Original Article

The impact of COVID-19 on Diabetic Ketoacidosis patients

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ABSTRACT

Background and aim: Describe the prevalence/outcomes of Diabetic Ketoacidosis (DKA) patients comparing pre- (March−April 2019) and pandemic (March−April 2020) periods.
Methods: Retrospective cohort of admitted pandemic DKA/COVID-19+ patients comparing prevalence/outcomes to pre-pandemic DKA patients that takes place in Eleven hospitals of New York City Health & Hospitals. Our included participants during the pandemic period were admitted COVID-19+ patients (>18 years) and during the pre-pandemic period were admissions (>18 years) selected through the medical record. We excluded transfers during both periods. The intervention was COVID-19+ by PCR testing. The main outcome measured was mortality during the index hospitalization and secondary outcomes were demographics, medical histories and triage vital signs, and laboratory tests. Definition of DKA: Beta-Hydroxybutyrate (BHBA) (>0.4 mmol/L) and bicarbonate (<15 mmol/L) or pH (<7.3).
Results: Demographics and past medical histories were similar during the pre-pandemic (n = 6938) vs. pandemic (n = 7962) periods. DKA prevalence was greater during pandemic (3.14%, 2.66−3.68) vs. pre-pandemic period (0.72%, 0.54−0.95) (p > 0.001). DKA/COVID-19+ mortality rates were greater (46.3% (38.4−54.3) vs. pre-pandemic period (18%, 8.6−31.4) (p < 0.001). Surviving vs. non-surviving DKA/COVID-19+ patients had more severe DKA with lower bicarbonates by 2.7 mmol/L (1.0−4.5) (p < 0.001) and higher both Anion Gaps by 3.0 mmol/L (0.2−6.3) and BHBA by 2.1 mmol/L (1.2−3.1) (p < 0.001).
Conclusions: COVID-19 increased the prevalence of DKA with higher mortality rates secondary to COVID-19 severity, not DKA. We suggest DKA screening all COVID-19+ patients and prioritizing ICU DKA/COVID-19+ with low oxygen saturation, blood pressures, or renal insufficiency.

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1. Introduction

Background: Diabetes Mellitus (DM) is not a risk for developing COVID-19 [1,2]. Diabetics have worse outcomes once infected with COVID-19 [1,3−6]. Diabetic Ketoacidosis (DKA), a potentially lethal complication of diabetes, was recently described in 110 COVID-19 patients with a 45% mortality rate in a systematic review by Pal et al. of 19 case series [7]. Yet case series cannot describe an association, much less a cause-and-effect relationship between COVID-19 and DKA.

A large retrospective cohort study by Liu et al. of the 18 public hospitals in the Hong Kong Hospital Authority found a significant decrease in admissions for hyperglycemia (incidence rate 0.66, 0.60−0.74) and hypoglycemia (0.76, 0.63−0.83) comparing pre-and pandemic periods [8]. Yet, Liu et al. found no difference (1.0 (0.74−1.34) in the prevalence of DKA compared pre-to their pandemic periods [8]. Liu et al. hypothesized that patient concerns regarding contracting COVID-19 kept many away from visits for routine hyper- and hypoglycemia, leaving all but the sickest DKA to seek medical care. Lawrence et al. in a retrospective study of an Australian tertiary pediatric hospital, concluded similarly to Liu et al.'s study, that the fear of contracting COVID-19 kept many potential patients from seeking routine medical care [9]. In contrast to Liu et al.'s finding, Lawrence et al. reported a significant increase in the prevalence of DKA (73%−26% p < 0.007) pre-to pandemic period, ascribed to delays in DM treatment and DKA diagnosis.

Importance: Unfortunately, the association of COVID-19 and DKA could not be established in the studies by either Liu et al.'s or Lawrence et al.'s studies since Liu et al. did not report any of their DKA patient's COVID-19 status, and none of Lawrence et al.'s DKA patients were COVID-19 positive. To illustrate an association between COVID-19 and DKA will require a large enough database of

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admitted patients with COVID-19 and DKA with a multi-year design comparing pre-and pandemic periods.

