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.
| Characteristic                                      | All patients (n = 658) | Ketosis (n = 42) | Non-ketosis (n = 616) | P   |
|----------------------------------------------------|------------------------|------------------|-----------------------|-----|
| **Age, years**                                     |                        |                  |                       | 0.003 |
|                                                   | 47.0 (38.0–70.3)        | 58.0 (43.0–67.0) |                       |     |
| **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 |
| Hypertension                                       | 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) x10^9/L                     | 5.5 (3.5–9.1)          | 5.2 (4.1–6.7)    | 0.404                 |         |
| Neutrophils (1.8–6.3) x10^9/L                    | 3.8 (1.9–6.4)          | 3.4 (2.4–4.6)    | 0.069                 |         |
| Lymphocytes (1.1–3.2) x10^9/L                    | 1.1 (0.9–1.6)          | 1.2 (0.8–1.7)    | 0.410                 |         |
| Eosinophils (0.02–0.52) x10^9/L                  | 0.00 (0.00–0.03)       | 0.03 (0.00–0.09) | 0.041                 |         |
| Basophils (0–0.06) x10^9/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) x10^9/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) x10^9/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 (%)**

|                     | All patients (n = 658) | Ketosis (n = 42) | Non-ketosis (n = 616) | P       |
|---------------------|------------------------|------------------|-----------------------|---------|
| Rehabilitation      | 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.
MATERIALS AND METHODS

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.

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.

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 Ketone bodies 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

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 (42.0–70.0) years, and 297 (45.1%) were men. The most common symptoms at disease onset were fever (21.4%) and cough (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 (67.0%) 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 ketosis 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.

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**                        |                 |                  |                       | 0.008 |
|                                       | 56.0 (49.0–73.0) | 41.0 (30.0–56.0)  |                       |       |
| **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                 |       |
| Hypertension                          | 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                 |       |
| Characteristic | Ketosis (n = 42) | Non-diabetes (n = 27) | P       |
|---------------|----------------|-----------------------|---------|
|               | Diabetes (n = 15) |                       |         |
| 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 (15.9–35.9) | 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 excess (−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: Diabetes 10 (66.7), Non-diabetes 23 (85.2), P = 0.313
- Died: Diabetes 5 (33.3), Non-diabetes 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. 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; 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, which is more common in people with type 1 diabetes. However, it can also occur in type 2 diabetes and viral infection. 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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