Clinical Profile and Outcomes of Diabetic Ketoacidosis during the COVID-19 Pandemic in North India

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Abstract

Although recent data have shown a declining trend in mortality in diabetic ketoacidosis (DKA), the outcomes are likely to be different during the coronavirus (COVID-19) pandemic. We conducted a prospective cohort study to evaluate the spectrum and outcomes of adult DKA during the pandemic and document differences in DKA patients with or without COVID-19. A total of 169 patients (mean age 44 years) were admitted at the Emergency Department of PGIMER, Chandigarh (India), from January 2020 to June 2021. The precipitating factors were noncompliance with antidiabetic therapy (77.5%), infections (62.7%), and noninfectious conditions (21.3%). Thirty-nine (23.1%) patients had COVID-19, including 31 with severe infection. DKA severity and resolution, ventilator requirement, hospital stay, and mortality were similar in the patients with or without COVID-19. In-hospital mortality was 39.6% (n = 67). The independent mortality predictors were ventilator requirement (*p*-0.000), an infection trigger (*p*-0.049), and hyperosmolarity (*p*-0.048). DKA mortality is increased significantly during the pandemic.

Keywords

diabetic ketoacidosis, coronavirus disease 2019, COVID-19, noncompliance, predisposition, mortality

Introduction

Diabetes mellitus (DM) is a significant public health problem worldwide, and with about 17% of total global cases, India has the dubious distinction of being the diabetic capital of the world.[1,2] Diabetic ketoacidosis (DKA) is a hyperglycemic crisis frequently requiring admission to emergency department (ED) and critical care units. This life-threatening condition is usually precipitated by exogenous insulin deficiency (poor compliance or poor control) and infections (mainly pulmonary, urinary tract, or skin and soft tissue).[3–6] Global and recent Indian data have shown a declining trend in mortality in DKA patients down to <1%.[2,5–7]

During the coronavirus (COVID-19) pandemic, the care of the diabetic population has been severely affected because of health care setting closures and public health measures to prevent the spread of COVID-19. A delay in the diagnosis, poor adherence to prescribed antidiabetic medications, or poor glycemic control have all probably increased acute (e.g. DKA) or chronic (e.g. micro- or macro-vascular disease) complications. Moreover, a potential diabetogenic effect of severe acute respiratory syndrome

coronavirus (SARS-CoV) is well described and postulated through its tropism to angiotensin-converting enzyme-2 receptors, expressed in β-cells, microvasculature, and ductal cells of the pancreas.[8–10]

This study tries to investigate the impact of the COVID-19 pandemic on DKA. We investigate the clinical and laboratory profile and outcomes of DKA patients during the pandemic in north India. We also study the differences in presentation and outcomes in DKA patients with and without COVID-19 infection.

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Methods

Ours was a hospital-based prospective observational study conducted in the ED (Department of Internal Medicine) of PGIMER, Chandigarh, an academic hospital in north India, from 1st January 2020 to 30th June 2021. Patients aged 18 years and above with a diagnosis of DKA were included. Ethical clearance was obtained from the institution's ethical review committee (INT/IEC/2021/SPL-1013). We received written, informed consent from all study patients or the legally authorized representative if the patient could not give consent. There was no financial support or funding source for the study.

Enrolled patients underwent history taking, physical examination, and the relevant laboratory testing. The estimation of plasma glucose and ketone (beta-hydroxybutyrate) levels was done with the capillary prick method using test strips and an electrochemical principle system. Venous blood (preferably from a central line) was used instead of capillary blood in patients with hypotension. Other basic investigations included blood gas analysis, complete blood count (hemoglobin, leukocytes, and platelets), biochemistry panel (serum electrolytes, blood urea, creatinine, and bilirubin), chest radiography, and electrocardiography. Additional diagnostic investigations, such as cultures or microscopic examinations of blood or other body fluids, radioimaging (ultrasonography, computed tomography), glycated hemoglobin, or serological studies, were performed as appropriate.

Anion gap $(mEq/L) = Na^+-[(Cl^-) + (HCO_3^-)]$ (reference range, 10 ± 2 mEq/L). Effective plasma osmolality $(mOsm/kg) = 2$ x measured Na^+ (mEq/L) + Glucose (mg/dL)/18 (normal range, 285–295 mOsm/kg).

