RESEARCH ARTICLE

# Comparison of ketoacidosis in type 1 and 2 diabetic patients with and without concurrent COVID-19 and determining the factors affecting their treatment and survival: a retrospective cohort study

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## Abstract

**Objective:** To assess the incidence of diabetic ketoacidosis in coronavirus disease-2019 patients and their survival rate, and to compare their outcomes with diabetic ketoacidosis patients without coronavirus disease-2019.

**Method:** The retrospective cohort study was conducted at Aga Khan University Hospital, Karachi, and comprised data March 1, 2020, to March 31, 2021, related to patients. who had diabetic ketoacidosis with coronavirus disease-2019 in group A, and those who had diabetic ketoacidosis without coronavirus disease-2019 in group B. Data included age, gender, duration and type of diabetes and the final outcome. Data was analysed using SPSS 25.

**Results:** Of the 120 patients, 40(33.3%) were in group A; 21(52.5%) males and 19(47.5%) females, with 22(55%) aged 45-64 years. There were 80(66.6%) patients in group B; 42(52.5%) males and 38(47.5%) females, with 36(45%) aged <45 years ($p>0.05$). The mortality was higher in group A patients13(32.5%) compared to those in group B 10(12.5%) ($p<0.05$). The data analysis was performed with the Statistical Package for Social Sciences (SPSS), V.25. Survival analysis showed that age, dyslipidaemia, history of cardiac revascularisation, acute respiratory distress syndrome, ventilator requirement, and severity of coronavirus disease-2019 were significantly associated with mortality ($p<0.05$).

**Conclusion:** Patients of diabetic ketoacidosis with coronavirus disease-2019 had poor survival outcomes compared to diabetic ketoacidosis patients without coronavirus disease-2019.

**Key Words:** Diabetes mellitus, Diabetic ketoacidosis, COVID-19, Mechanical ventilator, Acidosis.

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## Introduction

Diabetic ketoacidosis (DKA) is a serious metabolic complication of diabetes mellitus (DM). It occurs because of relative or complete insulin deficiency, leading to decreased glucose utilisation and unregulated lipid metabolism. It is often precipitated by severe intercurrent illnesses, including infections, and poor compliance to drug therapy. It can also occur as an initial presentation of DM.[1]

The American Diabetes Association (ADA) defines DKA as the triad of metabolic acidosis, hyperglycaemia and elevated ketones, with specific clinical parameters of serum glucose >250mg/dL, arterial potential of hydrogen (pH) <7.3, serum bicarbonate <18mmol/L, ketonuria or ketonemia, and anion gap >10.[2] Diabetes United Kingdom (UK) criteria include ketones, but excluded the anion gap.[3] According to the 2018 Diabetes Canada Clinical Practice guidelines, there are no definitive criteria for DKA diagnosis.[4]

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Traditionally, DKA is associated more commonly with type 1 DM, but DKA occurring with type 2 DM (T2DM) is also well recognised. A retrospective review reported that the incidence of DKA in T2DM increased by 4.24% annually between 1992 and 2013[5]

DKA is associated with an increased burden on the healthcare system, accounting for approximately 6.3% of yearly hospitalisation and 0.4% of patient mortality.[6] Thus, early recognition of the signs and symptoms of DKA with a high index of suspicion and timely intervention is essential to prevent associated morbidity and mortality.[7]

Since the advent of the coronavirus disease-2019 (COVID-19) pandemic in December 2019, there have been over 626 million cases of COVID-19 worldwide, causing over 6.5 million deaths.[8] More than 1.5 million cases and around 30,139 COVID-19 deaths have been reported in Pakistan.[9] Data from various countries has shown that DM as a comorbid condition is associated with high morbidity and mortality in patients hospitalised with COVID-19.[10] DKA is reported to be a risk factor for a worsening prognosis associated with COVID-19 not only because of the changes induced by hyperglycaemia, but also due to other pathologies.[11-14] Likewise, the entry of the virus into the pancreatic beta (·̣·) cells has been proposed to be a

risk factor for both the occurrence of DKA and the worsening of blood sugar levels in these patients.[15]