At the end of 2019, New York City Health and Hospitals unified its eleven public hospitals under a single electronic medical record system (Epic Systems Corporation, Verona, WI.), allowing for an easily searchable database for all ED visits and hospital admissions. We conducted a retrospective cohort study of COVID-19 positive patients admitted in New York Health & Hospitals' eleven-hospital system for the same timeframe during the pandemic compared to the previous pre-pandemic period. The eleven hospitals of NYC H&H serve as New City's safety-net health system caring for all patients irrespective of class and insurance status. This hospital system serves patients from all socioeconomic and racial backgrounds. The eleven hospitals of NYC H&H have had over 1.1 million patients, including 380 000 uninsured patients per year [10].

Goals of this investigation: We will describe the prevalence and outcomes of DKA among admitted COVID-19 positive patients admitted across NYC H&H and investigate possible predictors of mortality comparing pre-and pandemic periods. Further characterization of these parameters is necessary for future treatment preparation, allocation of resources, prognostication, and improving clinical decision making.

2. Methods

2.1. Study design

We conducted a retrospective cohort study of a prospectively collected database of admitted COVID-19 positive patients during the pandemic period. We compared the prevalence and outcomes of DKA patients to the same timeframe one year previous. The study was approved with exemption from informed consent by the institutional review boards (IRB) of the Biomedical Research Alliance of New York City and NYC Health & Hospital.

2.2. Study setting and population

Admitted COVID-19 positive patients across the eleven hospitals of NYC H&H were retrospectively enrolled during the COVID-19 pandemic surge period of March 1, 2020, to April 27, 2020, and compared to 1 year before the COVID-19 pandemic for the exact dates March 1, 2019, through April 27, 2019. Inclusion criteria: Admitted 18 years of age or older (the age cut-off for adult emergency department patients in our institution) who tested COVID-19 by PCR. We did not limit our inclusion criteria to only those patients with respiratory complaints but included any patient with any reason for admission who tested positive for COVID-19. Patients with DKA were defined as those that met the criteria set forth by the American Diabetes Association (ADA) 2017. Patients with DKA had to meet these criteria: an elevated serum ketone (Beta-Hydroxybutyric acid) greater than the upper limit of the normal range (0.4 mmol/L) and serum bicarbonate <15 mmol/L or blood pH < 7.3. The ADA dropped the requirement for hyperglycemia to cover patients on an SGL2 inhibitor with DKA and euglycemia. Exclusion criteria: Patients transferred from other institutions or inpatient services are not primarily present through the emergency departments. Patients were enrolled by convenience sample. Treating physicians were not blinded to vital signs or results of laboratory testing. Patient workup and treatment were not specified in the study protocol.

2.3. Measurements

Data were electronically abstracted from the electronic medical record (EPIC, Verona, Wisconsin). All patients had demographic information, past medical histories, initial triage vital signs, labs recorded, and the first 96 h of hospitalization, including laboratory tests, imaging studies, procedures (mechanical ventilation, central lines), and medications. Outcomes such as lengths of hospital and Intensive Care Unit stay, mortality, and eventual placement were also recorded.

2.4. Laboratory testing

Basic Metabolic Panel (BMP) and Beta-Hydroxybutyrate (BHB) were tested by a Cobas 8000 Roche Diagnostics Machine (Company) in Indianapolis, IN USA. Venous Blood Gas (VBG) analysis by IF GEM5000 Werfen Bedford MA, USA, Complete Blood Counts Sysmex XN-9000, Sysmex America Inc., Lincolnshire, Illinois, USA.

