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## Retrospective Study

# Clinical and biochemical predictors of intensive care unit admission among patients with diabetic ketoacidosis

Adeel Ahmad Khan, Fateen Ata, Phool Iqbal, Mohammed Bashir, Anand Kartha

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## Abstract

### BACKGROUND

Diabetic ketoacidosis (DKA) contributes to 94% of diabetes-related hospital admissions, and its incidence is rising. Due to the complexity of its management and the need for rigorous monitoring, many DKA patients are managed in the intensive care unit (ICU). However, studies comparing DKA patients managed in ICU to non-ICU settings show an increase in healthcare costs without significantly affecting patient outcomes. It is, therefore, essential to identify suitable candidates for ICU care in DKA patients.

### AIM

To evaluate factors that predict the requirement for ICU care in DKA patients.

### METHODS

This retrospective study included consecutive patients with index DKA episodes who presented to the emergency department of four general hospitals of Hamad Medical Corporation, Doha, Qatar, between January 2015 and March 2021. All adult patients (> 14 years) fulfilling the American Diabetes Association criteria for DKA diagnosis were included.

### RESULTS

We included 922 patients with DKA in the final analysis, of which 229 (25%) were managed in the ICU. Compared to non-ICU patients, patients admitted to ICU were older [mean (SD) age of 40.4 ± 13.7 years vs 34.5 ± 14.6 years;  $P < 0.001$ ], had a higher body mass index [median (IQR) of 24.6 (21.5-28.4) kg/m<sup>2</sup> vs 23.7 (20.3-27.9) kg/m<sup>2</sup>;  $P < 0.030$ ], had T2DM (61.6%) and were predominantly males (69% vs 31%;  $P < 0.020$ ). ICU patients had a higher white blood cell count [median (IQR) of



15.1 (10.2-21.2)  $\times 10^3$ /uL *vs* 11.2 (7.9-15.7)  $\times 10^3$ /uL,  $P < 0.001$ ], urea [median (IQR) of 6.5 (4.6-10.3) mmol/L *vs* 5.6 (4.0-8.0) mmol/L;  $P < 0.001$ ], creatinine [median (IQR) of 99 (75-144) mmol/L *vs* 82 (63-144) mmol/L;  $P < 0.001$ ], C-reactive protein [median (IQR) of 27 (9-83) mg/L *vs* 14 (5-33) mg/L;  $P < 0.001$ ] and anion gap [median (IQR) of 24.0 (19.2-29.0) mEq/L *vs* 22 (17-27) mEq/L;  $P < 0.001$ ]; while a lower venous pH [mean (SD) of 7.10  $\pm$  0.15 *vs* 7.20  $\pm$  0.13;  $P < 0.001$ ] and bicarbonate level [mean (SD) of 9.2  $\pm$  4.1 mmol/L *vs* 11.6  $\pm$  4.3 mmol/L;  $P < 0.001$ ] at admission than those not requiring ICU management of DKA ( $P < 0.001$ ). Patients in the ICU group had a longer LOS [median (IQR) of 4.2 (2.7-7.1) d *vs* 2.0 (1.0-3.9) d;  $P < 0.001$ ] and DKA duration [median (IQR) of 24 (13-37) h *vs* 15 (19-24) h,  $P < 0.001$ ] than those not requiring ICU admission. In the multivariate logistic regression analysis model, age, Asian ethnicity, concurrent coronavirus disease 2019 (COVID-19) infection, DKA severity, DKA trigger, and NSTEMI were the main predicting factors for ICU admission.

### CONCLUSION

In the largest tertiary center in Qatar, 25% of all DKA patients required ICU admission. Older age, T2DM, newly onset DM, an infectious trigger of DKA, moderate-severe DKA, concurrent NSTEMI, and COVID-19 infection are some factors that predict ICU requirement in a DKA patient.

**Key Words:** Diabetic ketoacidosis; Type 1 diabetes mellitus; Type 2 diabetes mellitus; Intensive care unit; Critical care outcomes; Length of stay

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**Core Tip:** Diabetic ketoacidosis (DKA) patients requiring intensive care unit (ICU) support are older, have worse inflammatory markers, and have more severe DKA compared to those not requiring ICU admission. Older age, type 2 diabetes mellitus (T2DM), newly diagnosed DM during DKA episode, an infectious trigger of DKA, moderate-severe DKA, concurrent NSTEMI, and coronavirus disease 2019 infection are some factors that predict ICU requirement in a DKA patient.