Overall morbidity and mortality rate amongst individuals infected with COVID-19 presenting with DKA reportedly approached 50%.[16,17] The presentation and treatment outcomes for COVID-19 patients presenting with DKA has remained an area of debate. Firstly, patients with COVID-19 may present with symptoms atypical of DKA, leading to missed or delayed diagnoses. Secondly, the underlying respiratory insufficiency with COVID-19 pneumonia and attempts to keep a conservative fluid strategy renders the usual infusion of large fluid volumes in DKA patients challenging for those with concomitant DKA and COVID-19 pneumonia. This leads to a wide variation in management protocols. There are very few studies that have reported the impact of DKA on COVID-19 prognosis. So far, the literature is only in the form of case series and reports, with very few large-scale studies.[13,18-20] Besides, there has been a paucity of such data from developing nations, with the studies conducted in developed countries having a limited number of patients.[18,21,22]

The current study was planned to assess DKA incidence in COVID-19 patients and their survival rate, and to compare their outcomes with DKA patients without COVID-19 in a tertiary care setting of a developing country.

## Materials and Methods

The retrospective cohort study was conducted at Aga Khan University Hospital, Karachi, and comprised data from March 1, 2020, to March 31, 2021, related to DKA patients with COVID-19 in group A, and those without COVID-19 in group B. Data collection was started after approval from the Aga Khan University Ethics Review committee (ERC) (Number: 2020-5065-11506). Data was retrieved from the Hospital Information Management Service (HIMS) records after approval from the institutional ethics review committee (ERC). A ratio of 1:2 between group A and group B. Cases with missing data were excluded.

The sample size for this study was determined based on the availability of patients with concomitant COVID-19 and DKA during the selected study period. Out of 3189 COVID-19 patients admitted, 60 had concomitant DKA, and after excluding 20 patients due to incomplete data, 40 patients were included in the study. To maintain a ratio of 1:2 between COVID-19 patients with DKA and patients with only DKA, 80 patients with only DKA were selected, resulting in a total sample size of 120.

This approach is supported by the concept of Purposive Sampling, which involves selecting participants based on their characteristics or eligibility that are relevant to the study.[23] In this case, the sample size was determined by the number of patients with the desired characteristics (concomitant COVID-19 and DKA, or only DKA) available during the study period.

Baseline characteristics included age, gender, duration and type of DM, initial COVID-19 symptoms, blood glucose levels, comorbidities, duration of admission, length of intensive care unit (ICU) stay, time to resolve DKA, and patient outcome (discharged or expired).

COVID-19 cases were considered confirmed based on their positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) reverse transcription-polymerase chain reaction (RT-PCR), while DKA was considered confirmed in the light of ADA criteria comprising blood sugar level >250mg/dl along with serum bicarbonate level <18mEq/L or arterial blood gas (ABG) with a potential of hydrogen (pH) <7.30 with ketonuria or ketonemia, and high anion gap of >12mEq/L.[2] Patients labelled non-DKA at the time of presentation were excluded.

The association of age, body mass index (BMI), acute respiratory distress syndrome (ARDS) status, plasma glucose levels on admission, duration of DM, insulin infusion, use of steroids, need for mechanical ventilation (MV), length of hospital stay (LOS), length of ICU stay and discharge status were compared between the groups.

Data was analysed using SPSS 25. Data was expressed as mean +/- standard deviation or as frequencies and percentages, as appropriate. Chi-square and Fisher exact tests were used, as appropriate. Mortality and LOS were assessed using Cox proportional hazard regression, and the findings were expressed as crude hazard ratio (cHR) with 95% confidence interval (CI). P<0.05 was considered statistically significant.

## Results

Of the 3,189 COVID-19 patients admitted during the study period, 60(1.9%; 95% CI: 1.4-2.4%) had concomitant DKA. From among them, 20(33.3%) cases were excluded due to incomplete data. As such, there were 40(66.6%) patients in group A. During the same timeline, 208 patients were admitted with DKA without COVID-19. Of them, 80(38.5%) were included in line with the predetermined 1:2 ratio.

