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BRIEF REPORT

COVID-19 infection may cause ketosis and ketoacidosis

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Abstract

The present study included 658 hospitalized patients with confirmed COVID-19. Forty-two (6.4%) out of 658 patients presented with ketosis on admission with no obvious fever or diarrhoea. They had a median (interquartile range [IQR]) age of 47.0 (38.0–70.3) years, and 16 (38.1%) were men. Patients with ketosis were younger (median age 47.0 vs. 58.0 years; $P = 0.003$) and had a greater prevalence of fatigue (31.0% vs. 10.6%; $P < 0.001$), diabetes (35.7% vs. 18.5%; $P = 0.007$) and digestive disorders (31.0% vs. 12.0%; $P < 0.001$). They had a longer median (IQR) length of hospital stay (19.0 [12.8–33.3] vs. 16.0 [10.0–24.0] days; $P < 0.001$) and a higher mortality rate (21.4% vs. 8.9%; $P = 0.017$). Three (20.0%) out of the 15 patients with diabetic ketosis developed acidosis, five patients (26.7%) with diabetic ketosis died, and one of these (25.0%) presented with acidosis. Two (7.4%) and four (14.3%) of the 27 non-diabetic ketotic patients developed severe acidosis and died, respectively, and one (25.0%) of these presented with acidosis. This suggests that COVID-19 infection caused ketosis or ketoacidosis, and induced diabetic ketoacidosis for those with diabetes. Ketosis increased the length of hospital stay and mortality. Meanwhile, diabetes increased the length of hospital stay for patients with ketosis but had no effect on their mortality.

KEYWORDS
COVID-19, DKA, infection, ketoacidosis, ketosis

1 | INTRODUCTION

In December 2019, unexplained viral pneumonia occurred in Wuhan, Hubei province, in China.[1,2] A novel coronavirus, later named COVID-19 by the World Health Organization, was isolated from patients with this pneumonia.[3] The clinical symptoms of COVID-19 infection vary but mainly involve fever and cough. COVID-19 mostly manifests as mild upper respiratory disease and gastrointestinal disease, severe viral pneumonia with systemic organ failure, or even death.[4,5] However, little attention has been paid to metabolic diseases caused by COVID-19, especially in patients with diabetes mellitus.

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TABLE 1 Characteristics and clinical outcomes of patients with ketosis or non-ketosis infected with COVID-19

Characteristic	All patients (n = 658)		
	Ketosis (n = 42)	Non- ketosis (n = 616)	*P*
Age, years	47.0 (38.0–70.3)	58.0 (43.0–67.0)	0.003
Gender, n (%)			
Female	26 (61.9)	335 (54.4)	0.441
Male	16 (38.1)	281 (45.6)	
Clinical symptoms			
Temperature on admission, °C	36.7 (36.5–37.4)	36.5 (36.3–36.9)	0.517
Fever, n (%)	28 (66.6)	413 (67.0)	0.960
Cough, n (%)	20 (47.6)	238 (38.6)	0.249
Fatigue, n (%)	13 (31.0)	65 (10.6)	<0.001
Chest pain, n (%)	1 (2.4)	14 (2.3)	1.000
Chest tightness, n (%)	11 (26.2)	68 (11.0)	0.003
Diarrhoea, n (%)	2 (4.8)	16 (2.6)	0.731
Headache, n (%)	2 (4.8)	9 (1.5)	0.321
Nausea and vomiting, n (%)	5 (11.9)	39 (6.3)	0.280
Shortness of breath, n (%)	11 (26.2)	92 (14.9)	0.052
Chronic disease, n (%)			
Cerebrovascular disease	5 (11.9)	48 (7.8)	0.513
Coronary heart disease	6 (14.3)	53 (8.6)	0.333
Heart failure	2 (4.8)	6 (1.0)	0.150
Diabetes	15 (35.7)	114 (18.5)	0.007
Hypertention	12 (28.6)	208 (33.8)	0.490
Digestive disorder	13 (31.0)	74 (12.0)	< 0.001
COPD	0 (0)	19 (28.8)	0.497
Solid tumour	2 (4.8)	15 (2.4)	0.677
Chronic renal disease	1 (2.4)	17 (2.8)	1.000
Hepatitis	1 (2.4)	6 (1.0)	0.934
Complications, n (%)			
Acute liver injury	6 (14.3)	33 (5.4)	0.042
Septic shock	3 (7.1)	32 (5.2)	0.850
Acute respiratory distress syndrome	12 (28.6)	83 (13.5)	0.007
DKA	3 (7,1)	0 (0)	< 0.001
Acidosis	5 (11.9)	25 (4.1)	0.048
Lung CT images, n (%)			
Unilateral pneumonia	14 (33.3)	137 (22.2)	0.098
Bilateral pneumonia	28 (66.7)	479 (77.8)	0.098
Multiple mottling and ground-glass opacity	27 (64.3)	412 (66.9)	0.730
Treatment strategies, n (%)			
Antibiotics	41 (97.6)	481 (78.1)	0.002
Antiviral drugs	41 (97.6)	576 (93.5)	0.461
Antifungal agents	1 (2.4)	17 (2.8)	1.000
Hormones	26 (61.9)	279 (45.3)	0.037
Immunoglobulin	10 (23.8)	111 (18.0)	0.349
Invasive mechanical ventilation	9 (21.4)	42 (6.7)	0.002
Non-invasive mechanical ventilation	9 (21.4)	63 (10.2)	0.046

