Comparison of a ‘two-bag system’ versus conventional treatment protocol (‘one-bag system’) in the management of diabetic ketoacidosis

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ABSTRACT

Objective We compared the conventional ‘one-bag’ protocol of management of diabetic ketoacidosis (DKA) with the ‘two-bag protocol’ which utilizes two bags of fluids, one containing saline and supplemental electrolytes and the other containing the same solution with the addition of 10% dextrose.

Research design and methods A retrospective chart review and analysis was done on adult patients admitted for DKA to the Riverside University Health System Medical Center from 2008 to 2015. There were 249 cases of DKA managed by the one-bag system and 134 cases managed by the two-bag system.

Results The baseline patient characteristics were similar in both groups. The anion gap closed in 13.56 hours in the one-bag group versus 10.94 hours in the two-bag group (p value <0.0002). None of the individual factors significantly influenced the anion gap closure time; only the two-bag system favored earlier closure of the anion gap. Plasma glucose levels improved to <250 mg/dL earlier with the two-bag protocol (9.14 vs 7.82 hours, p=0.0241). The incidence of hypoglycemic events was significantly less frequent with the two-bag protocol compared with the standard one-bag protocol (1.49% vs 8.43%, p=0.0064). Neither the time to improve serum HCO3 level >18 mg/dL nor the hospital length of stay differed between the two groups.

Conclusions Our study indicates that the two-bag protocol closes the anion gap earlier than the one-bag protocol in adult patients with DKA. Blood-glucose levels improved faster with the two-bag protocol compared with the one-bag protocol with fewer associated episodes of hypoglycemia. Prospective studies are needed to evaluate the clinical significance of these findings.

INTRODUCTION

Nearly 10% of the population in the USA has diabetes mellitus.1 Diabetic ketoacidosis (DKA) is a well-known, serious, acute metabolic complication. While it is primarily associated with type 1 diabetes mellitus two-thirds of the time, it also occurs in type 2 diabetes mellitus approximately 34% of the time,2 often as a manifestation of the syndrome of ketosis-prone diabetes.2 The incidence of DKA continues to rise. The Centers for Disease Control and Prevention (CDC) estimates that there were 140,000 hospital discharges from DKA in 2009 in the USA, about 75% increase over the last two decades3 with an estimated cost annually of >$2 billion and accounts for >500,000 hospital days per year.4

Along with identification of triggering factors, management of DKA involves correction of hyperglycemia, volume depletion, acid–base derangements and electrolyte imbalances.2 Because of the complexities in the management protocol, many cases of DKA are managed in intensive care units (ICUs) across the USA.5 Losses of fluids and electrolytes are significant causes of mortality and morbidity.

Significance of this study

What is already known about this subject?

► The two-bag protocol for treating diabetic ketoacidosis (DKA) has been used in pediatric patients with some benefit and cost savings as outlined in the introduction section.

What are the new findings?

► This study was conducted in adult subjects with DKA. Our study indicates that the two-bag protocol closes the anion gap earlier than the one-bag protocol in adult patients with DKA. Blood glucose levels improved faster with the two-bag protocol compared with the one-bag protocol with fewer associated episodes of hypoglycemia.

How might these results change the focus of research or clinical practice?

► The two-bag protocol could potentially be beneficial in treating patients with DKA compared with the conventional one-bag protocol. Prospective studies need to be designed to evaluate the benefit of the two-bag system in reducing intensive care unit stay and overall cost reduction in DKA management.
in DKA. The mortality is <1% in American adults, however, rises to >5% in the elderly population with significant comorbidities. In the USA, the age-adjusted mortality rate for hyperglycemic crisis declined between 1980 and 2009. In 2009, hyperglycemic crises caused 64% lower mortality than in 1980.

Evidence-based guidelines for the diagnosis and management of DKA have been published periodically in North America and Europe, improving the understanding and facilitating the development of management protocols. The outcomes of DKA have been shown to improve with adherence to treatment guidelines. Minor variants of the commonly used treatment protocol for DKA based on the published guidelines use insulin infusions and intravenous electrolyte solution and dextrose solution when blood sugar drops below 250 mg/dL. In order to correct dehydration in patients with DKA, intravenous electrolyte solutions are administered at the beginning of the treatment. As the blood glucose levels fall, a new bag of intravenous fluid with different dextrose concentrations would be ordered, and multiple sequential changes of bags would occur during the course of treatment. Despite their proven effectiveness, a varying degree of non-adherence to guidelines has been documented in the literature compromising the success of published protocols. Successful implementation of the conventional DKA protocol requires not only careful assessment of the clinical status of the patient and laboratory values, but frequent changes to intravenous fluids between saline and dextrose solutions.

