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Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Clinical profile and outcomes in COVID-19 patients with diabetic ketoacidosis: A systematic review of literature

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ARTICLE INFO

Article history:

Received 5 August 2020

Accepted 14 August 2020

Keywords:

COVID-19

Diabetic ketoacidosis

Hyperglycemic hyperosmolar syndrome

Subcutaneous insulin therapy

ABSTRACT

Background and aim: To conduct a systematic literature review and analyze the demographic/biochemical parameters and clinical outcomes of COVID-19 patients with diabetic ketoacidosis (DKA) and combined DKA/HHS (hyperglycemic hyperosmolar syndrome).

Methods: PubMed, Scopus, Embase, and Google Scholar databases were systematically searched till August 3, 2020 to identify studies reporting COVID-19 patients with DKA and combined DKA/HHS. A total of 19 articles reporting 110 patients met the eligibility criteria.

Results: Of the 110 patients, 91 (83%) patients had isolated DKA while 19 (17%) had DKA/HHS. The majority of the patients were male (63%) and belonged to black ethnicity (36%). The median age at presentation ranged from 45.5 to 59.0 years. Most of the patients (77%) had pre-existing type 2 diabetes mellitus. Only 10% of the patients had newly diagnosed diabetes mellitus. The median blood glucose at presentation ranged from 486.0 to 568.5 mg/dl, being higher in patients with DKA/HHS compared to isolated DKA. The volume of fluid replaced in the first 24 h was higher in patients with DKA/HHS in contrast to patients with DKA alone. The in-hospital mortality rate was 45%, with higher mortality in the DKA/HHS group than in the isolated DKA group (67% vs. 29%). pH was lower in patients who had died compared to those who were discharged.

Conclusion: DKA in COVID-19 patients portends a poor prognosis with a mortality rate approaching 50%. Differentiating isolated DKA from combined DKA/HHS is essential as the latter represents nearly one-fifth of the DKA cases and tends to have higher mortality than DKA alone.

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1. Introduction

People with diabetes mellitus (DM) represent a highly vulnerable population at a high-risk of poor prognosis with the novel coronavirus disease (COVID-19). The presence of DM increases the probability of severe disease, admission to the intensive care unit, and mortality due to COVID-19 [1–4]. Impaired host defense, immune dysregulation with an increased predisposition to cytokine storm, and altered angiotensin-converting enzyme 2 (ACE2) expression have been implicated as the underlying pathophysiological mechanisms [3,5].

As with other severe infections [6], diabetic ketoacidosis (DKA)

has been reported in patients with COVID-19 [7–24]. With regard to coronaviruses, it has been shown that SARS-CoV (responsible for the SARS outbreak in 2003) binds to ACE2 in the pancreatic islets leading to islet damage and acute diabetes [25]. As SARS-CoV-2 (causative organism of COVID-19) also binds to ACE2, the virus might also result in acute diabetes [26]. This theoretical pathophysiology could lead to insulinopenia and increased risk of DKA, especially in patients with pre-existing DM [13]. Besides, interleukin-6, an important cytokine of the hyper-inflammatory state in COVID-19, has also been found to be elevated in DKA and serves as a driver of ketogenesis [27]. Thus, although there is insufficient data, DKA may be more prevalent in COVID-19 and SARS-CoV-2 may pose an increased risk over other infectious diseases of equivalent severity [13]. Apart from DKA, occasional cases of combined DKA and hyperglycemic hyperosmolar syndrome (HHS) have also been reported in COVID-19 [22,28].

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The clinical outcome of COVID-19 patients with DKA has been somewhat conflicting across studies; while one study found a mortality rate of 50% in COVID-19 patients with DKA [9], another study found that patients with DKA were more likely to survive compared to non-DKA patients [17]. Moreover, patients with combined DKA and HHS tend to have higher mortality than either DKA or HHS alone [29], however, similar comparative data in COVID-19 is lacking.

The aim of the study was to provide a comprehensive systematic literature review of DKA and combined DKA/HHS in patients with confirmed COVID-19 in order to analyze the demographic and biochemical parameters and the clinical outcomes.