Based on American Diabetes Association (ADA) criteria, DKA was diagnosed with plasma glucose $\geq$ 14mmol/L, blood pH $\leq$ 7.30, bicarbonate $\leq$ 18 mEq/L, serum anion gap >10 mEq/L, and presence of ketosis (plasma ketone $\geq$ 3 mmol/L).[11] DKA patients with plasma glucose >600 mg/dL and plasma osmolarity >320 mOsm/kg were defined as combined DKA/HHS (hyperosmolar hyperglycemic syndrome).[11,12] The severity of DKA was defined according to the blood pH, i.e., mild DKA- pH 7.25-7.30, moderate- pH 7.00-7.24, and severe- pH <7.00.[11] Criteria for resolution of DKA include a plasma glucose <11mmol/L and at least 2 of the following criteria: normalization of the anion gap, a pH >7.3, and serum bicarbonate $\geq$ 15 mEq/L.[11]

DM was classified according to World Health Organization criteria.[13] Tachycardia was defined with heart rate >100 beats/ minutes, and hypotension with systolic blood pressure <90 mm Hg or mean arterial pressure <65 mm Hg. A white blood cell count $>11 \times 10^9$ /L was taken as leucocytosis. For electrolyte disorders, we used serum sodium levels <135 mEq/L for hyponatremia, >145 mEq/L for hypernatremia, serum potassium levels <3.5 mEq/L for hypokalemia, and >5.5 mEq/L for hyperkalemia.

The study patients were treated according to the standard guidelines. DKA management was according to ADA statements.[11] Infections were managed with usual care following the guidelines of the 'Surviving Sepsis Campaign'.[14] The patients received empirical antimicrobial agents at the discretion of treating clinicians. The diagnosis, defining severity, and management of COVID-19 was modified according to the available recommendations by the Infectious Diseases Society of America and the National Institutes of Health during the pandemic.[15,16] All patients were followed throughout their hospital stay. Outcomes were recorded as the time required for resolution of DKA, in-hospital death or survival, and length of hospital stay (days).

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 25 for Mac. The discrete data were recorded as frequency and percentage, and continuous data as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR). The study patients were divided into two groups based on the presence or absence of COVID-19 infection, i.e., COVID-19 and non-COVID-19. Between-group differences in the categorical variables were evaluated using the Chi-square test or the Fisher exact test. Differences in the continuous variables were analyzed using the analysis of variance (ANOVA) test, the unpaired Student t-test, or the Mann-Whitney U test. Multivariate logistic regression was performed to predict mortality after adjusting for other factors, and odds ratio (OR) and 95% confidence interval (CI) were calculated. All the hypothesis tests were two-sided. Statistical significance was considered for P-value <0.05.

Results

A total of 169 patients with DKA were enrolled. The most common type of DM was type 2 (n = 91, 53.8%), followed by type 1 (n = 54, 32.0%), chronic pancreatitis (n = 7, 4.1%), latent autoimmune diabetes in adults (n = 4, 2.4%), steroid-induced (n = 2, 1.2%), and unclassified (n = 11, 6.5%). DKA was the first presentation of DM in 24 (18.9%). The remaining 145 patients had a median duration of 6 years (IQR, 3.0-10.0) of pre-existing DM, including 45 (26.6%) with micro- or macrovascular complications and 17 (10.1%) with previous episodes of DKA (i.e. recurrent DKA during the current admission). A total of 39 (23.1%) patients were diagnosed as COVID-19 with a positive result on real-time reverse-transcriptase-polymerase chain reaction testing for SARS-CoV-2 of the nasopharyngeal swab or endotracheal aspirate samples. Table 1 shows the study patients' baseline sociodemographic and clinical characteristics, including comparing COVID-19 and non-COVID-19 groups. No between-group differences were apparent for DKA parameters and basic laboratory profiles (Table 2).

The precipitating factors for DKA were noncompliance with antidiabetic therapy (n = 131, 77.5%), infections (n =

Table 1. Baseline sociodemographic and clinical characteristics of the adult patients with DKA with a comparison between COVID-19 and non-COVID-19 groups.

