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Original Article

Clinical characteristics and outcomes of COVID-19 patients with prediabetes

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ABSTRACT

Background and aims: We aimed to examine the clinical characteristics and outcomes of coronavirus disease 2019 (COVID-19) patients with prediabetes.
Methods: This was a retrospective cohort study of 102 COVID-19 patients admitted to a tertiary care hospital in India between May and October 2020.
Results: Most patients had a poor clinical profile on admission. They had high rates of invasive mechanical ventilation (48%), intensive care unit admission (48%), complications (72.6%), and mortality (32.4%).
Conclusion: People with prediabetes are at high risk for poor outcomes from COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a global health threat, and there have been nearly 175 million confirmed cases, including 3.7 million deaths, as of early June 2021 [1]. Several studies have now well established that COVID-19 patients with diabetes often present with a poor clinical profile on hospital admission and experience severe outcomes, including death [2–6]. However, little is known about the clinical characteristics and outcomes of COVID-19 patients with prediabetes [7,8].

2. Methods

We conducted a retrospective cohort study of 102 COVID-19 patients with prediabetes who were admitted to a tertiary care hospital in Chennai, India, between May and October 2020. Prediabetes was defined as HbA1c 5.7–6.4% in those with no prior history of diabetes [9]. Patients' clinical signs and symptoms, demographics, comorbidities, physical measurements, laboratory investigations, reverse transcription polymerase chain reaction (RT-PCR) results, chest computed tomography (CT) findings, treatment measures, complications, and clinical outcomes were extracted from the case report forms. RT-PCR, blood tests, and chest CT were done within 24 h to 3 days of hospital admission. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study equation [10]. Acute respiratory distress syndrome (ARDS) and septic shock were diagnosed as per the interim guidance of the World Health Organization for COVID-19 [11]. Acute kidney injury was defined according to the Kidney Disease Improving Global Outcomes classification [12]. Data are summarized using mean (SD, standard deviation) or median (interquartile range) for continuous variables, depending on the distribution, and with n (%) for categorical variables. Clinical characteristics on admission between survivors and non-survivors were compared using Student's *t*-test or Mann-Whitney *U* test for continuous variables, and Chi-square test or Fisher's exact test for discrete variables, as appropriate. A two-sided alpha of <0.05 was considered statistically significant. Analyses were conducted using Stata/MP version 15.1 for Windows (Stata Corp LP, College Station, TX).

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Table 1
Clinical signs and symptoms of COVID-19 patients with prediabetes on admission.