2. Material and Methods

2.1. Search strategy and selection of studies

A systematic review of the literature was performed as per the PRISMA guidelines [30] across PubMed, Scopus, Embase and Google Scholar databases till August 3, 2020 using the following keywords: “COVID-19”, “diabetic ketoacidosis”, “ketosis”, “ketonemia”, “hyperglycemic emergencies”, “hyperglycemic crises” with interposition of the Boolean operator “AND”/“OR”. The search was conducted independently by two authors (RP and MB). Articles hence identified were further screened. Duplicate articles, articles in non-English language, reviews, and comments/communications and articles not pertaining to DKA in patients with COVID-19 were excluded. Finally, a total of 19 articles met the eligibility criteria and were included (Fig. 1). The included articles and the number of patients in each article have been summarized in Table 1.

2.2. Data extraction

The following data were extracted from the included studies: sex, age of the patient at presentation, ethnicity, type of diabetes mellitus (pre-existing T1DM vs. pre-existing T2DM vs. newly diagnosed DM), ongoing medications, body mass index (BMI), biochemical investigations (blood glucose, pH, bicarbonate, anion gap, glycated hemoglobin) and clinical outcomes.

2.3. Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 23.0 software program (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to check the normality of individual patient data, wherever available. Normally distributed data were expressed as mean \pm standard deviation (SD), while non-parametric data were expressed in median (interquartile range, IQR). The comparison of biochemical parameters between groups (DKA vs. combined DKA and HHS; discharged vs. deceased) were made using Mann-Whitney U test. A p value < 0.05 was considered significant.

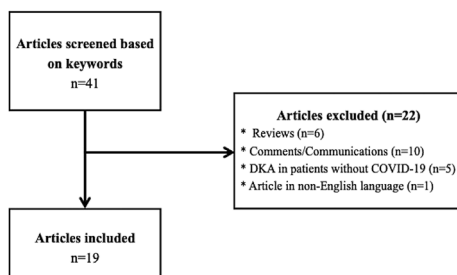


Fig. 1. Flowchart showing the study selection process.

3. Results

3.1. Demography

A total of 110 COVID-19 patients diagnosed with DKA were included in the final analysis. Amongst these 110 patients, 91 (83%) patients had DKA alone while 19 (17%) patients had combined DKA/HHS [22,28]. The demographic data have been presented in Table 2. Notably, the majority of the patients (63%) were male. The median age at presentation ranged from 45.5 years to 59.0 years. In the 28 patients in whom individual data was available, only one patient belonged to the pediatric age group [16]. The majority of the patients were black (African-American/Black African/African/Afro-Caribbean) ($n = 30$, 36%), followed by Hispanic ($n = 19$, 23%) and White (Caucasian) ($n = 10$, 12%) ethnicity. The majority of the patients (77%) had pre-existing T2DM. The use of SGLT2 inhibitors was reported in 7 patients.

3.2. Biochemical parameters at presentation

The biochemical parameters at admission have been summarized in Table 3. The median blood glucose at presentation ranged from 486.0 mg/dl to 568.5 mg/dl. On separately analyzing patients in whom individual data were available ($n = 25$), it was found that patients with combined DKA and HHS ($n = 6$) had significantly higher blood glucose than those with DKA alone ($n = 22$) ($p = 0.004$). Three patients had blood glucose < 250 mg/dl at presentation (euglycemic DKA) [11,13,23]; two were on SGLT2 inhibitor therapy [11,13] while one patient had gestational DM [23]. There was no difference in glycated hemoglobin (HbA_{1c}) ($p = 0.225$), pH ($p = 0.144$), bicarbonate ($p = 0.242$), and anion gap ($p = 0.478$) between patients with DKA vs. those with combined DKA and HHS.