Normal Range Values for Chemistry (BMP) and Venous Blood Gas (VBG) Complete Blood Count machines: Chemistry (BMP): Sodium (Na) (mmol/L) (135−146), Potassium (K) (mmol/L) (3.5−5.0), Chloride (Cl) (mmol/L) (98−106), HCO3 (Bicarbonate) (mmol/L) (24−31), Blood Urea Nitrogen (BUN) (mg/dl) (6-20), Creatinine (CRE) (mg/dl) 0.50−0.90, Anion Gap (AG) (Na-[Cl + HCO3])(mmol/L) (5-15), Glucose (GLU) (mg/dl) (70−99), Beta_OHButyrate (BHB) (mmol/L) (0.00−0.40). Venous Blood Gas (VBG) - pH (units) (7.32−7.42), PCO2 (partial pressure of Carbon Dioxide) (mmHg) (32−45), HCO3 (mmol/L) (22−29), Sodium (mmol/L) (135−145), K (mmol/L) (3.5−5.0), Potassium (mmol/L) (3.5−5.0) Chloride (mmol/L) (101−111), Anion Gap (AG) (Na-[Cl + HCO3])(mmol/L) (5-15), Lactate mmol/L (0.5−2.2), GLU (mg/dl) (70−99). Complete Blood Counts (CBC) − WBC (4.50−10.90 K/μl), RBC (4.20−61.0 M/μl), HGB (14.0−18.0 g//dl), PLT (130−400 K/μl).

2.5. Data analysis

We compared data to historical controls at our hospital system in 2019, the year before the pandemic for the same timeframe of March 1 − April 27. Initial vital signs, laboratory parameters such as pH, BHBA, bicarbonate, AG, glucose concentration, BUN, Cre, and patient mortality were compared.

The data were reported as means or counts and percentages with 95% confidence intervals. Group comparisons were analyzed by Student's t-tests or Fisher's Exact Test, where appropriate, and odds ratios to predict mortality. All tests were two-tailed. Alpha was set at 0.05. IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

3. Results

3.1. Characteristics of study subjects

We retrospectively reviewed hospital admissions in the eleven New York City Health & Hospitals hospitals from two timeframes, pre-pandemic March 1, 2019, through April 27, 2019, and for the same period in 2020 (pandemic period). The pre-pandemic period included all admissions; the pandemic timeframe includes only those admitted with a positive COVID-19 test. The number of COVID-19+ admissions (n = 7692) during the pandemic period was greater than all the admissions pre-pandemic (n = 6938), but this is still an underestimate of the actual burden of patients during the pandemic period, which does not account for those non-COVID-19 admissions.

3.2. All admitted patients pre- vs. pandemic patients

Table 1 compares the demographics of admitted patients for the two groups, pre-pandemic (n = 6938) and pandemic (n = 7692) for

Table 1
Demographics and initial vital signs of admitted PatientsPre- versus pandemic timeframes.

Characteristic	Pre-Pandemic (n = 6938)	Pandemic (n = 7962)
Study Periods	March 1 - April 27, 2019	March 1 - April 27, 2020
Age (yrs.)	59.40 (58.95−59.85)	62.73 (62.37−63.09)
Gender (m) (n,%)	3964, 57.1%	4799, 62.4%
Race (%)		
Other	40%	49%
Black	29%	34%
White	22%	11%
Asian	9%	6%
American Indian or Alaskan	0%	0%
Other Pacific Islander	0%	1%
Ethnicity (%)		
Non-Hispanic	57%	45%
Hispanic	28%	38%
Unknown	8%	13%
Asian	6%	4%
Past Medical History (%)		
Hypertension	67.55%	72.56%
Diabetes	52.61%	60.51%
Cardiac	43.94%	36.13%
Pulmonary	41.19%	33.68%
Endocrine (Non-DM))	27.42%	27.85%
Renal	19.35%	20.61%
Psychiatric	18.04%	13.75%
Cancer	13.66%	9.00%
Neurologic	10.29%	5.74%
Gastrointestinal	7.90%	3.94%
AIDS/HIV	3.92%	2.75%
Other	45.15%	23.03%

this study. The demographics appear very similar between each time frame. During the pandemic period, the patients appear slightly older, 62.3 years compared to 59.4 years pre-pandemic. There appear to be more males (63% vs. 57%), a higher percentage of Blacks (49% vs. 40%), and Hispanics (38% vs. 28%) admitted in the pandemic period. Comparing past medical history, pandemic patients had a higher percentage of Hypertension (73% vs. 68%) and Diabetes Mellitus (61% vs. 53%) than those in the pre-pandemic timeframe. Mortality rates during the pandemic period 30.16% (29.14% - 31.20 were significantly ($p < 0.001$) higher than the pre-pandemic timeframe 3.21% (2.28%−3.66%).