	All (n = 102)	Survivor (n = 69)	Non-survivor (n = 33)	P value
Age (years), mean (SD)	48.4 (15.1)	44.9 (13.6)	55.7 (15.7)	0.001
Male, n (%)	73 (71.6)	49 (71.0)	24 (72.7)	0.86
Positive RT-PCR, n (%)	88 (86.3)	62 (89.9)	26 (78.8)	0.13
Area of lung injury (from chest CT images), n (%)				
0−25%	38 (37.3)	37 (53.6)	1 (3.0)	<0.001
>25−50%	25 (24.5)	23 (33.3)	2 (6.1)	
>50%	39 (38.2)	9 (13.0)	30 (90.9)	
Body mass index (kg/m^2), mean (SD)	27.6 (5.1)	26.9 (4.3)	29.0 (6.3)	0.044
Clinical symptoms, n (%)				
Fever	81 (79.4)	53 (76.8)	28 (84.9)	0.35
Fatigue	83 (81.4)	56 (81.2)	27 (81.8)	0.94
Cough	66 (65.4)	42 (60.9)	24 (75.0)	0.17
Sputum	53 (52.0)	31 (44.9)	22 (66.7)	0.040
Sore throat	82 (80.4)	52 (75.4)	30 (90.9)	0.06
Running nose	37 (36.3)	27 (39.1)	10 (30.3)	0.39
Odynophagia	33 (32.4)	22 (31.9)	11 (33.3)	0.88
Headache	57 (55.9)	39 (56.5)	18 (54.6)	0.85
Dizziness	49 (48.0)	31 (44.9)	18 (54.6)	0.36
Chest pain	20 (19.6)	10 (14.5)	10 (30.3)	0.06
Chest tightness	37 (36.3)	23 (33.3)	14 (42.4)	0.37
Dyspnea	68 (66.7)	41 (59.4)	27 (81.8)	0.025
Nausea	22 (21.6)	13 (18.8)	9 (27.3)	0.33
Vomiting	21 (20.6)	12 (17.4)	9 (27.3)	0.25
Diarrhea	23 (22.6)	11 (15.9)	12 (36.4)	0.021
Abdominal discomfort	22 (21.6)	15 (21.7)	7 (21.2)	0.95
Loss of smell	41 (40.2)	32 (46.4)	9 (27.3)	0.07
Loss of taste	41 (40.2)	32 (46.4)	9 (27.3)	0.07
Loss of appetite	51 (50.0)	34 (49.3)	17 (51.5)	0.83
Sleep disturbances	29 (28.4)	22 (31.9)	7 (21.2)	0.26
Palpitation	41 (40.2)	24 (34.8)	17 (51.5)	0.11
Vital signs, mean (SD)				
Heart rate (beats/min)	90.9 (14.9)	86.9 (12.6)	99.3 (16.0)	<0.001
Respiratory rate (beats/min)	24.6 (6.2)	22.0 (4.4)	30.1 (5.7)	<0.001
Sp02 (%)	88.0 (13.6)	95.6 (3.0)	72.2 (13.7)	<0.001
Comorbidities[a], n (%)				
Obesity (BMI ≥30 kg/m^2)	27 (26.5)	17 (24.6)	10 (30.3)	0.54
Hypertension	53 (52.0)	34 (49.3)	19 (57.6)	0.43
Chronic kidney disease	10 (9.8)	5 (7.3)	5 (15.2)	0.29
Coronary artery disease	10 (9.8)	4 (5.8)	6 (18.2)	0.07
Chronic liver disease	10 (9.8)	4 (5.8)	6 (18.2)	0.07
Cerebrovascular accident	8 (7.9)	5 (7.4)	3 (9.1)	0.71

Abbreviations: SD standard deviation, RT-PCR reverse transcription polymerase chain reaction, CT computed tomography, BMI body mass index.
P values comparing survivors and non-survivors are from *t*-test, Mann-Whitney *U* test, Chi-square test, or Fisher's exact test.
[a] Comorbidities were self-reported, except BMI which was estimated based on measured height and weight.

3. Results

3.1. Clinical characteristics

About 86.3% had a positive RT-PCR, while the rest (13.7%) were diagnosed based on clinical signs and symptoms and chest CT findings being consistent with COVID-19 disease. The mean age was 48.4 (SD: 15.1) years, and 73 (71.6%) were male. About 38.2% of patients had infiltrates occupying >50% of the lung area on the chest CT. The most common symptoms on admission were fatigue (81.4%), sore throat (80.4%), fever (79.4%), and dyspnea (66.7%). Slightly more than two-thirds (68.6%) had one or more comorbidities; hypertension (52.0%) and obesity (26.5%) were the most common ones. The majority had elevated levels of D-dimer (52.5%), C-reactive protein (CRP) (98.6%) and interleukin-6 (IL-6) (84.3%), prolonged prothrombin time (55.9%), and low eGFR (57.8%). Levels of leucocytes were increased in 41.2%, ferritin in 35.6%, urea in 34.3%, total bilirubin in 47.5%, alanine aminotransferase in 31.4% and aspartate aminotransferase in 39.2%, and platelet and albumin levels were decreased in 13.7% and 33.3% of patients, respectively. Lymphocytopenia was present in a quarter (24.5%) of patients.

3.2. Outcomes

Nearly half (48.0%) required invasive mechanical ventilation (IMV), and they were transferred to the intensive care unit (ICU). The most common complications were ARDS (59.8%) and septic shock (43.1%). The mean hospital stay was 10.6 (SD: 4.7) days. 33 (32.4%) died during hospitalization.