3.3. Treatment and clinical outcomes

The majority of the patients were initially managed with a standard treatment protocol for DKA with intravenous fluids and insulin infusion. The median (IQR) volume of fluid replaced in the first 24 h was 3.8 (3.0–5.0) liters and 5.0 (4.0–6.0) liters for patients with DKA and combined DKA/HHS, respectively [22]. In another series, the median (IQR) volume of fluid replaced was 3.0 (1.0–8.0) liters in the initial 24 h [9]. Only 8 patients reported in 2 studies were treated with subcutaneous insulin [9,13]. Four patients had thromboembolic events [11,15,18,20]. Data on the final outcome (in terms of discharged, deceased, or hospitalized) was available for 78 patients [7–16,18–21,23,24,28]. Among these 78 patients, 41 (52.5%) were discharged, 35 (45.0%) were deceased and 2 (2.5%) had remained hospitalized. Table 4 summarizes the clinical and biochemical predictors of final outcome in 27 patients (with individual patient data) who had either been discharged ($n = 17$) or deceased ($n = 10$) [7,8,10–16,18–21,23,24,28]. All the deceased individuals were males. Patients with DKA/HHS had higher mortality compared to patients with isolated DKA (67% vs. 29%). In addition, deceased patients had lower pH at admission than those who were discharged ($p = 0.017$).

4. Discussion

To the best of our knowledge, this is the first comprehensive systematic review of DKA in patients with COVID-19. Amongst 110 cases hitherto described in the literature, 91 patients had DKA alone while 19 patients had combined DKA/HHS. The majority of the patients was male (63%) and had pre-existing T2DM (77%). Apart from blood glucose, none of the biochemical parameters at presentation was significantly different between the DKA and DKA/

Table 1
Summarizing the articles included in the systematic review.

Number of patients reported by article	Number of articles	Reference number	Individual patient data available
1	11	[7,8,11,12,14–16,18–20,23]	Yes
2	2	[13,24]	Yes
3	1	[21]	Yes
4	1	[10]	Yes
6	1	[28]	Yes
8	1	[17]	No
24	1	[22]	No
50	1	[9]	No

Table 2
Showing demographic parameters of the COVID-19 patients with DKA (and combined DKA/HHS).

Parameter	Value
Age (years) [Median (IQR)]	45.5 (36.2–57.7) [7,8,10–16,18–21,23,24,28] ^a 57.0 (48.0–64.0) [22] ^b
Sex (N = 102) ^c	59.0 (42.3–70.0) [9] Male (n = 64, 63%) Female (n = 38, 37%)
Ethnicity ^d (N = 84)	Black (n = 30, 36%) ^e Hispanic (n = 19, 23%) White (Caucasian) (n = 10, 12%) Asian (n = 6, 7%) Mixed (n = 4, 5%) Others (n = 8, 9%) Unknown (n = 7, 8%)
Type of diabetes ^f (N = 97)	Pre-existing T1DM (n = 12, 12%) Pre-existing T2DM (n = 74, 77%) Newly diagnosed (n = 10, 10%) Gestational DM (n = 1, 1%)
Use of SGLT2 inhibitors ^g	7
BMI (kg/m ²) [Median (IQR)]	26.6 (23.7–32.3) [7,11–13,16,28] ^h 24.7 (21.3–28.5) [22] ^b 27.1 (23.2–33.0) [9]

COVID-19: Novel coronavirus disease; DKA: Diabetic ketoacidosis; HHS: Hyperglycemic hyperosmolar syndrome; IQR: Interquartile range; SGLT2: Sodium-glucose transporter 2; BMI: Body mass index.

^a Age calculated from individual patient data available from 16 studies.

^b Only data of patients with isolated DKA has been shown.

^c Individual data on patient sex were available in 102 patients from 18 studies [7–16,18–24,28].

^d Individual data on patient ethnicity were available in 84 patients from 4 studies [9,10,22,28].

^e Patients with black ethnicity include African-American, Black African, African and Afro-Caribbean patients.

^f Individual data on type of diabetes were available in 97 patients from 15 studies [7,9–14,16,18–20,22–24,28].

^g Use of SGLT2 inhibitors was reported in 7 patients from 5 studies [9–11,13,22].

^h BMI calculated from individual patient data available from 6 studies.

HHS groups. The in-hospital mortality rate was 45%, with higher mortality in the DKA/HHS group than in the isolated DKA group (67% vs. 29%). pH was lower in patients who had died compared to those who were discharged.