The ‘two-bag system’ was first described in the early 1990s in pediatric patients. As opposed to the conventional protocol (one-bag system), the two-bag system uses two bags of fluids with identical electrolyte content but different dextrose concentrations, 0% and 10%. The two bags are connected in a ‘Y’ fashion and by adjusting the infusion rates from each bag, the concentration of dextrose can be customized to prevent unpredictable excursions in blood glucose. The two-bag system has been more commonly used and exclusively studied in the pediatric population and has been found to be cost effective. It has also been shown to result in more rapid improvement in bicarbonate and ketone correction and a trend toward faster improvement of hyperglycemia in DKA. In one study, the two-bag system was well received by nursing and house staff because it was less labor intensive than the traditional one-bag system.

To our knowledge, the two-bag system has not been compared with the one-bag system in the adult DKA population in the published literature. We performed a retrospective cohort study comparing the traditional one-bag protocol previously used at our institution with the newly initiated two-bag protocol. The primary purpose of our study is to compare the time to correction of the anion gap in adult patients with DKA.

**RESEARCH DESIGN AND METHODS**

Our study focused on adult patients with the diagnosis of DKA between the years of 2008 and 2015 who were admitted to the inpatient services of Riverside University Health System Medical Center. Our hospital is a safety-net hospital that serves the residents of Riverside County, California, with approximately 189,000 outpatient visits, 21,900 inpatient admissions, and 100,000 emergency room visits annually. Our hospital treated patients with DKA with a hospital-wide protocol that used the conventional one-bag system until 2013 when the treatment approach transitioned to the two-bag system (supplementary appendix 1). In our hospital, after initial diagnosis of DKA in the emergency room, the DKA protocol is initiated by ER physicians. In our institution, the DKA protocol is a hospital-wide protocol, which is followed in the inpatients units as well as in the emergency room. Any patient who requires an insulin drip automatically gets admitted to the ICU. If there is a delay in getting an ICU bed, the protocol is carried out in the ER. In our patient population, except a small group of patients with a diagnosis of mild DKA in the ER who improved on subcutaneous insulin therapy, all other patients were admitted for ICU care.

All adult patients over the age of 18 years with an admitting diagnosis of DKA were retrospectively identified from the medical record searching through ICD-9-CM codes 250.10 (DKA in type 1 diabetes) and 250.11 (DKA in type 2 diabetes) diagnosis. Once a list of the patients was gathered, the diagnosis of DKA was verified. The following criteria were used to define DKA, a blood glucose ≥250 mg/dL, and two of the following three criteria: serum bicarbonate (HCO₃) <18 mEq/L; serum beta-hydroxybutyrate (BHB) >3 mmol/L; and pH <7.30. Patients with a diagnosis of hyperosmolar hyperglycemic state as a final diagnosis in the chart were excluded. Ketosis from any other etiology, for example, alcoholic ketoacidosis, starvation ketosis, as a final diagnosis in the chart was excluded. Our chart review confirmed that there were no pregnant patients on our list eliminating any case of DKA associated with pregnancy. During initial chart review, we did not include any patient with DKA who was not started on an insulin drip eliminating cases of DKA treated with a subcutaneous insulin protocol. We identified 383 patients admitted with DKA that received treatment with either the one-bag system (n=249) or the two-bag system (n=143). Data were extracted from individual chart review using a standard data collection instrument that recorded the following information at the time of admission: patient’s age and sex, hemoglobin A1c (HgbA1c), body weight, body mass index (BMI), pH, anion gap, admission blood glucose, comorbidities, HCO₃, serum BHB, and the time of initiation and discontinuation of the DKA protocol. We also captured changes in anion gap, serum glucose, and bicarbonate level as patients received treatment for DKA.
**Study outcomes**

During the treatment of DKA, hyperglycemia is corrected faster than the ketoacidosis. Thus, we chose closure of the anion gap as our primary outcome measure which served as a surrogate for the resolution of DKA. Our secondary outcome was time to reach plasma glucose <250 mg/dL, time to reach HCO₃⁻ level >18 mmol/L, and hospital length of stay.