Parameter	Total (n = 169)	COVID-19 (n = 39)	Non-COVID-19 (n = 130)	P- value
Age (years) (mean ± SD)	43.7 ± 17.0	46.9 ± 17.1	42.7 ± 16.9	0.180
Older age ≥60 years (n, %)	44 (26.0%)	13 (33.3%)	31 (23.8%)	0.236
Males (n, %)	92 (54.4%)	16 (41.0%)	76 (58.5%)	0.055
Diabetes mellitus types (n, %)				
Type 1	54 (32.0%)	10 (25.6%)	44 (33.8%)	0.321
Type 2	91 (53.8%)	25 (64.1%)	66 (50.8%)	
Others[a]	24 (14.2%)	4 (10.3%)	20 (23.1%)	
DKA as first presentation of diabetes mellitus (n, %)	26 (15.4%)	2 (5.1%)	24 (18.5%)	**0.043**
Pre-existing diabetes mellitus (n, %)	143 (84.6%)	37 (94.9%)	106 (81.5%)	
Medical comorbidities (n, %)				
Hypertension	47 (27.8%)	13 (33.3%)	34 (26.2%)	0.401
Others[b]	26 (15.4)	7 (17.9)	19 (14.6)	
None	105 (62.1%)	22 (56.4%)	83 (63.8%)	
Shortness of breath (n, %)	102 (60.4%)	29 (74.4%)	73 (56.2%)	**0.042**
Altered mental status (n, %)	87 (51.5%)	15 (38.5%)	72 (55.4%)	0.064
Nausea and vomiting (n, %)	84 (49.7%)	17 (43.6%)	67 (51.5%)	0.384
Abdominal pain (n, %)	71 (42.0%)	8 (20.5%)	63 (48.5%)	**0.002**
Fever (n, %)	71 (42.0%)	22 (56.4%)	49 (37.7%)	**0.038**
Cough (n, %)	26 (15.4%)	13 (33.3%)	13 (10.0%)	**0.000**
Polydipsia or polyuria (n, %)	11 (6.5%)	1 (2.6%)	10 (7.7%)	0.255
Pulse (per min) (mean ± SD)	112.7 ± 22.8	112.1 ± 23.0	112.9 ± 22.8	0.849
Tachycardia (n, %)	117 (69.2%)	25 (64.1%)	92 (70.8%)	0.429
Systolic blood pressure (mm Hg) (mean ± SD)	111.6 ± 26.0	121.4 ± 24.5	108.6 ± 25.9	**0.007**
Diastolic blood pressure (mm Hg) (mean ± SD)	68.9 ± 17.9	73.0 ± 13.6	67.6 ± 18.8	0.098
Mean arterial pressure (mm Hg) (mean ± SD)	68.2 ± 19.6	73.7 ± 19.1	66.6 ± 19.5	**0.045**
Hypotension (n, %)	83 (49.1%)	16 (41.0%)	67 (51.5%)	0.249
GCS score (median, IQR)	13 (9.0-15.0)	14 (9.0-15.0)	12 (8.7-15.0)	0.160
GCS score ≤8 (n, %)	41 (24.3%)	9 (23.1%)	32 (24.6%)	0.844
Need of invasive ventilation (n, %)	36 (21.3%)	8 (20.5%)	28 (21.5%)	0.891

[a]*Others include chronic pancreatitis (n = 7), latent autoimmune diabetes in adults (n = 4), steroid-induced (n = 2), and unclassified (n = 11).*
[b]*Others include hypothyroidism (n = 7), previous tuberculosis (n = 7), epilepsy (n = 3), celiac disease (n = 2) malignancy (n = 2), and post-renal transplant (n = 2), chronic hepatitis B or C (n = 2), and psychiatric disorders (n = 1).*
Abbreviation: COVID-19- coronavirus disease 2019, DKA- diabetic ketoacidosis, GCS- Glasgow coma scale