Diabetic ketoacidosis is the most common hyperglycemic crisis, which also includes HHS and the combined syndrome of DKA and HHS, often referred to as hyperosmolar ketoacidosis [31]. Diabetic ketoacidosis occurs in the setting of relative or absolute insulin deficiency that tips the insulin:glucagon ratio in favor of glucagon; this leads to reduced glucose utilization and unchecked lipolysis, causing excessive formation of ketone bodies and finally metabolic acidosis [32,33]. Although DKA is more likely to occur in T1DM, it is estimated that the majority of the DKA cases worldwide occur in patients with T2DM due to its higher prevalence [33]. Diabetic ketoacidosis is itself a pro-inflammatory state [27], but is often precipitated by an underlying illness. Infections are the commonest precipitating factors [33–35]. Urinary tract infections and

pneumonia account for the majority of the infections [36]. Likewise, reports of DKA and DKA/HHS in patients with COVID-19 have emerged.

There are theoretical concerns that the SARS-CoV-2, just like its cousin the SARS-CoV, could bind to ACE2 expressed on the pancreatic islets, leading to islet destruction and acute diabetes [25,26]. In a patient with underlying DM (especially T2DM), the destruction of the residual β -cells by the virus would result in a state of complete insulinopenia, thereby precipitating DKA [13]. Moreover, the pro-inflammatory milieu seen even in non-severe patients with COVID-19 would theoretically promote ketogenesis, hence, predisposing an individual to ketosis [27]. In a series of 658 hospitalized patients (129 had DM) with confirmed COVID-19 from China, 42 (6.4%) presented with either urine or serum ketones. The presence of ketosis was associated with higher rates of acute respiratory distress syndrome, acute liver injury, the requirement for mechanical ventilation, a longer length of hospital stay, and mortality. Of the 42 patients with ketosis, 15 (35.7%) had diabetes mellitus; of these 15 patients, 3 had concomitant acidosis, amounting to DKA. Hence, the overall prevalence of DKA amongst patients with DM in the series was 2.3% [21]. On the contrary, in a retrospective single-center study from the United Kingdom, the prevalence of DKA in 87 COVID-19 patients with DM was 9.2% [17]. In another series from the United Kingdom, the prevalence of DKA in confirmed COVID-19 patients was 5.9% [10]. The marked dissimilarity in the prevalence of DKA may be explained based on differences in the population studied and the underlying COVID-19 disease severity.

In our systematic review, we found that the majority (63%) of the reported cases of DKA (or DKA/HHS) were male. Gender difference as a risk factor for DKA is controversial; some studies consider female sex as a risk factor [37], while others have shown no significant differences in males and females [38]. The preponderance of male cases among DKA patients could be due to the fact that COVID-19 tends to be more severe in males, resulting in more hospitalizations and deaths compared with females [39,40]. Similarly, the relative absence of pediatric COVID-19 patients with DKA also underscores the fact that children tend to have lower rates of severe COVID-19 [41]. Regarding ethnicity, we found that 36% of the patients belonged to black ethnicity, while 23% were Hispanic, 12% were Caucasian and only 7% were Asian. In general, BAME (Black, Asian and Minority Ethnic) individuals are at an increased risk of acquiring SARS-CoV-2 infection and of worse clinical outcomes from COVID-19 compared to White individuals [42]. In addition, ethnic minorities are also at a higher risk of DKA [43]. Taken together, the high prevalence of DKA in people with black ethnicity is ably explained. On the contrary, the underrepresentation of the Asian population could be fallacious as all the studies reporting patient ethnicity were either from the United Kingdom or from the United States of America [9,10,22,28].

Regarding the type of DM, we found that the majority of COVID-19 patients with DKA (77%) had underlying T2DM, likely because of

Table 3

Showing biochemical parameters at presentation in COVID-19 patients with DKA (and combined DKA/HHS).

Biochemical parameter at presentation	Value ^a
Blood glucose (mg/dl)	568.5 (385.5–889.7) [7,8,10–16,18–21,23,24,28] ^b 486.0 (396.0–558.0) [22] ^g 506.5 (252.0–1485.0) [9]
HbA _{1c} (%)	11.7 (9.5–13.2) [10–13,16,19,23,24,28] ^c 12.4 (10.7–14.2) [22] ^g
pH	7.17 (6.99–7.24) [7,8,10–16,18,21,23,24,28] ^d 7.20 (6.90–7.30) [22] ^g
Bicarbonate (mmol/l)	8.0 (6.0–12.5) [7,8,10–14,16,23,24,28] ^e 11.8 (7.8–15.4) [22] ^g
Anion gap (mEq/l)	29.0 (18.0–32.0) [7,8,12,13,15,20,24,28] ^f 14.8 (10.4–20.5) [22] ^g 28.1 (14.3–41.2) [9]

COVID-19: Novel coronavirus disease; DKA: Diabetic ketoacidosis; HHS: Hyperglycemic hyperosmolar syndrome; HbA_{1c}: Glycated hemoglobin.