3.3. Survivors vs. non-survivors

Non-survivors were older and had a greater frequency of sputum, dyspnea, and diarrhea (all $p < 0.05$). They also had a greater lung injury, and a higher mean body mass index, heart rate, and respiratory rate, and a lower Spo2 (all $p < 0.05$) (Table 1). Non-survivors had higher levels of total leucocytes, neutrophils, neutrophil-to-lymphocyte ratio, D-dimer, ferritin, CRP, IL-6, international normalized ratio, urea, creatinine, alanine aminotransferase, 2-hr postprandial glucose and HbA1c, and lower levels of eGFR and albumin (all $p < 0.05$) (Table 2). All non-survivors required IMV and were admitted to the ICU compared to 23.2% and 23.2%, respectively, of survivors (both $p < 0.001$). Almost all

Table 2
Laboratory findings, treatment measures, complications, and outcomes of COVID-19 patients with prediabetes.

	Normal range	All (n = 102)	Survivor (n = 69)	Non-survivor (n = 33)	P value
Laboratory findings, median (IQR) or mean (SD)					
Total leucocytes (cells per mm^3)	4000–10000	8250 (6200–12400)	6600 (5200–10000)	14000 (10100–26000)	<0.001
Neutrophils (cells per mm^3)	1600–8000	5826.5 (3410–10050)	4092 (2880–7138)	11400 (7700–21320)	<0.001
Lymphocytes (cells per mm^3)	800–4000	1409 (840–2240)	1504 (948–2226)	1100 (738–2250)	0.67
Neutrophil-to-lymphocyte ratio	0.78–3.53	4.9 (2.1–10.4)	2.6 (1.7–7.2)	9 (6.3–15.0)	<0.001
Platelet count (cells per mm^3)	150000–400000	243500 (187000–312000)	240000 (190000–284000)	252000 (163000–359000)	0.51
D-dimer (ng/ml)[a]	<250	257 (202–657)	222 (183–280)	2061.5 (371–4991)	<0.001
Ferritin (ng/ml)[a]	M: 24-336 F: 11-307	245 (123–412)	192 (104–305)	421 (231–591)	<0.001
C-reactive protein (mg/l)[a]	<10	65 (25–160)	40 (16.4–104)	140 (62.7–200)	0.001
Interleukin-6 (pg/ml)	0–5	16.9 (8–32)	12 (6–22)	38 (18–109)	<0.001
Prothrombin time (in seconds)	11–13.5	14 (12–16)	14 (12–16)	14 (12–16)	0.97
aPTT (in seconds)	30–40	28.5 (5.7)	28.5 (6.3)	28.5 (4.4)	0.98
International normalized ratio (%)	0.8–1.1	1.17 (0.16)	1.13 (0.13)	1.24 (0.19)	0.001
Urea (mg/dl)	7–18	12.5 (10–34)	11 (8–14)	44 (18–70)	<0.001
Creatinine (mg/dl)	0.7–1.3	0.9 (0.8–1.3)	0.8 (0.7–1.0)	2.1 (1.1–3.6)	<0.001
eGFR (ml/min/1.73 m^2)[b]	90–120	78.6 (41.4)	95.9 (32.2)	42.5 (34.9)	<0.001
Total bilirubin (mg/dl)[a]	0–1	1.0 (0.8–1.3)	1.0 (0.9–1.2)	1.2 (0.6–1.6)	0.49
Total protein (g/dl)	6.4–8.3	6.6 (0.6)	6.7 (0.5)	6.5 (0.6)	0.06
Albumin (g/dl)	3.5–5.0	3.6 (0.5)	3.7 (0.5)	3.3 (0.4)	<0.001
Globulin (g/dl)	2.3–3.5	3.1 (0.6)	3.0 (0.5)	3.2 (0.6)	0.08
Alanine aminotransferase (U/l)	0–46	38 (24–56)	32 (22–45)	45 (38–94)	0.001
Aspartate aminotransferase (U/l)	0–49	42.5 (28–65)	40 (28–61)	48 (34–89)	0.13
Fasting plasma glucose (mg/dl)	<100	118.8 (19.3)	118.1 (19.9)	120.2 (18.3)	0.61
2-hr post prandial plasma glucose (mg/dl)	<140	186.4 (34.8)	176.1 (33.4)	207.7 (27.4)	<0.001
HbA1c (%)	<5.7%	5.9 (0.2)	5.9 (0.2)	6.0 (0.2)	<0.001
Treatment measures, n (%)					
Favipiravir	NA	102 (100)	69 (100)	33 (100)	–
Remdesivir	NA	75 (73.5)	42 (60.9)	33 (100)	<0.001
Dexamethasone	NA	102 (100)	69 (100)	33 (100)	–
Ceftriaxone	NA	49 (48.0)	16 (23.2)	33 (100)	<0.001
Low molecular weight heparin	NA	102 (100)	69 (100)	33 (100)	–
Non-invasive mechanical ventilation	NA	64 (62.3)	33 (47.8)	31 (93.9)	<0.001
Invasive mechanical ventilation	NA	49 (48.0)	16 (23.2)	33 (100)	<0.001
Intensive care unit admission	NA	49 (48.0)	16 (23.2)	33 (100)	<0.001
Complications, n (%)					
Acute respiratory distress syndrome	NA	61 (59.8)	28 (40.6)	33 (100)	<0.001
Septic shock	NA	44 (43.1)	15 (21.7)	29 (87.9)	<0.001
Thrombosis	NA	11 (10.8)	5 (7.3)	6 (18.2)	0.10
Acute kidney injury	NA	31 (30.4)	8 (11.6)	23 (69.7)	<0.001
Clinical outcomes, mean (SD)					
Number of hospital days	NA	10.6 (4.7)	9.0 (4.1)	14.1 (4.0)	<0.001