TABLE 1 (Continued)

Characteristic	All patients (n = 658)		
	Ketosis (n = 42)	Non- ketosis (n = 616)	*P*
Blood biochemical variables			
Leukocytes (3.5–9.5) 10^9/L	5.5 (3.5–9.1)	5.2 (4.1–6.7)	0.404
Neutrophils (1.8–6.3) 10^9/L	3.8 (1.9–6.4)	3.4 (2.4–4.6)	0.069
Lymphocytes (1.1–3.2) 10^9/L	1.1 (0.9–1.6)	1.2 (0.8–1.7)	0.410
Eosinophils (0.02–0.52) 10^9/L	0.00 (0.00–0.03)	0.03 (0.00–0.09)	0.041
Basophils (0–0.06) 10^9/L	0.01 (0.01–0.02)	0.02 (0.01–0.02)	0.861
Lymphocyte percentage (20%–50%)	21.6 (11.7–31.7)	25.8 (15.9–34.6)	0.182
Neutrophil percentage (40%–75%)	68.5 (62.6–83.1)	64.5 (55.5–76.0)	0.096
Monocyte percentage (3%–10%)	6.6 (4.4–8.2)	7.0 (5.4–9.2)	0.519
Eosinophil percentage (0.4%–8%)	0.0 (0.0–0.6)	0.6 (0.1–1.7)	<0.001
Basophil percentage (0%–1%)	0.2 (0.1–0.3)	0.3 (0.2–0.4)	0.022
Platelets (125–350) 10^9/L	172.5 (145.0–222.8)	192.0 (154.0–247.0)	0.195
Haemoglobin (130–175 g/L)	132.0 (120.8–140.8)	128.0 (119.0–139.0)	0.381
Monocytes (0.1–0.6) 10^9/L	0.3 (0.2–0.5)	0.4 (0.3–0.5)	0.867
Activated partial thromboplastin time (20–40) s	29.1 (25.1–31.3)	27.9 (24.9–31.0)	0.524
Fibrinogen (2–4) g/L	2.9 (2.6–3.6)	2.8 (2.3–3.3)	0.073
Prothrombin time (9–13) s	11.4 (10.8–11.7)	11.5 (11.0–12.0)	0.385
International normalized ratio (0.7–1.3)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	0.406
D-dimer (0–1) μg/mL	0.7 (0.4–1.9)	0.5 (0.2–1.3)	0.632
Albumin (40–55) g/L	39.4 (34.9–42.7)	39.5 (36.1–43.1)	0.542
Globulin (20–40) g/L	28.4 (24.1–31.3)	26.9 (24.4–30.8)	0.757
Albumin-to-globulin ratio (1.2–2.4)	1.4 (1.2–1.6)	1.5 (1.2–1.7)	0.639
Alanine aminotransferase (9–50) U/L	15.7 (10.9–28.8)	19.7 (13.8–34.3)	0.299
Aspartate aminotransferase (15–40) U/L	24.7 (16.8–37.3)	21.0 (16.0–30.6)	0.185
Total bilirubin (2–20.4) μmol/L	9.3 (6.2–13.8)	9.6 (7.0–13.6)	0.977
Serum urea (1.7–8.3) mmol/L	4.3 (3.0–5.9)	4.1 (3.2–5.4)	0.463
Serum creatinine (57–111) μmol/L	55.6 (42.4–65.2)	65.7 (52.0–79.8)	0.116
Alkaline phosphatase (40–150) U/L	60.8 (44.8–60.8)	60.8 (46.0–60.8)	0.266
pH value (7.35–7.45)	7.42 (7.41–7.46)	7.42 (7.41–7.44)	0.463
Creatine kinase (38–174) U/L	91.5 (47.0–166.8)	88.0 (52.0–132.0)	0.437
Lactate dehydrogenase (80–285) U/L	214.6 (152.3–282.5)	191.0 (150.0–216.0)	0.264
Creatine kinase isoenzyme (0–25) IU/L	9.0 (6.0–11.5)	8.4 (6.0–10.3)	0.920
Alpha-hydroxybutyrate dehydrogenase (72–182) U/L	170.5 (119.8–216.0)	149.0 (118.3–167.0)	0.276
γ-Glutamyltransferase (10–60) U/L	17.5 (13.6–34.3)	21.1 (13.3–38.9)	0.562
Glucose (3.9–6.1) mmol/L	5.6 (4.7–10.5)	5.5 (4.8–6.9)	0.035
Procalcitonin (< 0.04) ng/mL	0.11 (0.05–0.24)	0.05 (0.04–0.10)	0.834
C-reactive protein (0–0.5) mg/dL	3.5 (1.4–6.5)	0.9 (0.1–3.4)	<0.001
Hospital stays, days	19.0 (12.8–33.3)	16.0 (10.0–24.0)	<0.001
Clinical outcomes, n (%)			
Rehabilitation discharge	33 (78.6)	561 (91.1)	0.017
Died	9 (21.4)	55 (8.9)	