**Sample size calculation**

Because we could not find any prior study focusing on the timing of the closure of the anion gap addressing our research question, we took a small convenience sample of seven patients who were recently admitted with the diagnosis of DKA. The average time to close the anion gap was 10.4 hours with an SD of 6.4 hours. We decided that a 15% difference in time from this average would be considered clinically significant. Using an effect size of 0.25, an unpaired two-sided t-test, an alpha of 0.05, a beta of 0.2, and a power of 80%, the calculated sample size was 199 per group.

**Data analysis**

The descriptive analysis comparing the baseline characteristics of the two cohorts used the two-independent samples t-test for continuous variables and χ² test for proportions for categorical variables. Outcome measures comparing the one-bag versus two-bag protocols used the two-independent samples t-test to compare the time to closure of the anion gap (primary outcome measure) and time to reach plasma glucose <250 mg/dL, time to reach HCO₃⁻ level >18 mmol/L, and hospital length of stay (secondary outcome measures). The relationship between the time to closure of the anion gap and admission variables was assessed using the Pearson product–moment correlation. To further compare the times to closure of the anion gap between the two protocols while statistically controlling for the effects of admission variables that were not of primary interest, an analysis of covariance (ANCOVA) model was developed using time to closure of the anion gap as the dependent variable, and the following admission variables as covariates: patient’s age, weight, BMI, admission pH and anion gap, BHB, blood urea nitrogen (BUN), serum creatinine, serum blood glucose, HgbA1c, and the Charlson Comorbidity Index. A stepwise model selection method was used to determine the significant variables in the ANCOVA model. Data were entered into a Microsoft Excel spreadsheet and analyzed using SAS V.9.3.

This study was prospectively approved by the Institutional Review Board (IRB) of the Riverside University Health System Medical Center.

**RESULTS**

A total of 383 patients admitted with DKA to our hospital were eligible for the study. In total, 249 patients admitted with DKA had received the conventional one-bag system and 134 patients were treated with the newly adopted two-bag system.

As shown in Table 1, the mean age of the patients was approximately 37 years and similar in the one-bag and two-bag cohorts. Patients of both groups had uncontrolled diabetes mellitus, with an average HgbA1c over 11 (11.7% vs 11.6%). Average BMIs were comparable in both groups (25.8 vs 24.4) as were body weights (75.5 vs 71.3 kg). Patients presented with a serum pH averaging 7.20 in both groups, and similar corrected anion gap levels (23.4 vs 23.8). Overall, the severities of patients’ DKA at presentation were comparable with 25.70% versus 24.63% in mild DKA, 31.33% versus 38.81% in moderate DKA, and 42.97% versus 36.57% in severe DKA between one-bag and two-bag groups, respectively. Patients in both groups presented with significant hyperglycemia with blood glucose levels exceeding 400 mg/dL (473 vs 511 mg/dL). Interestingly, the BHB level was significantly higher in the two-bag group cohort (7.8 vs 4.4 mmol/L).

**CONCLUSIONS**

The purpose of this retrospective cohort study was to determine if a two-bag system significantly influenced resolution of DKA in adult patients presenting with DKA. Since anion gap is widely used by clinicians as a surrogate of resolution of DKA in our analysis. The time to close anion gap was 13.56 hours in the conventional one-bag system protocol (table 2). This time period was decreased significantly to 10.94 hours in the patient group treated with two-bag protocol (p=0.0002). Time to reach plasma glucose below 250 mg/dL was significantly shorter with the two-bag protocol (p=0.0241). Time to raise serum HCO₃⁻ >18 mmol/L was not statistically significant between the two groups, although it was shorter in the two-bag group (p=0.90). The incidence of hypoglycemic events, defined as a blood sugar <70 mg/dL, was significantly less frequent with the two-bag protocol compared with the standard one-bag system (1.49% vs 8.49%, p=0.0064). The length of hospital stay was also modestly decreased by one half day in the two-bag group, although this difference did not reach statistical significance (p=0.099). The correlation coefficients between time to closure of the anion gap and admission variables are close to zero, indicating a very weak correlation between time to closure of the anion gap and the admission variables (table 3). In the ANCOVA model, the effects of all admission variables were not significant, except for the Charlson Comorbidity Index (t=-2.97, p=0.003). The protocol effect adjusted for the Charlson Comorbidity Index was significant in the ANCOVA model (t=3.10, p=0.0021), which further indicates the significant difference in the time to closure of the anion gap between the two protocols.
Table 1  Clinical characteristics of the study population

