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Original Article

Sweetness and positivity together aren't a happy ending: Case controlled study amongst severe COVID-19 for impact of diabetes mellitus on survival

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ABSTRACT

Background: India is the epicenter of diabetes mellitus (DM). The relationship between COVID and DM in age/gender-matched non-diabetics has not been studied yet. The role of DM in predicting the disease severity and outcome in COVID patients might provide new insight for effective management.

Methods: We conducted a prospective comparative study at a COVID care center from 25th April–31st May 2021. Among 357 severe-COVID patients screened, all consecutive diabetes (n-113) and age/gender-matched non-diabetes (n-113) patients were recruited. All diabetics and non-diabetics at admission were subjected to high resolution computed tomography (HRCT) chest and inflammatory markers (C-reactive protein (CRP), D-dimer, ferritin, interleukin-6 (IL-6), lactate dehydrogenase (LDH), Neutrophil-Lymphocyte Ratio (NLR)) before starting anti- COVID therapy. Statistical analysis was done using JMP 15·0 ver·3·0·0.

Results: The prevalence of DM among the screened population (n-357) was 38·37%. The mean age of the study population was 61y with male preponderance (57%). There was no statistical difference in the HRCT-score or inflammatory markers in the two groups except for higher NLR (p-0·0283) in diabetics. Diabetics had significantly inferior overall survival (OS) (p-0·0251) with a 15d-OS of diabetics vs. non-diabetics being 58·87%, 72·67%, and 30d-OS of diabetics vs. non-diabetics being 46·76%, 64·61%, respectively. The duration of the hospital stay was not statistically different in the two groups (p-0·2).

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Conclusion: The mortality is significantly higher in severe-COVID patients with DM when compared to age/gender-matched non-diabetics. There was no significant difference in most inflammatory markers/CT at admission between the two groups.

Introduction

Coronaviruses (CoV) are enveloped viruses with a single-stranded, positive-sense RNA genome known to cause respiratory infections in humans.[1] In general, human CoV infection leads to mild upper respiratory infection in most immunocompetent individuals. COVID-19 originated in Wuhan, China, in December 2019. On 11th March 2020, the World Health Organization (WHO) had declared COVID-19 a pandemic because of alarming levels of its spread, severity, and inaction.[2] Globally as of 31st May 2021, approximately 1,72,242,495 confirmed cases of COVID-19, including 3,709,397 deaths, were reported to WHO.[3] Patients at risk for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have been characterized as having preexisting diseases, such as hypertension, cardiovascular disease, diabetes, chronic respiratory disease, obesity, or cancer.[4] A meta-analysis suggested that the mortality was higher among diabetes with COVID-19.[5] India is one of the epicenters of the global diabetes mellitus pandemic. The relationship between the severity of COVID in Diabetics independent of confounding variables such as age and gender has not been studied extensively from India and hence merits further research.[6–13]

This study was conducted to explore the relationship between underlying diabetes mellitus (DM) and the outcomes (duration of hospital stay and mortality) compared to age and gender-matched non-diabetic severe COVID-19 patients in a prospective fashion. In addition, we explored the impact of Diabetes mellitus on the severity of the disease at admission (radiological/serological markers).

Materials and methods

Study design

We conducted a prospective observational study at the COVID care center in India from 25th April 2021 to 31st May 2021. This center cared for RT-PCR positive severe COVID cases (defined as SpO_2 levels< 90% at room air at initial presentation).[14] The institutional ethical committee approved the study, and informed consent was obtained from all the diabetics and non-diabetics. The study was done in accordance with the Declaration of Helsinki.

Patients

All consecutive severe COVID-19 patients admitted during the study period (n-357) were enrolled and screened for inclusion/exclusion criteria (Supplementary Fig. 1). Diabetes data was obtained as part of the medical history of the individual patients, and details of the type of therapy/duration of Diabetes were recorded. These patients with a history of DM type 2 were labeled as "known diabetics (KD)." All other patients were subjected to random blood glucose (RBS) and HbA1C at admission, and those who fit into the diagnosis of DM type 2 as per ADA guidelines were labeled as "freshly detected diabetes (FDD)."[15] All people with diabetes, whether known or freshly detected (KD/FDD), were labeled as "diabetics." Those individuals who were initiated on steroids or any form of COVID-directed therapy before admission to the hospital and steroid-induced hyperglycemia (SIH) amongst patients other than KD/FDD were excluded from the study. All diabetics were managed with basal-bolus insulin based on seven-point glucose profile testing to ensure tight glycemic control during the total hospitalization as per the prevailing national guidelines.[16] All severe COVID patients without diabetes matched for age and gender with diabetics in a 1:1 ratio were labeled as "non-diabetics."