There were 21(52.5%) males and 19(47.5%) females in group A, with 22(55%) aged 45-64 years. In group B, there were 42(52.5%) males and 38(47.50%) females, with 36(45%) aged <45 years. DM duration, steroid use, MV, non-invasive MV (NIMV), ARDS, LOS, length of ICU stay and discharge status were significantly different between

**Table-1:** Demographic and clinical characteristics of the patients.

| Demographic and Clinical Characteristics | COVID-19 Status | | | | |
|---|---|---|---|---|---|
| | Yes (n=40) | | No (n=80) | | |
| | N | (%) | N | (%) | p-value |
| **Age Group (in years)** | | | | | 0.2209 |
| <45 years | 9 | 22.5% | 36 | 45.00% | |
| 45-64 years | 22 | 55.0% | 31 | 38.80% | |
| 65 years and above | 9 | 22.5% | 13 | 16.30% | |
| **Gender** | | | | | |
| Male | 21 | 52.50% | 42 | 52.50% | >0.999 |
| Female | 19 | 47.50% | 38 | 47.50% | |
| **BMI (in Kg/m$^2$)** | | | | | |
| 18.5-24.9 Kg/m$^2$ | 7 | 17.50% | 22 | 30.60% | 0.3784 |
| 25-29.9 Kg/m$^2$ | 22 | 55% | 33 | 45.80% | |
| ≥30 Kg/m$^2$ | 11 | 27.50% | 14 | 19.40% | |
| **Duration of Diabetes (in years)** | | | | | |
| <5 years | 2 | 30.00% | 43 | 55.10% | 0.01 |
| 5-9 years | 7 | 17.50% | 15 | 19.20% | |
| ≥10 years | 21 | 52.50% | 20 | 25.60% | |
| **Plasma Glucose on admission (in mg/dl)** | | | | | |
| 250-350mg/dl | 16 | 40.00% | 36 | 45% | 0.853 |
| 351-450 mg/dl | 13 | 32.50% | 25 | 31.30% | |
| >450 mg/dl | 11 | 27.50% | 19 | 23.80% | |
| **Insulin Infusion Duration (in days)** | | | | | |
| 1-2 days | 23 | 57.50% | 51 | 63.70% | 0.793 |
| 3-4 days | 15 | 37.50% | 26 | 32.50% | |
| >4 days | 2 | 5.00% | 3 | 3.80% | |
| **Steroids during hospital stay** | | | | | |
| No | 8 | 20.00% | 66 | 82.50% | <0.001 |
| Yes | 32 | 80.00% | 14 | 17.50% | |
| **Mechanical Ventilation** | | | | | |
| No | 24 | 60.00% | 64 | 80% | 0.02 |
| Yes | 16 | 40.00% | 16 | 20% | |
| **NIMV** | | | | | <0.001 |
| No | 10 | 25.00% | 55 | 68.80% | |
| Yes | 30 | 75.00% | 25 | 31.30% | |
| **ARDS** | | | | | |
| No | 22 | 55.00% | 69 | 86.30% | |
| Mild | 5 | 12.50% | 6 | 7.50% | 0.001 |
| Moderate | 6 | 15.00% | 2 | 2.50% | |
| Severe | 7 | 17.50% | 3 | 3.80% | |
| **Length of Hospital Stay (in days)** | | | | | |
| <5 days | 7 | 17.50% | 42 | 52.50% | 0.001 |
| 5-9 days | 19 | 47.50% | 20 | 25% | |
| ≥10 days | 14 | 35.00% | 18 | 22.50% | |
| **Length of ICU Stay (in days)** | 0 | 0.00% | 3 | 3.80% | |
| 1- 4 days | 17 | 42.50% | 55 | 68.80% | 0.012 |
| 5-9 days | 17 | 42.50% | 16 | 20% | |
| >10 days | 6 | 15.00% | 6 | 7.50% | |
| **Discharge Status** | | | | | |
| Discharge Alive | 27 | 67.50% | 70 | 87.50% | 0.009* |
| Died during hospital stay (Expired) | 13 | 32.5% | 10 | 12.5% | |

COVID-19: Coronavirus disease-2019, BMI: Body mass index, NIMV: Non-invasive mechanical ventilation, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit..

the groups (Table 1).