3.3. Main results

3.3.1. Diabetic Ketoacidosis patients pre- vs. pandemic periods

Table 2 compares the demographics and laboratory results of the pre-and pandemic DKA patients. The prevalence of DKA on admission among COVID-19+ patients was significantly ($p > 0.001$) greater (3.14%, 2.66%−3.68%) than during the pre-pandemic time period (0.74%, 0.54%−0.97%). Past medical history of Diabetes Mellitus was similar ($p = 0.151$) in pre-pandemic DKA (91.5%, 79.5%−97.7%) and pandemic DKA (81.3%, 72.9%−87.5%) patients. Pandemic compared to pre-pandemic DKA patients were significantly ($p = 0.01$) older by 7.7 years (1.9 years−13.9 years) with similar gender distribution Males 51% vs. 63%, respectively. Pandemic DKA patients had significantly ($p = 0.001$) greater BMI's by 8.4 kg/m^2 (1.7 kg/m^2 - 6.4 kg/m^2) than pre-pandemic patients. Comparing initial vital signs, temperatures, heart and respiratory rates, and blood pressures were not clinically significant between pre-and pandemic DKA patients. Oxygen saturations were significantly ($p = 0.003$) lower by 4.7% (1.7%−7.8%) in pandemic versus pre-pandemic DKA patients.

Biomarkers of DKA severity glucose, pH, bicarbonate, and beta-hydroxybutyric acid levels were not significantly different between pre-and pandemic DKA patients. Serum sodium levels were not clinically significant between the two groups. Significantly

($p < 0.001$) higher potassium levels in the pandemic DKA patients were most likely related to the more severe renal insufficiency in the pandemic DKA patients, as evidenced by an elevated ($p < 0.001$) Blood Urea Nitrogen by 27.8 mg/dl (15.9 mg/dl - 39.6 mg/dl) and Creatinine ($p = 0.004$) by 1.37 mg/dl (0.45 mg/dl - 2.29 mg/dl). Complete Blood Counts between pre-and post-pandemic DKA patients were not clinically significant. The DKA mortality rates were significantly ($p < 0.001$) greater during the pandemic period (46.3% (38.4%−54.3%) compared to the pre-pandemic time period (17.7%, 8.4%−30.1%).

3.3.2. COVID -19+ Diabetic Ketoacidosis survivors vs. non-survivors

Table 3 compares survivors versus non-survivors for the 147 DKA/COVID-19+ patients. COVID-19 had a significant impact on mortality rates in DKA/COVID-19+ with a rate of 46.3% (38.4%−54.3%) (68/147). Non-survivors were significantly ($p < 0.001$) older by 10.2 yrs (4.8 yrs − 15.7 yrs). Gender distribution and BMI were both similar between survivors and non-survivors. Temperature and heart rates were not significantly clinically different between the two groups. Yet, blood pressure was significantly lower in non-survivors with systolic BP lower by 28.7 mmHg (20.3 mmHg−30.4 mmHg) and diastolic BP lower by 22.0 mmHg (16.8 mmHg−27.1 mmHg). Respiratory rates were also higher in non-survivors by 4.0 BPM (2.4 BPM − 5.7 BPM), which parallels the significantly lower oxygen saturation in the non-survivors by 10.2% (6.4%−16.8%). More severe renal insufficiency was found in the non-survivors than survivors by increases in Blood Urea by 16.8 mg/dl (3.6 mg/dl - 30.1 mg/dl) and Cre 0.9 mg/dl (0.11 mg/dl - 1.95 mg/dl). Both SOFA (5.5 vs. 1.35) and qSOFA (0.29 vs. 1.24) were also significantly ($p < 0.001$) higher in the non-survivors.

We dichotomized the following variables (Age, Oxygen Saturation, systolic BP, BUN, Cre) to calculate the odds ratio to predict death. For ages greater than or equal to 80 years, the odds ratio was not statistically significant ($p = 0.06$) OR 3.17 (1.06−9.59). Using a cutoff of Oxygen Saturation of less than 95%, mortality was significantly greater ($p < 0.001$) OR 9.27 (4.09−21.05). Systolic blood

Table 2
Demographics and Initial Labs of Patients with Diabetic Ketoacidosis Pre-Pandemic vs. Pandemic Periods.