| Variable                        | One-bag system (total number=249) | Two-bag system (total number=134) | p Value |
|---------------------------------|------------------------------------|------------------------------------|---------|
|                                 | Number (100%)                      | Number (100%)                      |         |
|                                 | Mean (±SD)                         | Mean (±SD)                         |         |
| Age (years)                     | 249 (100%)                         | 134 (100%)                         | 0.23    |
|                                 | 37.7 (±14.9)                       | 36.1 (±14.8)                       |         |
| Male                            | 249 (100%)                         | 134 (100%)                         | 0.60    |
|                                 | 144 (57.8%)                        | 73 (54.5%)                         |         |
| Weight (kg)                     | 173 (69%)                          | 134 (100%)                         | 0.06    |
|                                 | 75.5 (±22.7)                       | 71.3 (±20.5)                       |         |
| BMI (kg/m²)                     | 152 (61%)                          | 125 (93%)                          | 0.11    |
|                                 | 25.8 (±7.1)                        | 24.4 (±5.86)                       |         |
| Initial pH                       | 177 (71%)                          | 102 (76%)                          | 0.94    |
|                                 | 7.21 ± 0.14                        | 7.24 ± 0.16                        |         |
| BHB (mmol/L)                    | 156 (63%)                          | 127 (95%)                          | <0.01   |
|                                 | 4.4 (±4.4)                         | 7.8 (±5.0)                         |         |
| BUN (mg/dL)                     | 249 (100%)                         | 134 (100%)                         | 0.49    |
|                                 | 23.1 (±14.4)                       | 23.8 (±14.3)                       |         |
| Creatinine (mg/dL)              | 249 (100%)                         | 134 (100%)                         | 0.12    |
|                                 | 1.48 (±1.68)                       | 1.40 (±0.90)                       |         |
| Admission serum glucose (mg/dL) | 233* (94%)                         | 134 (100%)                         | 0.05    |
|                                 | 473.6 (±198.0)                     | 511.7 (±193.3)                     |         |
| Anion gap (mmol/L)              | 249 (100%)                         | 134 (100%)                         | 0.52    |
|                                 | 23.4 (±6.3)                        | 23.8 (±5.9)                        |         |
| HgbA1c (%)                      | 204 (82%)                          | 134 (100%)                         | 0.70    |
|                                 | 11.7 (2.0)                         | 11.6 (2.0)                         |         |
| Charlson comorbidity index      | 249 (100%)                         | 134 (100%)                         | 0.36    |
|                                 | 1.66 (±1.18)                       | 1.54 (±1.11)                       |         |

Baseline data are means ± SD. Some data are missing or not recorded in the chart to account for less than the total numbers in each group.
*Sixteen missing values were recorded as ‘high’ by the glucometer (ie, >600 mg/dL) and were recorded as unmeasurable in the chart.
BHB, beta-hydroxybutyrate; BMI, body mass index; BUN, blood urea nitrogen; HgbA1c, hemoglobin A1c.

Table 2  Primary and secondary outcomes

| Outcome                          | One-bag system Mean (±SD) | Two-bag system Mean (±SD) | p Value |
|----------------------------------|---------------------------|---------------------------|---------|
| Primary outcome                  |                           |                           |         |
| Time to close anion gap (hours)  | 13.57 (±1.75)             | 10.95 (±1.63)             | <0.01   |
| Secondary outcomes              |                           |                           |         |
| Time to reach plasma glucose<250 mg/dL (hours) | 9.15 (±1.38)                                         | 7.82 (±1.28) | 0.02    |
| Time to reach serum HCO₃>18 mmol/L (hours) | 19.95 (±1.99)             | 18.50 (±2.28)             | 0.36    |
| Hospital length of stay (days)  | 4.86 (±3.63)              | 4.33 (±2.53)              | 0.09    |
| Hypoglycemia (BS<70 mg/dL)      | 8.43                      | 1.49                      | <0.01   |

Outcome measures comparing the one-bag versus two-bag protocols used the two independent samples t-test. For details, see online supplementary appendix 2.
of the groups given the limitation of collecting accurate data in our retrospective study. A comparison of the published studies to date on the two-bag DKA protocol has been summarized in table 4.