106, 62.7%), and non-infectious conditions (n = 36, 21.3%), including 101 (59.8%) patients with more than one triggers. In the COVID-19 group, 79.5% (n = 31) had a severe infection, including associated rhino-orbital mucormycosis, pulmonary mucormycosis, and pulmonary aspergillosis each in one. 20.5% (n = 8) had a mild or asymptomatic COVID-19 infection, including associated cellulitis and cholangitis in each one. Respiratory infections (n = 25) also remained prevalent in non-COVID-19 group, including community-acquired pneumonia (n = 16), tuberculosis (n = 7), mucormycosis (n = 1), and *Pneumocystis jirovecii* (n = 1). Other infectious syndromes were complicated urinary tract infections (n = 20), skin and soft tissue infections (n = 9), rhino-orbital mucormycosis (n = 5), sepsis of unknown primary focus (n = 3), acute meningoencephalitis (n = 2), dengue (n = 1), and multisite infections (n = 2). 96.4% (n = 163) study patients received empirical antibiotics, but only 25.4% (n = 43) had bacterial infections. Non-infectious triggers in

the study patients were infarction (n = 18; 10 coronary, 8 cerebral), cardiac arrhythmia and/or heart failure (n = 6), acute pancreatitis (n = 5), gastro-intestinal ulcer bleed (n = 3), intracerebral haemorrhage (n = 2), and epilepsy (n = 2). Non-infectious causes were present in 19 out of 44 (43.2%) older patients with DKA.

39.6% of DKA patients died. On univariate analysis, the baseline parameters associated with mortality in DKA are shown in Table 3. Among patients requiring ventilator requirement at admission (*p*- 0.000), an infection trigger (*p*- 0.049), and high serum osmolarity (*p*- 0.048), were found to be the independent predictors on a multivariate regression analysis after adjusting for other factors (Table 3). Overall, mortality was more in the COVID-19 group but this was not statistically significant. The median time required for DKA resolution (36 h) and duration of hospital stay (5 days) were similar in patients with or without COVID-19 (Table 4).

Table 2. Baseline laboratory characteristics of the adult patients with DKA with a comparison between COVID-19 and non-COVID-19 groups.

Parameter	Total (n = 169)	COVID-19 (n = 39)	Non-COVID-19 (n = 130)	P- value
Plasma glucose (mg/dL) (median, IQR)	450.0 (360.5 - 575.5)	467.0 (369.0 - 623.0)	446.0 (360.0 - 565.2)	0.485
Serum ketone (mmol/L) (mean ± SD)	5.1 ± 1.1	5.1 ± 1.2	5.1 ± 1.1	0.998
Blood pH (median, IQR)	7.19 (7.00 - 7.26)	7.20 (6.99 - 7.27)	7.18 (7.01 - 7.27)	0.722
pH 7.25 - 7.30 (mild DKA) (n, %)	48 (28.4%)	13 (33.3%)	35 (26.9%)	0.637
pH 7.0 - 7.24 (moderate DKA) (n, %)	80 (47.3%)	16 (41.0%)	64 (49.2%)	
pH <7.0 (severe DKA) (n, %)	41 (24.3%)	10 (25.6%)	31 (23.8%)	
Bicarbonate (mmol/L) (mean ± SD)	7.8 (4.0 - 12.0)	9.2 (3.6 - 13.0)	7.2 (4.0 - 12.0)	0.457
Anion gap (mEq/L) (median, IQR)	24.0 (20.0 - 30.0)	26.0 (20.0 - 29.0)	24.0 (19.7 - 30.2)	0.930
Plasma osmolality (mOsm/kg) (mean ± SD)	315.4 ± 32.6	311.0 ± 22.3	316.7 ± 35.0	0.344
Combined DKA/HHS (n, %)	18 (17.7%)	5 (12.8%)	13 (10.7%)	0.576
Hemoglobin (g/dL) (mean ± SD)	11.3 ± 2.6	11.0 ± 2.1	11.4 ± 2.7	0.472
Total leucocyte count (per µL) (median, IQR)	16000 (11850.0 - 20750.0)	15200 (12300.0 - 21600.0)	16200 (11700.0 - 20525.0)	0.661
Leucocytosis (n, %)	131 (77.5%)	32 (82.1%)	99 (76.2%)	0.439
Platelet count (per µL) (median, IQR)	240000 (179000.0 - 331500.0)	290000 (190000.0 - 355000.0)	235000 (171250.0 - 320000.0)	0.205
Sodium (mEq/L) (mean ± SD)	136.2 ± 9.4	135.1 ± 9.4	136.6 ± 9.4	0.394
Hyponatremia (n, %)	74 (43.8%)	18 (46.2%)	56 (43.1%)	0.734
Hypernatremia (n, %)	28 (16.6%)	4 (10.3%)	24 (18.5%)	0.227
Potassium (mEq/L) (mean ± SD)	4.6 ± 1.2	4.8 ± 1.0	4.5 ± 1.2	0.212
Hypokalemia (n, %)	31 (18.3%)	4 (10.3%)	27 (20.8%)	0.137
Hyperkalemia (n, %)	35 (20.7%)	8 (20.5%)	27 (20.8%)	0.972
Chloride (mEq/L) (mean ± SD)	103.0 ± 11.5	101.1 ± 11.0	103.6 ± 11.6	0.237
Blood urea (mg/dL) (median, IQR)	73.0 (39.0 -118.5)	82.0 (48.0 -117.0)	67.0 (36.7 - 121.2)	0.356
Creatinine (mg/dL) (median, IQR)	1.5 (0.9 - 2.9)	1.7 (1.1 - 3.0)	1.3 (0.8 - 2.9)	0.091
Bilirubin (mg/dL) (median, IQR)	0.5 (0.3 - 0.7)	0.5 (0.4 - 0.6)	0.4 (0.3 - 0.7)	0.382
Glycated hemoglobin (%) (mean ± SD) (n = 93)	13.2 ± 3.5	14.0 ± 3.6	13.0 ± 3.5	0.252