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; DKA, diabetic ketoacidosis.
Values are median (interquartile range), unless otherwise indicated.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Patients with COVID-19 who died or were discharged during the period from January 1 to March 3, 2020, were included in this retrospective cohort study. The study protocol was approved by the Ethics Committee of the Central Hospital, and the requirement for informed consent was waived because of the retrospective nature of our research.

2.2 | Data collection

Epidemiological, demographic and clinical data, as well as computed tomography (CT) images of lungs, laboratory investigations (viral nucleic acids test), treatment options, and management outcomes, were extracted from electronic medical records.

2.3 | Definitions

Ketosis was defined as positive urine ketone or serum ketone test results, while ketoacidosis was defined with a positive test result of urine ketone or serum ketone, and arterial pH < 7.35 or carbon dioxide combining power < 18 mmol/L.[6,7]

2.4 | Statistical analysis

Data are expressed as medians (interquartile range [IQR]) or percentages (%). We used the Mann–Whitney *U*-test, the chi-squared test or Fisher's exact test in order to compare the differences among various groups, including the differences between ketosis and non-ketosis groups or between diabetes and non-diabetes groups.

3 | RESULTS

This study included 658 hospitalized patients with confirmed COVID-19. Of these patients, 64 (9.7%) died, and 40 (62.5%) were men. The median (IQR) age was 57.5 (42.0–67.0) years, and 297 (45.1%) were men. The most common symptoms at disease onset were fever 441 (67.0%) and cough 258 (39.2%). Meanwhile, the majority of our patients had elevated levels of D-dimer, C-reactive protein and interleukin-6, decreased levels of lymphocytes and albumin, and CT imaging features of ground-glass opacification, which was consistent with previous studies.[1,3]