^a Data represented as median (interquartile range).

^b Blood glucose calculated from individual patient data available from 16 studies.

^c HbA_{1c} calculated from individual patient data available from 9 studies.

^d pH calculated from individual patient data available from 14 studies.

^e Serum bicarbonate calculated from individual patient data available from 11 studies.

^f Anion gap calculated from individual patient data available from 8 studies.

^g Only data of patients with isolated DKA has been shown.

Table 4

Showing comparison of clinical outcomes of COVID-19 patients with DKA (and combined DKA/HHS) in whom individual patient data were available (N = 27).

Parameter	Discharged (n = 17)	Deceased (n = 10)	p value
Age (years)	46.0 (33.5–54.0)	42.5 (34.2–59.7)	1.000
Sex	Male = 11 Female = 6	Male = 10 Female = 0	–
DKA vs. Combined DKA/HHS	DKA = 15 (71%) DKA/HHS = 2 (33%)	DKA = 6 (29%) DKA/HHS = 4 (67%)	–
Blood glucose (mg/dl)	463.0 (347.0–641.0)	801.5 (376.5–1080.5)	0.120
pH	7.23 (7.09–7.26)	7.00 (6.91–7.11)	0.017
Bicarbonate (mmol/l)	10.4 (6.0–15.0)	7.0 (5.7–8.0)	0.098
Anion gap (mEq/l)	25.5 (16.8–34.0)	29.0 (28.0–30.5)	0.806

COVID-19: Novel coronavirus disease; DKA: Diabetic ketoacidosis; HHS: Hyperglycemic hyperosmolar syndrome.

the higher prevalence of T2DM worldwide [33]. In 10 patients, DM was diagnosed at admission, categorizing them as newly diagnosed DM. Of these 10 patients, 7 had HbA_{1c} > 9.5% (ranging from 9.6% to 14.2%) [10,12,13,16,24,28], implying that these patients had underlying undiagnosed DM of significant duration prior to the present admission and unlikely to have resulted from the incident SARS-CoV-2 infection. Although data on HbA_{1c} were not available in rest of the 3 patients, one had a BMI of 42.56 kg/m² at the time of admission and was likely a case of hitherto undiagnosed T2DM [7].

Analyses of the biochemical parameters at admission showed that the median blood glucose ranged from 486.0 mg/dl to 568.5 mg/dl. In a series of 967 patients admitted with DKA, 176 had a viral infection (presumed). The mean blood glucose in these 176 patients was 640.0 mg/dl, not strikingly different from that seen in the COVID-19 patients [44]. However, patients presenting with DKA/HHS had significantly higher blood glucose than patients with isolated DKA, a feature that has been described in the literature [29]. DKA/HHS form a clinical entity distinct from DKA and HHS alone and some small studies have reported that up to 30% of DKA have combined features of DKA and HHS [45,46]. The diagnosis of DKA/HHS is based on the documentation of raised effective serum osmolality in a patient with biochemically confirmed DKA. The cut-off defining elevated effective serum osmolality in DKA/HHS is variable with some of the most recent large-scale studies using a threshold of 300 mOsm/kg. In general, patients with DKA/HHS tend to have higher mortality than those with isolated DKA or HHS even

after adjusting for age, sex, and BMI [29]. In addition, patients with combined DKA/HHS tend to be more volume depleted and hence require more intravenous fluids in the first 24 h [22]. Therefore, early differentiation of DKA/HHS from isolated DKA is essential. In our systematic review, we found that 17% of the patients had combined DKA/HHS. This could be an underestimation as very few studies had reported effective serum osmolality.