**Table-2:** Mortality outcomes in DKA patients with COVID-19.

| Demographic and Clinical Characteristics | COVID-19 Status | | | | |
|---|---|---|---|---|---|
| | Yes (n=40) | | No (n=80) | | |
| | Mean | SD | Mean | SD | p-value |
| Age Group (in years | 55.85 | 13.269 | 47.58 | 17.295 | 0.005 |
| Plasma Glucose on admission (in mg/dl) | 363.88 | 107.829 | 382.45 | 106.501 | 0.372 |
| Insulin Infusion Duration (in days) | 44.85 | 28.383 | 48.9 | 29.689 | 0.476 |
| Length of Hospital Stay (in days) | 9.93 | 7.072 | 7.49 | 8.169 | 0.11 |
| Length of ICU Stay (in days) | 6.38 | 5.564 | 4.1 | 4.071 | 0.012 |

DKA: Diabetic ketoacidosis, COVID-19: Coronavirus disease-2019, ICU: Intensive care unit, SD: Standard deviation.

**Table-3:** Distribution of demographic and health factors by survival status in DKA patients with COVID-19.

| Characteristics | COVID-19 positive patients who survived during hospitalization (n= 27) | COVID-19 positive patients died during hospitalization (n=13) | p value |
|---|---|---|---|
| **Age Group (in years)** | | | |
| <45 | 7(25.9) | 2(15.4) | |
| 45-64 | 17(63) | 5(38.5) | 0.04 |
| 65 and above | 3(11.1) | 6(46.2) | |
| Mean Age (SD) | 53 (13.5) | 61.7 (10.9) | |
| **Gender** | | | |
| Male | 13(48.1) | 8(61.5) | 0.42 |
| Female | 14(51.9) | 5(38.5) | |
| **BMI (in Kg/m$^2$)** | | | |
| 18.5-24.9 | 6(22.2) | 1(7.7) | 0.38 |
| 25-29.9 | 13(48.1) | 9(69.2) | |
| ≥30 | 8(29.6) | 3(23.1) | |
| **Previous history of DM** | | | |
| Yes | 24(88.9) | 13(100) | 0.53 |
| No | 3(11.1) | 0 | |
| **Type of diabetes** | | | |
| Pre-diabetes | 3(11.1) | 0 | |
| Type I | 2(7.4) | 0 | 0.25 |
| Type II | 22(81.5) | 13(100) | |
| **Duration of diabetes** | | | |
| <5 years | 16(59.3) | 11(84.6) | |
| 10-May | 4(14.8) | 1(7.7) | 0.26 |
| >10 | 7(25.9) | 1(7.7) | |
| **HTN** | | | |
| Yes | 19(70.4) | 12(92.3) | 0.22 |
| No | 8 (29.6) | 1 (7.7) | |
| **Dyslipidaemia** | | | |
| Yes | 4(14.8) | 6(46.2) | 0.052 |
| No | 23 (85.2) | 7 (53.8) | |
| **Cardiac revascularisation** | | | |
| Yes | 1(3.7) | 3(38.5) | 0.01 |
| No | 26 (96.3) | 10 (61.5) | |
| **COVID-19** | | | |
| Mild | 3(11.1) | 0 | |
| Moderate | 16(59.3) | 3(23.1) | 0.01 |