The characteristics and clinical outcomes of COVID-19 patients with ketosis or non-ketosis are summarized in Table 1. Forty-two (6.4%) out of 658 patients presented with ketosis on admission, with no obvious fever or diarrhoea. They had a median (IQR) age of 47.0 (38.0–70.3) years, while 16 (38.1%) were men. Patients with ketosis were younger (median age 47.0 vs. 58.0 years; $P = 0.003$) and had a greater prevalence of fatigue (31.0% vs. 10.6%; $P < 0.001$), diabetes (35.7% vs. 18.5%; $P = 0.007$) and digestive disorders (31.0% vs. 12.0%; $P < 0.001$). They had a longer median (IQR) length of hospital stay (19.0 [12.8–33.3] vs. 16.0 [10.0–24.0] days; $P < 0.001$) and a higher mortality rate (21.4% vs. 8.9%, $P = 0.017$).

The baseline characteristics and clinical outcomes of patients with and without diabetes and with ketosis who presented with COVID-19 infection are summarized in Table 2. A total of 129 patients (19.6%) had diabetes, with only one case of type 1 diabetes (Table 1). Fifteen (35.7%, median age 56.0 years) out of 42 patients with ketosis had diabetes, while 27 (64.3%, median age 41.0 years) did not have diabetes. Patients with diabetes were older (median age 56.0 vs. 41.0 years; $P = 0.008$), with a greater prevalence rate of coronary heart disease (40.0% vs. 0%; $P = 0.002$) and hypertension (53.3% vs. 14.8%; $P = 0.022$), and also had a longer median (IQR) length of hospital stay (33.0 [20.0–39.0] vs. 17.0 [10.0–22.0] days; $P = 0.003$). However, we noted no significant difference regarding the mortality rate (33.3% vs. 14.8%; $P = 0.313$).

Three (20.0%) out of the 15 patients with diabetic ketosis developed acidosis (case 1: male, age 26 years, pH 6.86, urine ketone +++, fasting plasma glucose 22.61 mmol/L, urine glucose ++++, lactate 1.7 mmol/L; case 2: male, age 54 years, pH 7.22, urine ketone +++, fasting plasma glucose 21.23 mmol/L, urine glucose ++++, lactate 1.7 mmol/L; case 3: female, age 44 years, pH 7.32, urine ketone +, fasting plasma glucose 16.55 mmol/L, urine glucose ++++, lactate 0.7 mmol/L). Five patients (26.7%) with diabetic ketosis died, and one (25.0%) of these presented with acidosis. Two (7.4%) and four (14.3%) of the 27 patients with non-diabetic ketotis developed severe acidosis (case 1: male, age 85 years, pH 7.11, urine ketone +, fasting plasma glucose 5.47 mmol/L, urine glucose negative, lactate 2.6 mmol/L; case 2: female, age 56 years, pH 7.15, urine ketone ++, fasting plasma glucose 4.63 mmol/L, urine glucose negative, lactate 1.0 mmol/L) and died, respectively, and one (25.0%) of those who died presented with acidosis.

Of the 42 patients with ketosis, four (44.4%) were men and their median (IQR) age was 69.0 (55.0–85.5) years, while nine patients (21.4%) died. All nine patients had a history of cardiovascular and cerebrovascular disease with no obvious history of respiratory disease, and died from multiple organ failure.

4 | DISCUSSION

In the present study, we reported that COVID-19 infection caused ketosis or ketoacidosis, and induced diabetic ketoacidosis (DKA) for those patients with diabetes. Ketosis increased the length of hospital stay and mortality. Meanwhile, diabetes increased the length of hospital stay for patients with ketosis but had no effect on their mortality.