Abbreviation: COVID-19- coronavirus disease 2019, DKA- diabetic ketoacidosis, HHS- hyperosmolar hyperglycemic syndrome

Discussion

Our study is an extensive series on DKA during the COVID-19 pandemic from a single-center, which provides the effects and consequences of the pandemic on the hyperglycemic crisis. Noncompliance with antidiabetic therapy was the most common trigger for DKA. Infections were the next common predispositions, with COVID-19 being the single most important infection. DKA patients with COVID-19 predominantly had respiratory symptoms and fever than typical features of ketoacidosis (e.g. abdominal pain, vomiting), which were prominent in the non-COVID-19 group. However, the severity of DKA, laboratory profile, the median time required for DKA resolution, and length of hospital stay were similar. We found considerably high DKA mortality during the pandemic. The mortality was associated with ventilator requirement at admission, an infection trigger, and hyperosmolarity.

Table 3. Multivariate logistic regression analysis of baseline parameters predicting mortality in adult DKA patients.

Parameter	OR (95% CI)	*p*-value
Older age >60 years (n, %)	0.960 (0.237 - 3.883)	0.955
Pre-existing type 2 diabetes mellitus (n, %)	0.614 (0.168 - 2.251)	0.462
Recurrent DKA (n, %)	0.159 (0.013 - 1.915)	0.148
Altered mental state (n, %)	1.188 (0.354 - 3.991)	0.780
Hyponatremia (n, %)	1.492 (0.388–3.991)	0.561
Blood urea (mg/dL) (median, IQR)	1.006 (0.995 - 1.017)	0.282
Serum osmolality (mOsm/L) (mean ± SD)	1.027 (1.000 - 1.055)	**0.048**
Infection trigger for DKA (n, %)	4.404 (1.007 - 19.250)	**0.049**
Infection trigger other than COVID-19 (n, %)	0.692 (0.185 - 2.594)	0.585
Need of invasive ventilation at admission (n, %)	287.725 (30.694 - 2697.170)	**0.000**

Abbreviation: COVID-19- coronavirus disease 2019, DKA- diabetic ketoacidosis

Table 4. Outcomes of DKA with a comparison between the COVID-19 and non- COVID-19 groups.

Parameter	Total (n = 169)	COVID-19 (n = 39)	Non-COVID-19 (n = 130)	P- value
Time required for resolution of DKA (hours) (median, IQR)	36.0 (24.0-48.0)	36 (24-54)	36 (24-48)	0.912
In-hospital mortality (n, %)	67 (39.6%)	20 (51.3%)	47 (36.2%)	0.090
Length of stay (days) (median, IQR)	5 (3- 10)	5 (6-11)	5 (3-9)	0.736

Abbreviation: COVID-19- coronavirus disease 2019, DKA- diabetic ketoacidosis.