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## INTRODUCTION

Diabetic ketoacidosis (DKA) is one of the most common acute complications of diabetes mellitus (DM). It contributes to 94% of diabetes-related hospital admissions[1]. DKA is classified as mild, moderate, and severe based on serum pH, bicarbonate, and mental status[2]. DKA-related admissions are rising, with an increase from 80000/year in 1988 to 140000/year in 2009[3]. DKA complicates patients with both type 1 diabetes mellitus (T1DM) and T2DM, with some studies reporting an equal proportion of T1DM and T2DM in DKA while others reported more prevalence of DKA in T1DM patients than T2DM [4,5]. It has a mortality rate between 3%-8%[6,7].

DKA management involves continuous intravenous (IV) insulin infusion, IV fluids, rigorous vital signs monitoring, hourly blood glucose, and frequent laboratory monitoring. Furthermore, patients with DKA are also at risk of several treatment-related complications, including hypoglycemia, hypokalemia, and cerebral edema[2]. Therefore, guidelines recommend managing DKA patients in ICU, leading to high ICU admission rates and healthcare costs[3,8,9]. Each DKA admission costs up to 17500 United States dollars, with annual expenses of DKA-related admissions amounting to 2.4 billion United States dollars[2]. However, studies on the benefits of routinely managing DKA patients in an ICU have mixed results. Karoli *et al*[10] reported no difference in mortality, length of stay, and DKA recurrence between patients with mild to moderate DKA treated in general wards compared to those treated in ICU. Chang *et al*[11] reported higher healthcare costs but no difference in mortality between hospitals with higher ICU utilization than those with lower ICU utilization. It is, therefore, imperative to identify DKA patients who will benefit from ICU care.

Qatar is a growing urbanized country in the Middle East with a high prevalence of DM. Hamad Medical Corporation (HMC) is the country's largest secondary and tertiary healthcare provider. Four major hospitals cover most of the population. These hospitals follow the same protocols in managing DKA. In this study, we aim to analyze the current practice in managing DKA in the four largest

hospitals in the state of Qatar. The objective is to identify the risk factors predicting ICU admission in DKA patients.

## MATERIALS AND METHODS

In this retrospective, cross-sectional study, we included consecutive patients with index DKA episodes presenting to the emergency department from four hospitals of HMC, Doha, Qatar, between January 2015 and March 2021.

### Inclusion criteria

All adult patients (> 14 years) fulfilling the criteria of DKA were included in the study. American Diabetes Association criteria were used for establishing the diagnosis of DKA and included the presence of high anion gap metabolic acidosis (pH < 7.3, bicarbonate < 18 mmol/L, anion gap > 10 mmol/L) and ketonemia/ketonuria[2]. Blood glucose > 250 mg/dL was not used in the DKA diagnosis criteria to include patients with euglycemic DKA.

### Exclusion criteria

Patients aged ≤ 14 years were excluded from the analysis. A total of 922 patients fulfilled the criteria of DKA and were included in the study. Data were extracted from electronic medical records (Cerner) by the members of the research study (PI and HHB). Demographic data included age, gender, ethnicity, body mass index (BMI), and comorbid conditions. All laboratory results at admission were recorded, including random blood glucose, glycated hemoglobin (HbA1C), beta-hydroxybutyrate (BHB), white blood cell (WBC) count, hemoglobin, urea, creatinine, sodium, potassium, venous pH, bicarbonate, chloride, lactate, and C-reactive protein (CRP). Results of blood cultures, urine cultures, and wound cultures were also recorded. Length of stay (LOS), duration of DKA, a requirement for ICU admission, and in-hospital mortality was recorded *via* chart review by the study team.