Ketones are formed in the liver from free fatty acids.[8] When ketone consumption decreases, it results in ketosis, which can be clinically evident by elevated blood concentrations of ketone bodies (β-hydroxybutyrate, acetoacetate and acetone).[9] Ketoacidosis, a

TABLE 2 Characteristics and clinical outcomes of patients with or without diabetes with ketosis who were infected with COVID-19

Characteristic	Ketosis (n = 42)		
	Diabetes (n = 15)	Non-diabetes (n = 27)	*P*
Age, years	56.0 (49.0–73.0)	41.0 (30.0–56.0)	0.008
Gender, n (%)			
Female	12 (80.0)	14 (51.9)	0.072
Male	3 (20.0)	13 (48.1)	
Clinical symptoms, n (%)			
Temperature on admission,°C	36.8 (36.5-37.5)	36.8 (36.4-37.6)	0.094
Fever	10 (66.7)	18 (66.7)	1.000
Cough	7 (46.7)	13 (48.1)	0.927
Fatigue	7 (46.7)	6 (22.2)	0.196
Chest pain	0 (0)	1 (3.7)	1.000
Chest tightness	5 (33.3)	6 (22.2)	0.676
Diarrhoea	0 (0)	2 (7.4)	0.746
Headache	1 (6.7)	1 (3.7)	1.000
Nausea and vomiting	3 (20.0)	6 (22.2)	1.000
Shortness of breath	3 (20.0)	8 (29.6)	0.754
Chronic disease, n (%)			
Cerebrovascular disease	4 (26.7)	1 (3.7)	0.088
Coronary heart disease	6 (40.0)	0 (0)	0.002
Heart failure	1 (6.7)	1 (3.7)	1.000
Hypertention	8 (53.3)	4 (14.8)	0.022
Digestive disorder	4 (26.7)	9 (33.3)	0.858
COPD	0 (0)	0 (0)	NA
Solid tumour	1 (6.7)	1 (3.7)	1.000
Chronic renal disease	1 (6.7)	0 (0)	1.000
Hepatitis	0 (0)	1 (3.7)	1.000
Complications, %			
Acute liver injury	2 (13.3)	4 (14.8)	1.000
Septic shock	1 (6.7)	2 (7.4)	1.000
Acute respiratory distress syndrome	6 (40.0)	6 (22.2)	0.387
DKA	3 (20.0)	NA	NA
Acidosis	3 (20.0)	2 (7.4)	0.478
Lung CT images, %			
Unilateral pneumonia	3 (20.0)	11 (40.7)	0.172
Bilateral pneumonia	12 (80.0)	16 (59.3)	0.172
Multiple mottling and ground-glass opacity	7 (46.7)	20 (74.1)	0.076
Treatment strategies, %			
Antibiotics	15 (100.0)	26 (96.3)	1.000
Antiviral drugs	14 (93.3)	27 (100.0)	1.000
Antifungal agents	0 (0)	1 (3.7)	1.000
Hormones	10 (66.7)	16 (59.3)	0.636
Immunoglobulin	4 (26.7)	6 (22.2)	1.000
Invasive mechanical ventilation	4 (26.7)	5 (18.5)	0.823
Non-invasive mechanical ventilation	4 (26.7)	5 (18.5)	0.823
Blood biochemical parameters, median (IQR)			
Leukocytes (3.5–9.5) 10^9/L	5.9 (4.0–12.2)	4.4 (3.1–7.9)	0.082

(Continues)

TABLE 2 (Continued)