The main tenets of DKA or DKA/HHS management include the triad of fluid resuscitation, potassium repletion, and insulin replacement [33,36]. Patients with DKA and combined DKA/HHS present with profound dehydration and fluids form the cornerstone of therapy. Administration of intravenous fluid corrects intravascular volume, improves renal perfusion, and thereby promotes glucosuria and ketonuria. The simultaneous decrease in the concentrations of circulating counter-regulatory hormones also reduces insulin resistance [33]. In adults with DKA, the American Diabetes Association and the UK guidelines recommend the use of isotonic saline (0.9% sodium chloride solution) for initial fluid replacement, administered at a rate of 500–1000 ml/h during the first 2–4 h [47,48]. However, in a patient with COVID-19, there are concerns about precipitating or exacerbating “lung leak” by liberal fluid administration resulting in increased extravascular lung water that would adversely affect gas exchange and worsen hypoxia [49]. Hence, the recently published UK guidelines by the National Inpatient Diabetes COVID-19 Response Group recommend conservative use of isotonic saline in COVID-19 patients with DKA. The

guidelines suggest that after an initial fluid bolus of 250 ml over 15 min, the subsequent infusion rate should be guided by the patient's weight and the pH at presentation. Patients with a $\text{pH} \leq 7.1$ would benefit from a more aggressive fluid replacement regimen than those with lesser degrees of acidosis [50]. Apart from protecting the lungs, a conservative fluid replacement strategy would also reduce the chances of development of hyperchloremic metabolic acidosis due to excessive chloride resulting from the administration of high volumes of saline [51]. However, conservative fluid replacement can lead to delayed clearance of serum ketones resulting in protracted ketonemia. We found that the strategic use of conservative fluid replacement was reported in 12 patients in only 1 series [22].

The usual route of insulin replacement in patients with DKA or combined DKA/HHS is intravenous infusion. Patients on intravenous infusion usually require intensive care unit (ICU) admission necessitating frequent glucose monitoring and periodic insulin dose adjustments. However, during a pandemic, minimizing nursing time at the bedside, protecting healthcare workers, and preserving personal protective equipment (PPE) is a priority. In addition, the increased demand for pumps to deliver vasopressors has led to concerns of possible shortages of infusion pumps and/or 50 ml syringes being available for insulin infusions to manage these hyperglycemic emergencies [50]. Nevertheless, most of the problems can be circumvented by the use of subcutaneous insulin therapy instead of intravenous insulin infusion. Several studies have demonstrated that the use of subcutaneous rapid-acting insulin analogues is a safe and effective alternative in mild/moderate uncomplicated DKA [13]. A Cochrane review evaluating 5 randomized controlled trials concluded that there are neither advantages nor disadvantages when comparing the effects of subcutaneous rapid-acting insulin analogues versus intravenous regular insulin for treating mild or moderate DKA [52]. Thus, amid the ongoing COVID-19 pandemic, subcutaneous insulin therapy can be an effective means of treating DKA while reducing ICU utilization, inadvertent exposure and PPE use. The National Inpatient Diabetes COVID-19 Response Group recommends the use of subcutaneous rapid-acting insulin analogues at an initial dose of 0.4 units/kg body weight every 4 hourly with the aim of reducing serum ketone by at least 2 mmol/l over 4 h. The dose needs to be reduced to 0.2 units/kg body weight once the blood glucose falls below 250 mg/dl. The guidelines also recommend the initiation or continuation of long-acting insulin preparation from the very outset when using subcutaneous strategies to treat DKA [50]. In our systematic review, we found that the use of subcutaneous insulin was limited to only 8 patients as reported in 2 studies [9,13]. Although it may seem advantageous, subcutaneous strategies are not recommended for patients with severe and/or complicated DKA in whom intensive monitoring and use of intravenous insulin is required. Irrespective of the degree of acidosis, patients with combined DKA/HHS require close monitoring and hence ICU care [13,48]. Concerning the dose of insulin infusion, Armeni *et al.* reported that 35% of the COVID-19 patients with hyperglycemic emergencies required an increase in the fixed dose of insulin infusion above the recommended insulin dose for DKA of 0.1 units/kg/hour [22]. The pro-inflammatory milieu induced by COVID-19 can lead to a high degree of insulin resistance, thereby increasing the insulin requirement. In addition, some of the medications used in the management of COVID-19, notably, corticosteroids, remdesivir, lopinavir/ritonavir, darunavir/cobicistat and interferon- $\beta 1$, can also worsen hyperglycemia [4,53].