Abbreviations: IQR interquartile range, SD standard deviation, aPTT activated partial thromboplastin time, eGFR estimated glomerular filtration rate, RT-PCR reverse transcription polymerase chain reaction, CT computed tomography, NA not applicable, M male, F female.
P values comparing survivors and non-survivors are from *t*-test, Mann-Whitney *U* test, Chi-square test, or Fisher's exact test.
[a] Data regarding D-dimer, ferritin and total bilirubin were missing for one participant, and C-reactive protein for 29 (28.4%) participants.
[b] eGFR was calculated using the Modification of Diet in Renal Disease formula.

complications were more common in non-survivors (all $p < 0.001$). The mean hospital stay was longer by five days among non-survivors ($p < 0.001$).

4. Discussion

Our study shows that the clinical profile of COVID-19 patients with prediabetes was generally poor on admission. They had high rates of IMV, ICU admission, complications, and mortality. Non-survivors had a greater lung injury and higher levels of several inflammatory and coagulation indices than survivors.

Prediabetes is characterized by chronic low-grade inflammation, impaired innate immunity, poor adaptive immune response to infections, and pro-coagulative state [13]. Thus, people with prediabetes are likely more prone to develop cytokine storm, which has been shown to be associated with increased severity of COVID-19, including death [14]. In line with this, the majority of our patients exhibited elevated levels of several inflammatory markers (e.g., CRP, ferritin, IL-6) and coagulation indices (e.g., D-dimer, prothrombin time). These parameters were higher among non-survivors. In addition, obesity and hypertension were common in our patients, the comorbidities that increase the risk of severe illness and death from COVID-19 [5,15]. These factors likely contributed to the increased disease progression, development of complications, and mortality in our patients.

The mortality rate in our study (32.4%) was higher than the rates reported in previous studies among COVID-19 patients with prediabetes. In a multi-centre study in Austria, of 47 patients with prediabetes (HbA1c 5.7–6.4% on admission), 7 (14.9%) had in-hospital death [16]. In a study from Mexico, of 125 patients with prediabetes (HbA1c 5-0.7-6.4% on admission), 27 (21.6%) died during hospitalization [17]. In a study from Dubai, 2 out of 10 (20%) patients with prediabetes (prior diagnosis or HbA1c 5.7–6.4% on admission) had in-hospital death [18]. The differences in mortality rates between studies are probably due to the variations in sample size, the severity of illness, age and sex distribution, and the presence of comorbidities.

Our study was constrained by the small sample size and lack of a

control group.

In conclusion, our study suggests that people with prediabetes are at high risk for severe illness and mortality from COVID-19. All COVID-19 patients should be screened with HbA1c on admission [19] so that those with prediabetes can be identified for close monitoring and early initiation of appropriate treatment to improve their prognosis.

Ethics approval

The study protocol was approved by the ethics committee of the Chettinad Hospital and Research Institute, Tamil Nadu, India (191/IHEC/Nov2020).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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