### Statistical analysis

We used descriptive statistics to present the demographic data of the study cohort. We classified DM as either type 1 or type 2 DM and whether it was new onset (diagnosed at the index DKA admission) or pre-existing. We categorized the cohort into four ethnic groups: Arab, Asian, African, and others. Ethnic-specific cut-off points were used to categorize BMI into normal, overweight, and obese. We classified patients into high metabolic risk based on the presence of one or more of the following factors: Obesity, hypertension, and dyslipidemia. Continuous variables were summarized as mean (SD) and median (IQR), while categorical variables were summarized as percentages. We compared continuous variables using unpaired *t*-test and Man-Whitney *U* as appropriate. We used the  $\chi^2$  and Fisher's tests to compare categorical variables. Factors predicting the ICU admission were assessed using univariate initially. We included all variables with  $P \leq 0.10$  in the multivariate logistic regression analysis. A *P* value of < 0.05 was considered significant. We used STATA 15 for the analysis. The statistical methods of this study were performed and reviewed by Mohammed Bashir from the Department of Endocrinology at Hamad Medical Corporation, Doha, Qatar.

## RESULTS

We included 922 patients with DKA in the final analysis, of which 229 (25%) were managed in the ICU. Compared to non-ICU patients, patients admitted to ICU were older [mean (SD) age of 40.4 ± 13.7 years *vs* 34.5 ± 14.6 years;  $P < 0.001$ ], had a higher BMI [median (IQR) of 24.6 (21.5-28.4) kg/m<sup>2</sup> *vs* 23.7 (20.3-27.9) kg/m<sup>2</sup>;  $P < 0.030$ ] and were predominantly males (69% *vs* 31%;  $P < 0.020$ ). DKA patients with T2DM were more likely to be admitted to ICU than T1D (61.6% *vs* 38.4%;  $P < 0.001$ ) (Table 1). DKA patients requiring ICU care had a higher WBC count [median (IQR) of 15.1 (10.2-21.2) × 10<sup>3</sup>/uL *vs* 11.2 (7.9-15.7) × 10<sup>3</sup>/uL,  $P < 0.001$ ], urea [median (IQR) of 6.5 (4.6-10.3) mmol/L *vs* 5.6 (4.0-8.0) mmol/L;  $P < 0.001$ ], creatinine [median (IQR) of 99 (75-144) mmol/L *vs* 82 (63-144) mmol/L;  $P < 0.001$ ], CRP [median (IQR) of 27 (9-83) mg/L *vs* 14 (5-33) mg/L;  $P < 0.001$ ] and anion at admission gap [median (IQR) of 24.0 (19.2-29.0) mEq/L *vs* 22 (17-27) mEq/L;  $P < 0.001$ ]. Patients requiring ICU admission had a lower venous pH [mean (SD) of 7.1 ± 0.15 *vs* 7.2 ± 0.13;  $P < 0.001$ ] and bicarbonate level [mean (SD) of 9.2 ± 4.1 mmol/L *vs* 11.6 ± 4.3 mmol/L;  $P < 0.001$ ] at admission than those not requiring ICU management of DKA ( $P < 0.001$ ) (Table 2).

Patients in the ICU group had a longer LOS [median (IQR) of 4.2 (2.7-7.1) d *vs* 2.0 (1.0-3.9) d;  $P < 0.001$ ] and DKA duration [median (IQR) of 24 (13-37) h *vs* 15 (19-24) h,  $P < 0.001$ ] than those not requiring ICU admission (Table 3). Concurrent coronavirus disease 2019 (COVID-19) infection was observed more in DKA patients who required ICU care (3.9% *vs* 0.3%;  $P < 0.001$ ). More patients in the ICU group had a consultation with a diabetes patient educator before the discharge than those managed

**Table 1 Comparison of demographics and baseline characteristics of diabetic ketoacidosis patients admitted to intensive care unit to those not admitted to intensive care unit, *n* (%)**

Baseline characteristics	Admitted to ICU ( <i>n</i> = 229)	Not admitted to ICU ( <i>n</i> = 693)	<i>P</i> value
Age, mean ± SD, yr	40.4 ± 13.7	34.5 ± 14.6	< 0.001
Gender			
Male	158 (69)	417 (60.2)	
Female	71 (31)	276 (39.8)	0.020
Ethnicities			
Arab	94 (41.1)	408 (58.9)	< 0.001
Asian	104 (45.4)	196 (28.2)	
Africans	23 (10.1)	67 (9.7)	
Others	8 (3.5)	22 (3.2)	
BMI, median (IQR), kg/m <sup>2</sup>	24.6 (21.5-28.4)	23.7 (20.3-27.9)	0.030
DM diagnosis			
T1DM	88 (38.43)	392 (56.6)	< 0.001
T2DM	141 (61.6)	301 (43.4)	
HbA1c at admission (mean ± SD), < 6.5 %	12.1 ± 2.7	12.0 ± 2.8	0.600
Triggering factors			
Non-compliance	45 (19.7)	217 (31.3)	0.001
Infection	77 (33.8)	164 (23.7)	
New onset DM	61 (26.7)	162 (23.4)	
Co-morbidities			
Dyslipidaemia	36 (15.7)	92 (13.3)	0.300
Stroke	9 (3.9)	17 (2.45)	0.200
Coronary artery disease	17 (7.4)	39 (5.63)	0.300
Heart failure	6 (2.6)	6 (0.9)	0.040
Hypertension	56 (24.4)	143 (20.6)	0.200
DM retinopathy	17 (7.4)	61 (8.8)	0.500
DM nephropathy	10 (4.4)	50 (7.2)	0.100
COVID-19 infection at admission	9 (3.9)	2 (0.3)	< 0.001