To our knowledge, this is the first study comparing the two-bag protocol with the conventional one-bag protocol in an adult population. Strengths of this study include the large sample size and similar patient populations as evidenced by the baseline characteristics of the study groups. The two study groups did not differ in age, BMI, HgbA1c, BUN/creatinine, initial blood sugar, anion gap, and vomiting, resulting in metabolic alkalosis. The bicarbonate level does not reflect the true level of acidosis in most situations, it is unreliable in cases of mixed acid–base disorders or in hyperchloremic metabolic acidosis presenting without a significant anion gap.27 Similarly, there are limitations in the interpretation of the bicarbonate level as a measure of acidosis as well. For example, many patients with DKA present with nausea and vomiting, resulting in metabolic alkalosis. The bicarbonate level does not reflect the true level of acidosis in

The key diagnostic feature in DKA is the elevation of total blood ketone concentrations in the background of relative or absolute insulin deficiency.2 In patients with DKA, metabolic alterations due to insulin deficiency result in the accumulation of ketoacids causing an anion gap metabolic acidosis. In our study, BHB, the main metabolic product of ketosis,25 26  was measured in the serum with a quantitative assay by the central laboratory as opposed to a semiquantitative nitroprusside reaction. Although the anion gap reflects the degree of acidosis in most situations, it is unreliable in cases of mixed acid–base disorders or in hyperchloremic metabolic acidosis presenting without a significant anion gap.27

| Reference | Study design | Hospital setting | Patients | Outcome measure |
|-----------|--------------|------------------|----------|----------------|
| Grimberg et al21 | Retrospective case–control | Single center inpatient— Philadelphia, Pennsylvania | 20 pediatric patients (mean age 12–13): 10 one-bag, 10 two-bag | Two-bag system decreased number of intravenous bags used, response time by nursing to make changes in intravenous fluids, and costs of intravenous fluid therapy |
| Poirier et al22 | Prospective non-blinded clinical trial | Single-center pediatric emergency room—Norfolk, Virginia | 33 pediatric patients (mean age 11–14): 16 one-bag, 17 two-bag | Two-bag system decreased the time for nursing to make changes in intravenous fluids No difference in blood glucose or bicarbonate correction nor the number of intravenous bags used |
| So and Grunewald er et al22 | Retrospective series | Single-center inpatient— Greensboro, North Carolina | 31 pediatric patients (mean age 13–14): 9 one-bag, 22 two-bag | Two-bag system corrected bicarbonate and ketone levels faster No time difference for blood glucose and pH correction |
| Current series 2010–2015 | Retrospective cohort | Single-center inpatient— Riverside, California | 383 adult patients (mean age 36–37): 249 one-bag 134 two-bag | Two-bag system closed the anion gap faster (10.94 vs 13.56 hours) No significant time difference in hospital length of stay |
such situations or during severe volume contraction. Therefore, the clinical decision-making involves evaluating multiple parameters of acid–base imbalance including serum anion gap, serum bicarbonate level, and measurement of serum pH. Our study did not compare resolution of acidosis by serial pH or beta-hydroxybutyrate measurements, which were not available in a large number of patients in our data set.

In our study, although the AG corrected earlier in DKA patients treated with the two-bag protocol, the time for serum bicarbonate level to reach >18 was similar in both groups. Additionally, improvement of the bicarbonate level lagged behind the anion gap closure. This may indicate that relative hyperchloremia, resulting from the large volume of normal saline infusions during volume resuscitation, leads to the correction of the AG. However, ketone levels remained elevated for a longer duration accompanied by reduced serum bicarbonate levels until finally correcting with the insulin infusion. Both protocols were based on guidelines of fluid resuscitation in patients with DKA published by ADA. Clinicians made the final decision regarding how much fluid was needed for a patient based on clinical findings, dehydration, and comorbidities. We could not collect the data on the total volume of intravenous fluid containing sodium chloride in our study population and do not know whether there was any difference in the intravenous fluid administered.