Another aspect of DKA management that needs to be considered is appropriate electrolyte management. Almost all patients with DKA have substantial potassium deficits at presentation. As insulin treatment is initiated, ketone production is suppressed, and acidosis begins to resolve. In addition, insulin drives potassium

back into the cell, and the individual can become severely hypokalemic. Thus, frequent monitoring of potassium and appropriate replacement is an integral part of the management of DKA. SARS CoV-2 binds to ACE2 with subsequent downregulation of the enzyme and reduced degradation of aldosterone, leading to hypokalemia [3]. Hence, there are concerns that patients with COVID-19 are at a higher risk of hypokalemia [54]; hence, hypokalemia can be expected to be all the more profound in COVID-19 patients with DKA. It thus becomes imperative to stringently monitor serum potassium and replenish it accordingly. Besides, patients with DKA/HHS are more prone to develop severe hypokalemia (serum potassium < 2.5 mEq/l) within first 48 h of treatment initiation compared to patients with isolated DKA, hence, monitoring serum potassium becomes all the more critical for the former group of patients [29]. In addition, hypophosphatemia is not uncommon in patients with DKA. Hypophosphatemia can lead to neuromuscular weakness and worsen respiratory failure in COVID-19 patients [55]. Hence, timely phosphate replacement is also crucial in such patients.

In the developed nations, the hospital case-fatality rates due to DKA have markedly declined, with current reported death rates being $< 1\%$ [34,56]. Mortality substantially increases in those with comorbidities and with advancing age, reaching up to 8–10% in those aged > 65 –75 years [35,57]. In DKA patients with underlying COVID-19, we found an in-hospital mortality rate of 45% with one series reporting a mortality rate as high as 50% [9]. As has been reported in the literature [29], we found that patients with DKA/HHS had higher mortality compared to DKA alone. Low pH at presentation was found to be significantly associated with in-hospital mortality. Admission blood glucose was not associated with patient outcomes. This underscores the importance of acidosis as predictive of mortality in patients with DKA (and combined DKA/HHS) and the known role of treatment protocols to target acidosis as the main goal of management, rather than reduction of blood glucose levels alone [29]. Four patients were reported to have arterial or venous thromboembolic events [11,15,18,20]; in addition, a 60-year-old man had presented with left hemiparesis and was found to have a right middle cerebral artery infarct, consistent with acute cerebrovascular accident [24]. An important complication of DKA includes the development of a hypercoagulable state with an increased risk of deep venous thrombosis [33]. The risk is expected to increase by multiple-folds in a patient with underlying COVID-19 as the disease has been found to aggravate the chances of thrombotic complications [58,59]. Thus, it is essential that all hospitalized COVID-19 patients with DKA are kept on low-molecular weight heparin (LMWH) prophylaxis and a low threshold is kept for ruling out any suspected thromboembolic event.

We do respect the limitations of the study. First, complete individual patient data were available in only 28 patients. Second, data on serum ketones, potassium, sodium, C-reactive protein, lactate dehydrogenase, and D-dimer were infrequently reported and hence were not separately analyzed. Third, details on fluid replacement and insulin dosage were not reported by majority of the studies. Lastly, the analysis of clinical outcomes involved a limited number of patients in whom individual data were available; large-scale studies are required to validate the results.

5. Conclusions

Diabetic ketoacidosis and combined DKA/HHS are not uncommon in COVID-19 patients with pre-existing diabetes mellitus and portend a poor prognosis with a mortality rate of nearly 50%. Males and individuals belonging to black ethnicity are especially at a high-risk. Measurement of effective serum osmolality is essential to differentiate isolated DKA from combined DKA/HHS as the latter

represents around one-fifth of the DKA cases and tends to have higher mortality than DKA alone. Conservative rather than liberal fluid replacement and subcutaneous instead of intravenous insulin regimen are practical and unique considerations in the management of DKA in patients with COVID-19.

Funding

None.

Data availability

Available on reasonable request to the corresponding author.

Contribution statement

Both RP and MB are the primary authors and had independently performed the literature search. UY had helped in statistical analysis. SB had edited the manuscript. All the four authors had approved the final version of the manuscript.

Declaration of competing interest

None.

Acknowledgement

None.

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