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| | | | |
|---|---|---|---|
| Severe | 8(29.6) | 10(76.9) | |
| **Plasma Glucose on admission** | | | |
| 250-350 mg/dl | 11(40.7) | 5(38.5) | 0.5 |
| 351-450 mg/dl | 10(37) | 3(23.1) | |
| >450 mg/dl | 6(22.2) | 5(38.5) | |
| **Insulin Infusion Duration** | | | |
| 1-2 days | 17(63) | 6(46.2) | 0.57 |
| >3 | 10 (37) | 7(53.9) | |
| **Steroids during hospital stay** | | | |
| Yes | 23(85.2) | 9(69.2) | 0.4 |
| No | 4(14.8) | 4(30.8) | |
| **Mechanical Ventilation** | | | |
| Yes | 5(18.5) | 11(84.6) | <0.001 |
| No | 22(81.5) | 2(15.4) | |
| **NIMV** | | | |
| Yes | 21(77.8) | 9(69.2) | 0.7 |
| No | 6(22.2) | 4(30.8) | |
| **ARDS** | | | |
| No | 17(63) | 5(38.5) | |
| Mild | 5(18.5) | 0 | 0.006 |
| Moderate | 4(14.8) | 2(15.4) | |
| Severe | 1(3.7) | 6(46.2) | |
| **Length of hospital stay** | | | |
| <5 days | 2(7.4) | 2(15.4) | 0.71 |
| 10-days | 17(63) | 7(53.8) | |
| >10 days | 8(29.6) | 4(30.8) | |
| **Length of ICU stay** | | | |
| <5 days | 13(48.1) | 4(30.8) | |
| 10-days | 11(40.7) | 6(46.2) | 0.46 |
| >10 days | 3(11.1) | 3(23.1) | |

DKA: Diabetic ketoacidosis, COVID-19: Coronavirus disease-2019, BMI: Body mass index, HTN: Hypertension, DM: Diabetes mellitus, NIMV: Non-invasive mechanical ventilation, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit, SDF: Standard deviation.

**Table-4:** Crude hazard ratio of factors associated with mortality in DKA patients.

| Factor | Crude Hazard Ratio (95.0% CI) |
|---|---|
| Having COVID-19* | 1.74 (0.76, 4.00) |
| Gender (Male)** | 0.62 (0.26, 1.49) |
| Age (in years) | 1.07 (1.03, 1.11) |
| Having HTN* | 2.51 (0.84, 7.49) |
| Having Dyslipidaemia* | 3.17 (1.22, 8.26) |
| Cardiac revascularisation * | 4.13(1.48,11.51) |
| Use of steroids during the hospital stay | 1.08 (0.47, 2.46) |
| **ARDS*** | |
| Mild | 1.654 (0.357, 7.651) |
| Moderate | 0.862 (0.180, 4.128) |
| Severe | 3.949 (1.527, 10.209) |
| Length of ICU Stay (in days) | 0.95 (0.88, 1.03) |
| **Plasma Glucose on admission***** | |
| 351-450 mg/dl | 0.62 (0.19, 2.00) |
| >450 mg/dl | 1.97 (0.66, 5.90) |
| Mechanical Ventilation* | 7.97 (2.53, 25.11) |

*Reference: No; **Reference: Female; *** Reference: 250-350 mg/dl DKA: Diabetic ketoacidosis, COVID-19: Coronavirus disease-2019, HTN: Hypertension, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit, CI: Confidence interval.

There were 13(32.5%) deaths in group A and 10(12.5%) in group B. Age and length of ICU stay were significantly associated with mortality (Table 2).

There were 27(67.5%) survivors in group A and 70(87.5%) in group B. Among the survivors, age, revascularisation, COVID-19 severity, MV and ARDS were significantly different between the groups (Table 3).

Patients with dyslipidaemia had a higher mortality risk than those with normal lipid profiles (cHR: 3.17; 95% CI: 1.22-8.26). Patients with a history of cardiac revascularisation in the past (cHR: 4.13; 95% CI: 1.48-11.51) had a higher risk of mortality compared to patients without a history of any intervention in the past. The presence of severe ARDS was more associated with death (cHR: 3.94; 95% CI: 1.53-10.21). Patients on MV had a higher risk of mortality compared to those who did not require MV support (cHR: 2.93; 95% CI: 1.20-7.14) (Table 4).

