in failure stage, ($n$ = 54) | $p$ |
|---|---|---|---|
| Length of hospital stay (d) | 11.9 ± 8.6 | 16.6 ± 17.7 | 0.068 |
| Incomplete recovery of renal function at discharge | 5 (5.9)[a] | 11 (20.4) | 0.009* |
| Hospital mortality | 4 (3.8) | 5 (9.3) | 0.167 |

[a] 5 of 85 episodes with AKI in risk and injury stages had incomplete recovery of renal function at discharge.
*$p < 0.05$. The data are presented as $n$ (%) or as the mean + the standard deviation.
AKI = acute kidney injury.

however, patients with infection-precipitated DKA who developed AKI seemed to have a lower mean age (44.7± 16.1 years), a higher incidence of AKI (86.9%) on the basis of the RIFLE criteria, but lower hospital mortality (4.3%), compared to previous studies of AKI in critically ill patients such as patients with severe sepsis and septic shock. In two separate studies, patients in the intensive care unit (ICU) who developed AKI had a mean age of 62.5 years[7] and 68.5 years,[8] an AKI incidence of 67%[7] and 10.8%[8], and ICU mortality rate of 17.1%[7] and 36.3%[8]. For severe sepsis-associated AKI or septic shock-associated AKI, based on the RIFLE criteria, recent retrospective studies report that patients in the septic AKI group had a mean age of 64.9—68 years, an AKI incidence of 57.7—64.4%, and a hospital mortality rate of 16.4—59.5%.[20,22,23] The observation that younger patients developed AKI in our study may be because most (56%) patients in this specific population of DKA were 18—44 years and 24% of patients were 45—65 years.[1] In adult patients with DKA, a mortality rate of up to 22% for patients older than 65 years and 2% for younger patients has been reported.[24] Death in these conditions is rarely the result of the metabolic complications of hyperglycemia or ketoacidosis, but is associated with the underlying precipitating illness.

A systemic review and meta-analyses of 31 observational studies, which enrolled more than 500,000 patients, demonstrated a significantly increased risk of AKI in critically ill patients with an older age, diabetes, probable hypertension, high baseline creatinine, heart failure, sepsis/systemic inflammatory response syndrome, use of nephrotoxic drugs, high severity of disease scores, use of vasopressors/inotropes, or high risk or emergency surgery.[25]

For patients with infection-precipitated DKA in this current study, a high corrected Na level (adjusted OR, 1.062; $p$ = 0.039), a high initial plasma glucose level (adjusted OR, 1.003; $p$ = 0.041), severe grade of DKA (adjusted OR, 13.41; $p$ = 0.045), and high APACHE II score (adjusted OR, 1.08; $p$ = 0.033) were independent risk factors for the development of failure-stage AKI, but it was not associated with a complicated or severe infection state, shock with vasopressor use, bacteremia, or inappropriate initial antimicrobial therapy. The mechanisms of DKA-associated AKI are most likely associated with the osmotic effect of hyperglycemia, hypovolemia, and metabolic complications of ketoacidosis.[3,26] The findings of our study indicate that the development of failure-stage AKI in infection-precipitated DKA may be similar to these mechanisms.

Acute kidney injury is an independent risk factor for mortality and significantly prolongs the hospital stay of critically ill patients, which multiple studies have confirmed.[5,7,15] Furthermore, there was almost a linear increase in the odds ratio for hospital mortality from AKI in the risk to failure stage.[6—8,15] However, our study demonstrated that failure-stage AKI in infection-precipitated DKA was not associated with a longer length of hospital stay and higher hospital mortality, whereas it was associated with a higher frequency of incomplete recovery of renal function at discharge. Adjusting for covariates, bacteremia was identified as an independent predictor of incomplete recovery of renal function at discharge. Piccinni et al[15] report that septic patients have more severe AKI and are more likely to receive renal replacement therapy with less frequency of renal function recovery in all incident admissions in 10 ICUs in Italy. Furthermore, a high serum lactate level tended to be associated with poor renal outcome. Increased serum lactate concentrations imply inadequate tissue oxygenation and organ dysfunction, which respond to

**Table 7** Independent risk factor for incomplete recovery of renal function at discharge in patients with infection-precipitated diabetic ketoacidosis who developed acute kidney injury

| Renal outcome | Complete recovery ($n$ = 123) | Incomplete recovery ($n$ = 16) | Univariate $p$ value | Adjusted odds ratio | 95% CI | Multivariate $p$ value |
|---|---|---|---|---|---|---|
| Elderly > 65 y | 11 (8.9) | 4 (25) | 0.073 | 0.477 | 0.04—6.34 | 0.575 |
| Lactate (mmol/L) | 2.4 ± 1.8 | 6.6 ± 6.3 | 0.026* | 1.26 | 0.99—1.60 | 0.056 |
| Shock with vasopressor use | 6 (5.4) | 6 (46.2) | < 0.001* | 3.35 | 0.39—28.67 | 0.269 |
| AKI in failure stage | 43 (35.0) | 11 (68.8) | 0.009* | 3.06 | 0.60—15.71 | 0.18 |
| Bacteremia | 19 (15.4) | 6 (37.5) | 0.031* | 5.86 | 1.10—31.1 | 0.038** |

*Univariate $p < 0.05$.
**Multivariate $p < 0.05$.
The data are presented as $n$ (%) or as the mean ± standard deviation.
AKI = acute kidney injury; CI = confidence interval.

glycolysis promoted by stress.[27] In a recent health technology assessment on the use of lactate levels in critically ill patients, the serum lactate concentration had a place in risk-stratification in the emergency department and in the ICU.[28] In addition, recent literature has demonstrated good results for using the serum lactate level as a prognostic measure and for therapeutic decisions and clinical classification in sepsis.[29]

There are limitations to our study. First, the retrospective nature of this study hindered the completeness of data acquisition (e.g., no data were available on urine output, which is a determinant in the RIFLE classification). Second, the data were collected from a single hospital; therefore, the incidence, severity, and outcomes of diseases may be biased for a relatively small specific cohort. Third, the duration of follow-up of renal outcome was short and there was a diverse end point at discharge.

In conclusion, the present study provided the demographic characteristics of infection-precipitated DKA and risk factors for the development of failure-stage AKI (based on the RIFLE classification), and its relevant clinical outcomes, which seem to differ in patients with severe sepsis-associated AKI or septic shock-associated AKI. For patients with infection-precipitated DKA, the treating clinician should be alert and aggressively monitor renal function if a patient presents with risk factors associated with the development of failure-stage AKI. When it occurs, bacteremia predicts a poor renal prognosis.

## Conflicts of interest

The authors declare that they have no conflicts of interest relevant to the manuscript that is being submitted to the Journal of Microbiology, Immunology and Infection.

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