Methodology

A detailed history for the comorbidities (hypertension, cardiovascular diseases, respiratory disorders, hypothyroidism, and CNS disorders), vaccination status, and COVID symptomatology (fever, dyspnea, cough, expectoration, hemoptysis, myalgia, headache, chest pain, ageusia, and diarrhea) with their timeline were recorded. As per protocol, all patients were subjected to high resolution computed tomography (HRCT) chest for severity score and inflammatory markers (C-reactive protein (CRP), D-Dimer, Ferritin, interleukin-6 (IL-6), lactate dehydrogenase (LDH), neutrophil–lymphocyte ratio (NLR)) before starting anti-COVID therapy. All patients were managed with currently prevailing protocol-based therapy guided by AIIMS/ICMR, including steroids, low molecular weight heparin (LMWH), vitamin, and minerals supplements.[17] Any unique outcomes in either diabetics or non-diabetics have been recorded. Patients were discharged uniformly based on the prevailing ICMR criteria.[18] The outcome parameters included days of hospitalization and details of mortality.

Statistical analysis

The data were analyzed using the JMP 15·0 ver·3·0·0. The continuous data were assessed for normal distribution. Nonparametric tests (Wilcoxon test) were applied for variables without normal distribution, and student's t-test was applied for variables with normal distribution. The continuous variables were represented as median (range; Mean ± SD) whereas qualitative variables were summarized

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as frequencies and proportions. The level of significance $p < 0{\cdot}05$ was considered significant. The survival analysis was done using Kaplan–Meier.

Results

The prevalence of DM among the screened population was 38·37% (n-137), of which 26·6% (n-95) were KD, and 11·76% (n-42) were FDD (Supplementary Fig. 1). The study population (n-226) was equally distributed among diabetics and non-diabetics. The median age of the study population is 61y (30–90; 60·82 ± 13·55y) with a male preponderance (57%, n = 128). The prevalence of KD and FDD was 35% (n-78) and 15% (n-35), respectively. Among KD, the median duration of diabetes was 10y (2-20y; 9·1 ± 4·83y); most were on oral antidiabetics (89·23%), with 10.77% individuals additionally on different forms of insulins. In our study, 15- and 30-days overall survival (OS) of the total study population were 63·35 and 51·97%, respectively, with median survival was not achieved during the study period. Among the entire study population, 18% (n = 40) and 4% (n-9) were vaccinated with 1 and 2 doses of Covishield. Hypertension was seen in 45% (n-101) with a median duration of 8·5y (1-30y; 9·225 ± 6·08), cardiovascular diseases in 4% (n-8) with a median duration of 15y (3–30; 15·67 ± 9·24 y), respiratory disorders in 1% (n-4) with a median duration of 15y, hypothyroidism in 6·63% (n-15) were noted. The summary of symptoms at admission to our center for the study population is enumerated in Supplementary Table 1. We did not have any cases of proven venous thromboembolism (VTE) in the complete study cohort. However, we had 7 cases of diabetic ketoacidosis (all in FDD) and 4 cases of mucormycosis (2 in KD, 2 in FDD) during illness. All cases of mucormycosis have succumbed to the illness.

The NLR was significantly higher in diabetics (p-0·0283). The median IL-6 in diabetics was higher than the non-diabetics, though not statistically significant (p-0·08). There was no difference in the CT score or other inflammatory markers between the two groups (Fig. 1). The median duration of the hospital stay amongst diabetics and non-diabetics was not statistically different (p-0·19). The NLR was higher in FDD than KD more than non-diabetics (p-0·028), where IL-6 was lowest in non-diabetics than KD/FDD (p-0·22). There was no statistical difference in CT severity score, CRP, D-dimer, ferritin, and LDH between the three groups (Fig. 2). The characteristics of the diabetics and non-diabetics are tabulated in Supplementary Tables 2A and B. The summary characteristics of the study population classified as KD, FDD, and non-diabetics are enumerated in Supplementary Table 3.