ICU: Intensive care unit; BMI: Body mass index; T1DM: Type 1 diabetes mellitus; DM: Diabetes mellitus; COVID-19: Coronavirus disease 2019.

in non-ICU settings (50.2% *vs* 33.6%; *P* < 0.001). No statistically significant differences in hbA1c, random glucose, BHB, and lactate levels were noted between the two groups.

Univariate and multivariate analysis identified age, Asian ethnicity, moderate DKA, severe DKA, infectious trigger, new-onset DM, concurrent COVID-19 infection, and NSTEMI as predictors of ICU admission in DKA patients (Table 4).

## DISCUSSION

This study investigated the factors predicting ICU admission in DKA patients. The ICU admission rate in the study was 25%. Patients in the ICU were older, had a higher BMI, were of Asian origin, and had predominantly T2DM. Patients in the ICU group had a higher proportion of severe DKA (58.5% *vs* 36.6%). Infection (33.8%) was the most common trigger of DKA, followed by the new onset of DM (26.7%). ICU patients had higher markers of inflammation (WBC and CRP), a longer LOS, and longer DKA duration than those who did not require ICU care. Older age, T2DM, newly onset DM, an infectious trigger of DKA, moderate-severe DKA, concurrent NSTEMI, and COVID-19 infection are



**Table 2 Comparison of laboratory parameters of diabetic ketoacidosis patients admitted to intensive care unit to those not admitted to intensive care unit**

Baseline characteristics	Units	Admitted to ICU (n = 229)	Not admitted to ICU (n = 693)	P value
Random blood glucose at admission, median (IQR)	mmol/L	24 (18.2-30.6)	23 (18.2-29.6)	0.290
White cell count at admission, median (IQR)	4-10 × 10 <sup>3</sup> /uL	15.1 (10.2-21.2)	11.2 (7.9-15.7)	< 0.001
Urea at admission, median (IQR)	mmol/L	6.5 (4.6-10.3)	5.6 (4.0-8.0)	< 0.001
Creatinine at admission, median (IQR)	umol/L	99 (75-144)	82 (63-114)	< 0.001
BHB at admission, median (IQR)	mmol/L	5.8 (4.6-7.1)	5.8 (4.5-7.4)	0.800
CRP at admission, median (IQR)	mg/L	27 (9-83)	14 (5-33)	< 0.001
Lactate at admission, median (IQR)	mmol/L	1.8 (1.2-3.1)	1.7 (1.1-2.7)	0.500
Serum pH at admission, mean ± SD	NA	7.10 ± 0.15	7.20 ± 0.13	< 0.001
Bicarbonate at admission, mean ± SD	mmol/L	9.2 ± 4.1	11.6 ± 4.3	< 0.001
Anion Gap at admission, median (IQR)	mEq/L	24.0 (19.2-29.0)	22 (17-27)	< 0.001
DKA severity	n (%)			
Mild		24 (10.5)	178 (25.7)	< 0.001
Moderate		71 (31.0)	261 (37.7)	
Severe		134 (58.5)	254 (36.6)	

ICU: Intensive care unit; BHB: Beta-hydroxybutyrate; CRP: C-reactive protein; DKA: Diabetic ketoacidosis; NA: Not available.