Characteristic	Ketosis (n = 42)		
	Diabetes (n = 15)	Non-diabetes (n = 27)	*P*
Neutrophils (1.8–6.3) 10^9/L	4.5 (2.8–10.2)	3.7 (1.8–5.3)	0.053
Lymphocytes (1.1–3.2) 10^9/L	1.0 (0.7–1.5)	1.2 (0.9–1.8)	0.548
Eosinophils (0.02–0.52) 10^9/L	0.00 (0.00–0.01)	0.00 (0.00–0.06)	0.391
Basophils (0–0.06) 10^9/L	0.01 (0.01–0.02)	0.01 (0.01–0.02)	0.315
Lymphocyte percentage (20%–50%)	12.7 (7.4–22.9)	23.9 (15.9–35.5)	0.030
Neutrophil percentage (40%–75%)	82.3 (70.1–86.7)	66.9 (56.3–73.4)	0.029
Monocyte percentage (3%–10%)	5.4 (4.4–6.9)	7.2 (4.3–8.5)	0.255
Eosinophil percentage (0.4%–8%)	0.00 (0.00–0.20)	0.10 (0.00–1.00)	0.121
Basophil percentage (0%–1%)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.781
Platelets (125–350) 10^9/L	173.0 (146.0–201.0)	170.0 (132.0–242.0)	0.648
Haemoglobin (130–175 g/L)	126.0 (116.0–134.0)	134.0 (123.0–144.0)	0.281
Monocytes (0.1–0.6) 10^9/L	0.4 (0.2–0.6)	0.3 (0.2–0.5)	0.569
Activated partial thromboplastin time (20–40) s	25.5 (23.3–30.0)	29.7 (27.5–32.6)	0.063
Fibrinogen (2–4) g/L	3.5 (2.7–4.5)	2.8 (2.5–3.3)	0.072
Prothrombin time (9–13) s	11.0 (10.6–11.6)	11.4 (11.1–11.9)	0.242
International normalized ratio (0.7–1.3)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	0.214
D-dimer (0–1) μg/mL	1.0 (0.5–2.6)	0.6 (0.3–1.2)	0.163
Albumin (40–55) g/L	35.6 (31.6–41.8)	40.8 (36.5–43.7)	0.017
Globulin (20–40) g/L	29.5 (25.3–34.3)	28.2 (23.6–30.8)	0.261
Albumin-to-globulin ratio (1.2–2.4)	1.3 (1.0–1.5)	1.5 (1.3–1.7)	0.029
Alanine aminotransferase (9–50) U/L	14.8 (10.9–33.3)	16.0 (10.9–28.5)	0.823
Aspartate aminotransferase (15–40) U/L	25.4 (18.3–45.6)	21.7 (16.6–32.8)	0.950
Total bilirubin (2–20.4) μmol/L	9.5 (5.6–19.8)	9.3 (6.6–11.3)	0.294
Serum urea (1.7–8.3) mmol/L	5.3 (3.6–6.9)	3.5 (2.9–4.7)	0.021
Serum creatinine (57–111) μmol/L	57.5 (40.7–65.6)	54.5 (45.8–63.9)	0.885
Alkaline phosphatase (40–150) U/L	60.8 (44.0–66.0)	55.0 (45.0–60.8)	0.768
pH value (7.35–7.45)	7.43 (7.40–7.46)	7.42 (7.40–7.45)	0.961
Ketone body (negative)	2 (1–2)	1 (1–2)	0.154
Standard bicarbonate ion (21–25) mmol/L	24.5 (19.5–26.4)	25.8 (25.8–27.4)	0.006
Actual bicarbonate ion (21–28) mmol/L	22.9 (19.0–26.0)	26.0 (25.0–28.1)	0.012
Base excee (−3–3) mmol/L	3.2 (1.9–4.4)	3.2 (2.4–3.5)	0.721
Lactate (0.5–2.2) mmol/L	1.3 (1.0–2.4)	2.1 (1.5–2.4)	0.417
Creatine kinase (38–174) U/L	128.0 (68.5–200.0)	77.0 (47.0–132.1)	0.633
Lactate dehydrogenase (80–285) U/L	253.0 (202.0–351.0)	202.0 (151.0–233.0)	0.345
Creatine kinase isoenzyme (0–25) IU/L	10.1 (9.0–15.0)	7.0 (6.0–11.0)	0.045
Alpha-hydroxybutyrate dehydrogenase (72–182) U/L	182.0 (158.0–257.0)	163.0 (116.0–190.0)	0.488
γ-Glutamyltransferase (10–60) U/L	21.2 (15.4–37.0)	16.8 (12.9–34.1)	0.951
Glucose (3.9–6.1) mmol/L	13.0 (9.2–16.6)	4.9 (4.6–5.6)	<0.001
HbA1c (< 6%)	9.0 (7.6–12.3)	5.6 (5.2–5.8)	<0.001
Procalcitonin (< 0.04) ng/mL	0.21 (0.05–0.32)	0.09 (0.05–0.24)	0.175
C-reactive protein (0–0.5) mg/dL	6.2 (2.9–8.8)	2.6 (0.7–4.9)	0.010
Hospital stays, days	33.0 (20.0–39.0)	17.0 (10.0–22.0)	0.003
Clinical outcomes, n (%)			
Rehabilitation discharge	10 (66.7)	23 (85.2)	0.313
Died	5 (33.3)	4 (14.8)	