DKA was previously considered a hallmark of type 1 DM but is increasingly associated with type 2 DM, as evident by more than half of cases being type 2 DM and more than one-fourth of older patients in the study.[4,5] About 15% of patients had new-onset DM presenting as DKA. COVID-19 patients usually had pre-existing DM, frequently type 2, as observed in other reports.[17,18] In the COVID-19 group, symptoms like shortness of breath, fever, and cough outnumbered the features of ketoacidosis (e.g. abdominal pain, altered mental status, nausea and vomiting, and low blood pressure), which were typically seen in the patients without COVID-19. However, the two groups were similar in at-admission ventilator requirement, DKA severity, and baseline laboratory characteristics.

Noncompliance with antidiabetic therapy was the most common trigger for DKA. A prevalence of 78% was much higher than previously observed, which might be attributed to the poor access or adherence to the medications and lack of regular medical follow-up during the pandemic.[2–6] Infections (63%) were the common predisposition, and COVID-19 (23%) remained the most prevalent infection. Concurring with previous studies, infections other than COVID-19 were similar in frequency (40%) and types (most commonly affecting respiratory or urinary tract).[2–6] Our study strengthens the previous observation that tuberculosis and mucormycosis (with or without COVID-19) are important infections in DM and DKA.[2,19] DKA in older patients was frequently associated with noninfectious conditions, such as cardiac emergencies and stroke. Given the infections are common triggers and sepsis identifying tools (e.g. Systemic Inflammatory Response Syndrome criteria) have poor specificity in the setting of DKA, ED physicians frequently prescribe empirical antibiotics.[2–4,20,21] A large majority of our patients received empirical antibiotics, but only one quarter had bacterial infections. These results invite further study to pave the way for an antibiotic stewardship program in DKA.

Worldwide and our centre's previous data showed a DKA mortality of <1% in the recent pre-COVID-19 era.[2,5–7] The much higher mortality in our study is probably attributed to the impact of the pandemic on DKA.[17,18] The ED and intensive care units, where DKA is primarily managed, are occupied mainly by the COVID-19 cases.[22] Moreover, the patients had to spend more time in the emergency room, waiting for a COVID-19 report before being further transferred accordingly. Thus, the intensive care management of DKA seems to have been compromised during the pandemic, which was reflected by ventilator requirement at admission as the strongest predictor of mortality in this study. Furthermore, hyperosmolality remained a worse prognostic sign, which typically requires careful fluid and electrolyte management with frequent monitoring of mental status and laboratory parameters.[5]

Confirming other recent observations, COVID-19 patients with DKA had severe infection with >50% mortality.[12,17,18,23–26] Because COVID-19 worsens hyperglycemia and causes ketoacidosis, and the presence of DKA further predisposes the development of acute respiratory distress syndrome (ARDS) and other organ failures, the combination acts as a vicious cycle in COVID-19 patients.[17,18,27] A few modifications in DKA management are advised during the pandemic, such as frequent subcutaneous rather than an intravenous infusion of rapid-acting insulin (given the paucity of nursing staff in resource constraint settings) and conservative fluid therapy in severe COVID-19 if associated with ARDS or acute kidney injury.[28,29]

Limitations

Though our study has a reasonable sample size, it is difficult to generalize the findings because of single tertiary-care center observation. Because the COVID-19 peaks during the study period might have significantly impaired the ability to provide a standard of care to DKA patients, the outcomes will vary according to the pandemic severity. We did not evaluate patients for euglycemic DKA and study a predisposition by sodium-glucose co-transporter-2 inhibitor agents.

Conclusion

Our study confirms that the COVID-19 pandemic has significant adverse effects and consequences on DKA. Noncompliance and infections are frequent precipitating causes. DKA severity and resolution, ventilator requirement, hospital stay, and mortality are similar in the patients with or without COVID-19. The mortality in DKA is increased significantly during the pandemic, with ventilator requirement, an infection trigger, and hyperosmolarity being strong mortality predictors. Prevention and treatment of DKA remain challenging during the pandemic and may

need modification according to the limited available resources.

Ethics approval

Yes. The Institutional Ethics Committee approved the study (INT/IEC/2021/SPL-1013).

Consent to participate: We obtained written, informed consent from all study patients or the legally authorized representative in case the patient is unable to give consent.

Author contributions

RK: collected patient data, drafted the manuscript
AS: revised the manuscript
AKP: analyzed the data, drafted and revised the manuscript, supervised the project
NS: revised the manuscript
PD: revised the manuscript
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