## Discussion

The evidence so far in the literature indicates the presence of a link between COVID-19 and DKA in both diabetic and non-diabetic patients. The effect of DKA on COVID-19 outcome seems to be discrepant, with studies showing varying rates of mortality.[18, 24]

The current study, to our knowledge, is the first to report the incidence and outcomes of DKA in COVID-19 from a large tertiary care hospital situated in the most populous and diverse city of Pakistan. The incidence of DKA in COVID-19 patients found in the study is almost similar to the incidence rate found in a study done in the United Kingdom.[20] The current study found significant differences between the mean ages of DKA patients with and without COVID-19, which is a finding corroborated by another study.[22] The other considerable result was the prevalence of T2DM in both groups (84%). However, even though DKA is considered the complication of type 1 DM (T1DM), it is also increasingly being recognised in T2Dm cases worldwide and has been labelled as ketosis-prone diabetes.[25] Categorising the type of diabetes is critical in management because treatment with oral antidiabetics is possible after the resolution of acute glucotoxicity. Additionally, with the new group of oral antidiabetics like sodium glucose transport protein 2 (SGLT2) inhibitors, its increased tendency to induce euglycaemic DKA renders it essential to prescribe these medications with extreme caution in such patients.

The other significant finding was in the difference between the mean duration of diabetes in the two groups, with the duration being more in patients with DKA and COVID-19 (11 years vs. 6.13 years). Although the

duration was not found to impact survival, it could be hypothesised that it could have been a risk factor for increased tendency to get COVID-19 because of impairment in the immune response.

Another difference was reported in the length of ICU stay where the patients with DKA and COVID-19 had a mean duration of 6 days, while DKA without COVID-19 patients had a duration of 4.1 days (p=0.012). A few studies have shown that patients with COVID-19 and T2DM have higher mortality rates and need ICU stays more often than patients without COVID-19.[26] An increase in DKA incidence in people with preexisting T2DM has also been reported.[27] Since 84.2% of the current sample consisted of those with preexisting T2DM, this becomes an important determinant of outcomes.

This shows that DKA is a possible complication arising in COVID-19 patients which has detrimental effects on the disease severity affecting LOS as well as mortality outcomes. A study showed people with COVID-19 and DKA took longer to achieve resolution of DKA which may provide a plausible explanation for longer hospitalisation of the subgroup.[28]

In the current study, patients with DKA and COVID-19 had poorer prognoses. Among the DKA-COVID-19 patients, 32.5% expired, while only 12.5% of DKA patients without COVID-19 expired. Additionally, trends of higher mortality in COVID-19 patients with DKA were reported in many other studies.[21,29,30] On the other hand, the high mortality rate of DKA without COVID-19 in the current patient population was a cause of serious concern. The reported mortality of DKA from Pakistan in 2004 in people with T2DM also concurs with the same rate.[31]

Countries with the highest COVID-19 mortality saw a significant peak in patients with DKA on follow-up after the first wave of the pandemic.[32,33] The current study also strengthened such observations.

In the current sample, dyslipidaemia, prior history of cardiac revascularisation, ARDS, and patients' MV status were higher mortality risks. Association of MV with higher mortality has previously been reported in a case series in which 6 out of 11 patients with DKA and COVID-19 on MV did not survive.[34]

The current study has limitations that are associated with its retrospective design, which limits the generalisability of the findings owing to its inability to establish the cause-effect relationship between risk factors and survival outcome. The strength of the study is the robust comparison of patients who had DKA with COVID-19 with those having DKA alone.

Key limitation of this study is that the sample size was determined based on available data rather than a priori sample size calculation. As a result, the study may lack generalizability. Additionally, the retrospective nature of the study limits the ability to draw causal inferences between risk factors and survival outcomes. While the comparison between patients with DKA and COVID-19 and those with only DKA offers valuable insights into outcome severity, these findings should be interpreted with caution due to the mentioned limitations.

## Conclusion

DKA patients with COVID-19 had poor survival outcomes compared to DKA patients without COVID-19.

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**Authors' Contribution:**
**AA:** Concept, methodology, investigation, writing, reviewing, editing and supervision.
**KB:** Investigation, data collection and writing.
**FK:** Data collection, cleaning, editing and formatting.
**SS:** Writing, reviewing, formatting and editing.
**MS:** Writing, reviewing, formatting, editing, revisions and submission.