Characteristics	Pre-Pandemic (n = 51)	Pandemic (n = 147)	p-Value
Age (years)	51.0 (45.5–56.6)	58.7 (55.8–61.6)	0.010*
Gender (male %)	63.3% (55.2%–71.0%)	51.0% (37.1%–64.1%)	0.137**
BMI (kg/m^2)	24.4 (22.3–26.5)	28.4 (27.2–29.7)	0.001*
Temperature (F^0)	98.1 (97.9- 98.3)	98.6 (98.8–98.9)	0.070
Heart Rate (B/min)	83.2 (78.2–87.8)	91.5 (87.9–95.0)	0.012*
Systolic Blood Pressure (mmHg)	120.2 (114.6–125.8)	110.8 (106.1–115.6)	0.014*
Diastolic Blood Pressure (mmHg)	72.8 (69.2–76.1)	62.1 (59.3–65.4)	<0.001*
Respiratory Rate (B/min)	18.1 (17.7–18.8)	20.6 (19.8–21.5)	0.001*
Oxygen Saturation (%)	97.3 (96.5–98.1)	92.5 (90.8–94.4)	0.003*
pH	7.19 (7.16–7.23)	7.18 (7.16–7.21)	0.716**
Bicarbonate (mmol/L)	14.0 (12.2–15.9)	13.5 (12.6–14.4)	0.518**
Anion Gap (mmol/L)	22.0 (19.7–24.4)	26.7 (25.3–28.1)	0.001*
Beta-Hydroxybutyrate (mmol/L)	4.62 (3.74–5.51)	4.04 (3.63–4.47)	0.201**
Lactate (mmol/L)	4.00 (2.85–5.17)	2.89 (2.40–3.39)	0.019*
Glucose (mg/dl)	361.2 (293.7–428.7)	545.1 (491.6–398.6)	0.061**
Sodium (mmol/Ll)	137.6 (135.7–139.6)	140.5 (138.9–142.1)	0.007*
Potassium (mmol/L)	4.57 (4.23–4.86)	5.17 (4.93–5.39)	<0.001*
Blood Urea Nitrogen (mg/d)	26.5 (20.9–32.1)	54.3–47.6 - 61.0)	<0.001*
Creatinine (mg/dl)	1.60 (1.09–2.12)	2.98 (2.46–3.49)	0.004*
White Blood Cell Count (10 [9]/L)	12.17 (10.42–13.92)	12.53 (11.554–13.53)	0.718**
Hemoglobin (g/L)	12.79 (12.11–13.47)	13.64 (13.21–14.07)	0.043*
Hematocrit (%)	39.06 (39.88–41.24)	43.78–42.42 - 45.11)	<0.001*
Platelet Count (10 [9]/L)	245.5 (219.5–271.5)	280.2 (261.4–298.9)	0.54**

- *p < 0.05.
- **NS.

Table 3
Demographics and initial labs COVID-19 positive patients with diabetic ketoacidosis survivors versus non-survivors.