**Table 3 Comparison of outcomes of diabetic ketoacidosis patients admitted to intensive care unit to those not admitted to intensive care unit**

Baseline characteristics	Units	Admitted to ICU (n = 229)	Not admitted to ICU (n = 693)	P value
Total length of stay, median (IQR)	d	4.2 (2.7-7.1)	2 (1-3.9)	< 0.001
DKA duration, median (IQR)	h	24 (13-37)	15 (19-24)	< 0.001
In-hospital mortality	n (%)	7 (3)	0	NA
Consult with diabetes educator	n (%)	115 (50.2)	233 (33.6)	< 0.001

ICU: Intensive care unit; NA: Not available.

some factors that predict ICU requirement in a DKA patient.

Due to the complexities of DKA management and the requirement for rigorous monitoring, there is a high rate of admission to the ICU in DKA patients. However, not all patients with DKA need ICU care [10,11]. In this study, the rate of ICU admission -25%- is much lower than similar published data. Despite the lower rate of ICU admissions, the overall mortality rate was 0.7% in our cohort which is lower than other studies. A study from Spain reported a higher rate of ICU admission (52%) in a cohort of 164 DKA patients despite having fewer cases with severe DKA (49.4% vs 58.5%) than our study. The overall mortality rate was also higher (1.2% vs 0.7%) as compared to our study[8]. Almazrouei *et al*[9] reported a 74% ICU admission rate and 1.8% overall mortality rate in DKA patients despite having a younger cohort (Mean age 30.6 years vs 36 years) and fewer cases of severe DKA (18.0% vs 58.5%) than our cohort. A lower ICU admission rate with a lower overall mortality rate in our cohort could be explained by the hospital-wide use of a DKA management protocol. The utility of mandatory DKA protocols in decreasing ICU utilization has been reported in the literature[12]. Our hospital employs a strict ICU admission criterion for DKA patients to optimize ICU bed utilization. This includes patients with hemodynamic instability, altered level of consciousness, septic shock, and those with underlying heart failure or end-stage renal disease. Lower overall mortality rate despite lower ICU admission rate indicates the success of ICU admission criteria in maintaining a balance between cost-effectiveness and patient safety.

Accurate identification of DKA patients who require ICU care can help lower healthcare costs and bed occupancy while at the same time improve clinical outcomes in patients at risk of worse outcomes.

**Table 4** Logistic regression analysis factors predicting intensive care unit admission in diabetic ketoacidosis patients

Characteristics (n)	Unadjusted OR (95%CI)	P value	Adjusted OR (95%CI)	P value adjusted
Age (yr)	1.02 (1.01-1.03)	< 0.001	1.020 (1.006-1.040)	0.010
Male gender	1.47 (1.07-2.02)	0.010	0.86 (0.60-1.20)	0.400
DM diagnosis				
T2D	2.08 (1.53-2.83)	< 0.001	1.2 (0.8-1.8)	0.400
Ethnicity				
Arab	1	< 0.001	1.70 (1.17-2.56)	0.005
Asian	2.3 (1.7-3.2)			
DKA trigger				
Non-compliance	1		1	
Infection	2.3 (1.5-3.4)	< 0.001	1.90 (1.22-3.06)	0.005
New DM	1.80 (1.17-2.80)	0.007	1.70 (1.06-2.76)	0.020
DKA severity				
Mild	1		1	
Moderate	2.01 (1.20-3.30)	0.006	2.60 (1.51-4.46)	0.001
Severe	3.90 (2.40-6.30)	< 0.001	4.70 (2.80-7.87)	< 0.001
NSTEMI during hospital stay	6.20 (1.54-25.00)	0.010	8.9 (1.2-66.9)	0.030
COVID-19 infection	14.13 (3-66)	0.001	7.8 (1.5-40.0)	0.010

DKA: Diabetic ketoacidosis; DM: Diabetes mellitus; T2DM: Type 2 diabetes mellitus; COVID-19: Coronavirus disease 2019; 95%CI: 95% confidence interval; OR: Odds ratio.