In this study, we only included patients with DKA admitted to the ICU setting. The pattern of ICU utilization for patients with DKA varies among institutions. More than 50% of patients with DKA are admitted to the ICU. The financial burden of DKA management is significant, with estimated mean expenses for a single hospitalization ranging from $7470 to $20,864. The itemized expense calculation of DKA costs shows that a significant cost in DKA management involves the cost of the ICU stay and laboratory testing. Although we found that the anion gap closure was earlier with two-bag protocol, whether this will result in any reduction of cost was not addressed in this study. A randomized prospective study needs to be designed to answer these questions. In our population, the average length of stay was >4 days in both groups. Although we could not compare duration of ICU stay, in patients treated with the two-bag protocol, the average length of hospital stay decreased by half a day, although the difference did not reach statistical significance. In a recent report published by the CDC, the average length of hospital stay was found to be decreased to 3.4 days for hospital discharges with DKA as the first-listed discharge diagnosis. The average length of hospital stay in our study was above the national average regardless of the protocol used. Multiple factors have contributed to the shortened length of hospital stay in the published literature including widespread use of protocols for DKA management, enhanced staff training, and involvement of specialized diabetes nurses. There are additional disease-specific factors that could influence the length of hospital stay including gastroparesis, concurrent infection, cognitive impairment, and rehabilitation requirements. Our study did not compare the disease-specific factors that potentially could have influenced the length of hospital stay. Although, as a safety net medical center, we serve a patient population with a low socioeconomic status and higher burden of comorbidities, which may contribute the longer length of stay in our study. Another study, in an inner-city population with predominantly African American patients, showed the average length of stay of 4.5 days, which is similar to our study.

This study had several limitations including a retrospective study design and a patient population limited to a single safety net medical center, which may limit its external applicability. The large Hispanic population that our hospital serves has a very high prevalence of obesity and uncontrolled diabetes. In addition, we could not reach our calculated sample size for 199 for the two-bag group (fell short by 56 patients), raising possibility of a type II error. Because of the retrospective nature of our study, we also cannot exclude the possibility that temporal changes in the management of DKA other than the introduction of the two-bag protocol could have occurred during the time span of the study that were not collected by our standardized data collection instrument.

To minimize this bias, management of DKA from 2008 to 2015 was driven by standardized hospital-wide protocols and the Charlson Comorbidity Indices in the two groups were comparable. In spite of this, some key laboratory information such as pH, BHB, and admission HbA1c was not systematically collected in all patients. For these three variables, no differences were found on admission between the two groups and in our ANCOVA model. While we found an approximate half-day reduction in the length of stay using the two-bag protocol, this difference was not statistically significant and our study may have been underpowered to detect this secondary outcome. Finally, inherent in any retrospective study, residual confounding from other unmeasured or inaccurately measured variables excludes any definitive statements of causality and we can only state that the two-bag protocol was associated with a faster time to closure of the anion gap and significantly fewer episodes of hypoglycemia.

Our study supports the use of the two-bag protocol as another method of DKA treatment. The fundamentals of DKA treatment, for example, volume repletion and correction of electrolyte imbalance, are similar in both groups. Two-bag protocol may be beneficial in certain clinical settings due to faster resolution of anion gap, faster rate of improvement of blood sugar, and lesser episodes of hypoglycemia. Future studies will indicate whether faster anion gap closure results in overall cost reduction of DKA management. Reduction of hypoglycemic events associated with the two-bag protocol has a direct impact on patient safety. The two-bag system can be easily adapted as an ICU protocol with minimal staff training. This study supports the use of the two-bag system in treating adult patients with DKA. A larger,
randomized prospective study to further study this issue would be beneficial.

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Data sharing statement Further details of the data and analysis for this study could be obtained by contacting the corresponding author (IM) of this manuscript. They have included almost all the data generated for this study in the manuscript. They did not include data of anion gap closure and serum bicarbonate improvement according to the severity of DKA (severity based on only admission data) and approved the final version of the manuscript submitted. KX performed and approved the final version of the manuscript submitted. They have included almost all the data generated for this study in the manuscript. They did not include data of anion gap closure and serum bicarbonate improvement according to the severity of DKA (severity based on only admission data) and approved the final version of the manuscript submitted.

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