Characteristics	Survivors (n = 79)	Non-Survivors (n = 68)	p-Value
Age (years)	53.9 (50.1–57.9)	64.2 (60.3–68.1)	<0.001*
Gender (m%)	58.2% (47.2%–68.5%)	69.2% (57.3%–78.9%)	0.231**
BMI	28.2 (26.3–30.10	28.7 (26.9–30.5)	0.602**
Temperature (F^0)	98.4 (98.1–98.7)	98.9 (98.1–98.7)	0.700*0
Heart Rate (B/min)	88.2 (84.8–91.6)	96.2 (88.9–103.4)	<0.001*
Systolic Blood Pressure (mmHg)	123.8 (119..6–128.0)	95.1 (87.3–102.8)	<0.001*
Diastolic Blood Pressure (mmHg)	72.3 (68.4–73.1)	50.3 (45.9–54.9)	<0.001*
Respiratory Rate (B/min)	19.0 (18.4–19.6)	23.0 (21.4–24.6)	<0.001*
Oxygen Saturation (%)	97.0 (96.5–97.5)	86.9 (83.2–90.6)	<0.001*
SOFA Score	1.35 (0.81–1.89)	5.54 (4.41–6.68)	<0.001*
qSOFA Score	0.29 (0.17–0.42)	1.24 (1.04–1.43)	<0.001
pH	7.17 (7.14–7.20)	7.20 (7.17–7.23)	0.413**
Bicarbonate (mmol/L)	12.17 (10.95–13.39)	14.92 (13.67–16.21)	<0.001
Anion Gap (mmol/L)	26.2 (23.9–28.4)	23.2 (20.8–25.5)	<0.001
Beta-Hydroxybutyrate (mmol/L)	6.09 (5.42–6.76)	4.04 (3.28–4.80)	<0.001
Lactate (mmol/L)	2.94 (2.05–2.94)	3.48 (2.45–4.51) (	0.251**
Glucose (mg/dl)	505 (456–572)	563 (484–642)	0.225**
Sodium (mmol/dl)	137.7 (137.7–141.6)	141.5 (138.8–144.2)	0.311**
Potassium (mmol/dl)	4.64 (4.62–5.21)	5.20 (4.92–5.48)	0.099**
Blood Urea Nitrogen (mg/d)	46.5 (37.0–55.9)	63.4 (54.1–76.6)	<0.001
Creatinine (mg/dl)	2.58 (1.85–3.31)	3.50 (2.76–4.23)	<0.001
White Blood Cell Count (10 [9]/L)	13.30 (11.90–14.71)	11.61 (10.22–13.04)	0.081**
Hemoglobin (g/L)	14.22 (13.69–14.75)	12.79 (12.29–13.66)	<0.001
Hematocrit (%)	45.2 (43.4–46.6)	41.7 (39.1–44.2)	<0.001
Platelet Count (10 [9]/L)	294 (268–320)	264 (236 291)	0.093**

- *p < 0.05.
- ** NS.

pressure less than 100 mmHg (p < 0.001) OR 9.98 (4.17–23.89) Renal insufficiency defined by BUN outside the normal range greater 20 mg/dl, (p = 0.040) OR 2.53 (1.11–5.77) and Cre greater than 0.9 mg/d (p = 0.015) OR 5.07 (1.40–18.39).

It appears that the survivors, not the non-survivors, had more severe DKA as having significantly (p < 0.001) lower bicarbonate by 2.7 mmol/L (1.0 mmol/L – 4.5 mmol/L) and significantly (p < 0.001) higher both AG by 3.0 mmol/L (0.2 mmol/L - 6.3 mmol/L) and BHBA by 2.1 mmol/L (1.2 mmol/L – 3.1 mmol/L).

4. Limitations

Our study was limited as it is a retrospective observational study comparing two separate time periods therefore causality in relationship to COVID-19 cannot conclusively be established. We were also limited as the only patients included in the study were the patients admitted through the Emergency Department and excludes any transfers to the NYCHHC hospitals.

5. Discussion

We found that COVID-19 had significant impacts on DKA patients. Comparing our pre-to pandemic periods, we found a greater than a 4+-fold increase in DKA prevalence (0.72% vs. 3.14%) with a 2+times higher DKA/COVID-19+ mortality rate (46.3% vs. 18.0%). Comparing DKA severity pre-and pandemic periods, we found similar pH, bicarbonate, beta-hydroxybutyric acid levels. High mortality rates of DKA/COVID-19+ were associated with COVID-19 biomarkers of lower oxygen saturations and blood pressures, higher degrees of renal insufficiency with higher SOFA and qSOFA scores, not DKA severity. No significant difference in pH, bicarbonate and beta-hydroxybutyric acid levels were found between survivor and non-survivor DKA/COVID-19+ patients.