Siregar *et al*[13] found an increased number of comorbid conditions, decreasing level of consciousness, history of prior DKA episodes and increase in lactate level as significant factors in the 72-h mortality prediction model in DKA patients. High blood glucose, urea, creatinine, sodium potassium and low pH within the first 24 h predicted in-hospital mortality in DKA patients in a study by Venkatesh *et al*[14]. Fever and quantity of insulin required during the initial 12 h of DKA are some other factors that are associated with increased risk of mortality in DKA patients[15]. Furthermore, during the recent COVID-19 pandemic, a study identified concurrent COVID-19 infection as a significant factor associated with increased mortality in DKA patients[7]. We found some additional factors compared to mortality-related factors previously reported in studies, and these include new-onset DM, the severity of DKA, Asian ethnicity, concurrent COVID-19 infection and NSTEMI. The authors suggest developing a clear algorithm for escalating and de-escalating care based on the above mentioned factors to identify DKA patients who might benefit from ICU care. This will decrease unnecessary ICU bed occupancy and reduce healthcare costs, and will enable the physicians to identify DKA patients at risk of worse outcomes. Most of the DKA patients are younger as compared to other patients and are prone to refusal of ICU admission based on their demographic profile. DKA management algorithm can alleviate this concern. Furthermore, an evidence-based DKA management algorithm can also contribute to decrease the variations in the DKA management practices among physicians.

A unique strength of this study is the inclusion of patients from multiple ethnic backgrounds, which allowed for identifying Asian ethnicity as being at high risk of requiring ICU admission. The study included DKA patients with both T1DM and T2DM, contributing to a larger and heterogenous sample size of DKA patients requiring ICU admission. We also categorized DKA patients according to the severity of DKA, with most patients in the ICU group belonging to moderate-severe DKA categories, thereby allowing accurate prediction of ICU care requirements in this group of patients. An important limitation of the study is the retrospective design which precludes adjustment for confounders. The long-term morbidity or mortality assessment of DKA patients after the index ICU admission was also not performed and need further studies in this regard.

## CONCLUSION

DKA patients requiring ICU support are older, have worse inflammatory markers and more severe

DKA compared to DKA patients not requiring ICU admission. It is important to identify suitable candidates requiring ICU care for DKA. Older age, T2DM patients, newly diagnosed DM during DKA episodes, an infectious trigger of DKA, moderate-severe DKA, concurrent NSTEMI and COVID-19 infection are some factors that predict ICU requirement in a DKA patient. Implementing the DKA management algorithm for escalation and de-escalation of care can help standardize DKA management practices and reduce variability in ICU admission rates.

## ARTICLE HIGHLIGHTS

### **Research background**

Diabetic ketoacidosis (DKA) is one of the most common acute complications of diabetes mellitus (DM). A significant number of DKA patients are admitted to the intensive care unit (ICU). However, not all DKA patients benefit from ICU admission.

### **Research motivation**

To identify patients who will benefit from ICU care is essential by looking into the factors that predict ICU admission in DKA patients.

### **Research objectives**

To identify various risk factors that predict the requirement for ICU care in DKA patients.

### **Research methods**

This is a retrospective cross-sectional study and included 922 adult patients with DKA. The study looked into the factors predicting ICU care requirements in DKA patients by logistic regression analysis.

### **Research results**

DKA patients (25% of all) were admitted to ICU. Patients in the ICU were older, had a higher BMI, were of Asian origin, and had predominantly T2DM. Patients in the ICU group had a higher proportion of severe DKA (58.5% *vs* 36.6%). Infection (33.8%) was the most common trigger of DKA, followed by the new onset of DM (26.7%). ICU patients had higher markers of inflammation (WBC and CRP), a longer LOS, and longer DKA duration than those who did not require ICU care. Older age, T2DM, newly onset DM, an infectious trigger of DKA, moderate-severe DKA, concurrent NSTEMI, and COVID-19 infection are some factors that predict ICU requirement in a DKA patient.

### **Research conclusions**

ICU admission rate in our DKA patients was lower than in other studies. Despite this, the overall mortality rate in our cohort was only 0.7%. Accurate identification of factors that predict ICU requirements in DKA patients can prevent unnecessary ICU bed occupancy and maintain a balance between cost-effectiveness and patient safety.

### **Research perspectives**

Further studies are needed to look into the factors that might predict the need for ICU care at the time of presentation in DKA patients.

## FOOTNOTES

**Author contributions:** Khan AA contributed to the study design, interpreted the data, and wrote the manuscript; Ata F conceptualized and designed the study, obtained ethical approval, and contributed to writing the manuscript; Iqbal P contributed to the acquisition of data and literature review; Bashir M and Kartha A are the co-last authors of the manuscript; Bashir M performed the statistical analysis and critically revised the manuscript's content; Kartha A was the overall supervisor of the study and contributed to the study design and revision of the manuscript; all authors approved the final version of the article.

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