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; DKA, diabetic ketoacidosis; HbA1c, glycated haemoglobin.
Values are median (interquartile range), unless otherwise indicated.

severe metabolic disorder characterized by the accumulation of ketone bodies and acidosis, is mostly seen in people with diabetes and is rarely induced by other pathological conditions.[10] In the present study, 42 patients with COVID-19 had ketosis, including 27 who did not have diabetes. Meanwhile, five patients with COVID-19 showed ketoacidosis, including three patients with diabetes and two without diabetes, which suggests that COVID-19 might accelerate fat breakdown and induce ketosis, with further development of ketoacidosis. However, a previous study reported that patients with ketosis tended to have type 2 diabetes[11]; therefore, non-diabetic patients with ketosis should control their diet and exercise frequently to reduce the risk of diabetes. Further research is needed to confirm such observations.

Diabetic ketoacidosis is a potentially fatal metabolic complication attributable to uncontrolled blood glucose,[12] which is more common in people with type 1 diabetes. However, it can also occur in type 2 diabetes and viral infection.[13] In the present study, three patients with COVID-19 had DKA, one of whom died. We should pay attention to COVID-19 patients with ketoacidosis, therefore, especially those with diabetes, in order to reduce the associated mortality from complications of COVID-19. Notably, the mechanism of COVID-19-induced DKA needs further research.

The study was limited because of the small number of patients with COVID-19 progressing from ketosis to ketoacidosis. Future studies should pay considerable attention to ketosis and ketoacidosis in such a population, as well as observe the long-term prognosis of the disease.

In conclusion, we reported that COVID-19 infection caused ketosis or ketoacidosis, and induced DKA for those patients with diabetes. Ketosis increased the length of hospital stay and mortality. Meanwhile, diabetes increased the length of hospital stay for patients with ketosis but had no effect on their mortality. The mechanism of COVID-19-induced ketosis, ketoacidosis or DKA needs further research.

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CONFLICTS OF INTEREST

The authors declare no competing interests.

AUTHORS CONTRIBUTIONS

A.P.D. and J.Y.L. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Contributions were as follows: J.Y.L. and A.P.D. conceived and designed the experiments; J.Y.L., X.F.W., H.M.Z. and A.P.D. performed the experiments; J.Y.L., X.F.W., J.C., X.R.Z. and A.P. D. analysed the data; J.Y.L. wrote the paper; J.Y.L., X.F.W. and J.C. contributed equally.

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REFERENCES

1. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020. https://doi.org/10.1001/jama.2020.1585.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
3. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020:382(18):1708–1720.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020. https://doi.org/10.1001/jama.2020.2648.
5. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513.
6. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care*. 2001;24(1):131-153.
7. Kraut JA, Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. *Nature Rev Nephrol*. 2012;8(10):589-601.
8. Azzam O, Prentice D. Lactation ketoacidosis: an easily missed diagnosis. *Intern Med J*. 2019;49(2):256-259.
9. Kovacs Z, D'Agostino DP, Diamond D, Kindy MS, Rogers C, Ari C. Therapeutic potential of exogenous ketone supplement induced ketosis in the treatment of psychiatric disorders: review of current literature. *Front Psych*. 2019;10:363.
10. Larroumet A, Camoin M, Foussard N, et al. Euglycemic ketoacidosis induced by therapeutic fasting in a non-diabetic patient. *Nutrition*. 2020;72:110668.
11. Mauvais-Jarvis F, Sobngwi E, Porcher R, et al. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. *Diabetes*. 2004;53(3):645-653.
12. Nyenwe EA, Kitabchi AE. The evolution of diabetic ketoacidosis: an update of its etiology, pathogenesis and management. *Metabolism*. 2016;65(4):507-521.
13. Tan H, Wang C, Yu Y. H1N1 influenza: the trigger of diabetic ketoacidosis in a young woman with ketosis-prone diabetes. *Am J Med Sci*. 2012;343(2):180-183.

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