Similar to our study, Ditkowsky et al. also reported a 3+-fold increase in DKA prevalence across a five-hospital NYC consortium during the pandemic period of March−May 2020 compared to the same months a year earlier [11]. Unlike our study, Ditkowsky et al. did not directly link COVID-19+ patients with a DKA diagnosis. The prevalence of DKA/COVID-19+ patients was also reported in retrospective studies by Goldman et al. and Akundi et al. [12,13]. Both Goldman et al. (1.8% (0.6%−4.8%)) and Akundi et al. (3.4% (1.6%−6.8%)) found a similar DKA/COVID-19+ prevalence to our study (3.14%), with only Li et al., finding a much lower rate 0.46% (0.1%−1.4%) [12−14]. The Li et al. study was in a very different population (China) compared to our study (US) and those by Goldman et al., (UK), and Akundi et al., (UK), which may in part explain the differences in DKA/COVID-19+ prevalence among the studies. These retrospective studies of DKA/COVID-19+ prevalence were also all in significantly smaller samples of COVID-19+ patients than ours (n = 7692), Li et al., (n = 658), Goldman et al., (n = 218), and Akundi et al., (n = 232), which may represent a sampling bias. Unfortunately, none of these studies, as opposed to ours, reported pre-pandemic DKA prevalence, so a direct comparison to the change in prevalence with COVID-19 between their studies and ours cannot be made.

The increased prevalence of DKA/COVID+ is multifactorial. As hypothesized by Liu et al. and Lawrence et al., a portion of the increased prevalence of DKA/COVID-19+ is a consequence of DM patients delaying regularly scheduled clinic visits for fear of contracting COVID-19 causing noncompliance with their insulin therapy [8,9].

Besides non-compliance with DM medications, increased DKA prevalence during the pandemic may be a direct effect of the SARS-COV-2 virus, decreasing insulin secretion by attacking pancreatic islet cells via binding to the ACE2 receptor [15]. Pancreatic injury in patients with severe COVID-19 manifest, with 17.91% and 16.41% having elevated amylase and lipase, respectively [16]. CT scans of patients with severe COVID-19 showed both focal enlargement of the pancreas or dilatation of the pancreatic duct without acute necrosis [16]. In addition, SARS-COV-2 direct attack on pancreatic islet cells by 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 [17].

In-hospital mortality of DKA in developed countries is reported to be less than 1% [18,19]. We found the mortality of patients with DKA/COVID-19+ to be 46.3%. Similar DKA/COVID-19+ mortality rates to our study (46%) were also reported by Pasquel et al. (30.5%) and Chamorro-Pareja et al. (50%) [20,21].

Similar to our which found increased renal insufficiency BUN >20 mg/dl (OR = 2.3) Cre >0.9 mg/dl (OR = 5.07) in our non-surviving DKA/COVID-19+, both Pasquel et al. and Chamorro-Pareja et al. also identified renal failure as an important predictor of DKA/COVID-19+ mortality [20,21].

In addition to our finding of increased renal insufficiency associated with higher DKA/COVID + mortality, we also identified

complications of COVD-19 as a risk factor. We surmise that the higher mortality rates in our DKA/COVID-19+ (46%) than our pre-pandemic DKA patients (18%) were due to more severe COVID-19, not DKA. Our deceased DKA/COVID-19+ patients' biomarkers of DKA were significantly less severe than survivors by having higher bicarbonates (15 mEq/L vs. 12 mEq/L) with lower AG (23 mEq/L vs. 26 mEq/L) and BHBA (4.0 mEq/L vs. 6.1 mEq/L) levels. Instead, we found that DKA/COVID-19+ nonsurvivors had more severe COVID-19 as evidenced by lower oxygen saturations (87% vs. 97%), with lower blood pressures (124/72 vs. 95/50) and higher SOFA scores (5.5 vs. 1.4).

Our findings have clinical implications for the care of COVID-19+ patients. We found a strong association of COVID-19 with the increased prevalence of DKA. We suggest screening all COVID-19+ patients for DKA with Beta-hydroxybutyric acid testing. If another COVID-19 surge occurs and ICU beds are limited, prioritizing DKA/COVID-19+ with renal insufficiency, low oxygen saturation, or blood pressure is reasonable compared to those without these markers.

In summary, our study found that it was not necessarily the patients with worse DKA that died but patients with worse COVID-19. This was seen as higher respiratory rates, worse renal failure, and higher SOFA scores were associated with higher mortality rates. This data helps characterize the prevalence and mortality associated with DKA and COVID-19 and helps guide future management strategies in these patients.

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