Diabetics had significantly inferior OS (p-0·0251) with a 15d-OS of diabetics/non-diabetics being 58·87%, 72·67%, and 30d-OS of diabetics/non-diabetics being 46·76%, 64·61%, respectively (Fig. 3A). The Median OS of diabetics being 20d and median OS not reached (NR) in non-diabetics. Comparison of the OS in three groups, non-diabetics had better survival compared to FDD than KD (p-0·08). The 15d-OS of KD/FDD/ND being 59·38%, 57·78%, 72·67% and 30d-OS of KD/FDD/ND being 43·57%, 57·8%, 64·61%, respectively (Fig. 3B). The Median OS of KD being 19d and not reached (NR) in FDD/ND. The median duration of the hospital stay amongst KD/FDD/ND were 9d (6–16), 9d (5–16), 10d (7–16), not statistically different (p-0·42).

Discussion

Diabetes mellitus is one of the most common metabolic and lifestyle disorders. India is the diabetes capital of the world. Approximately 30·42% of the individuals above the age of 60

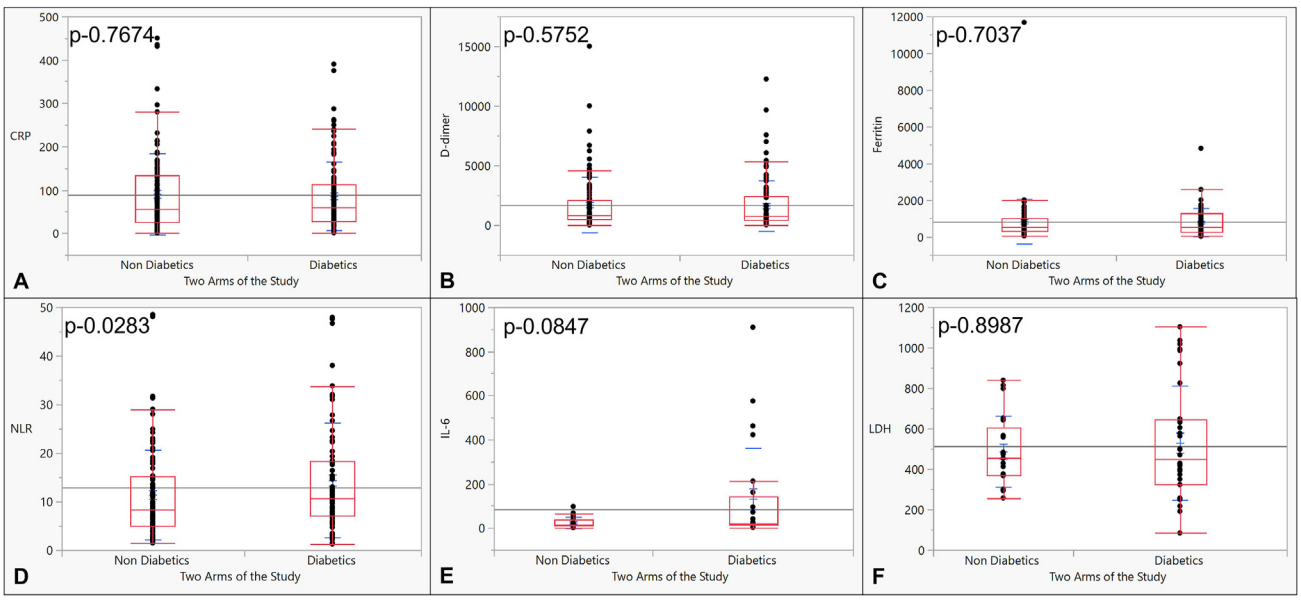

Fig. 1 – The difference in (A) CRP (B) D-dimer (C) serum ferritin (D) NLR (E) IL-6 and (F) LDH between diabetics and non-diabetics. *CRP-C reactive protein(mg/L); D-dimer(ng/mL); serum ferritin(ng/mL); NLR- neutrophilic lymphocytic ratio; IL-6-interleukin 6(pg/ml); LDH- lactate dehydrogenase(IU/L).*

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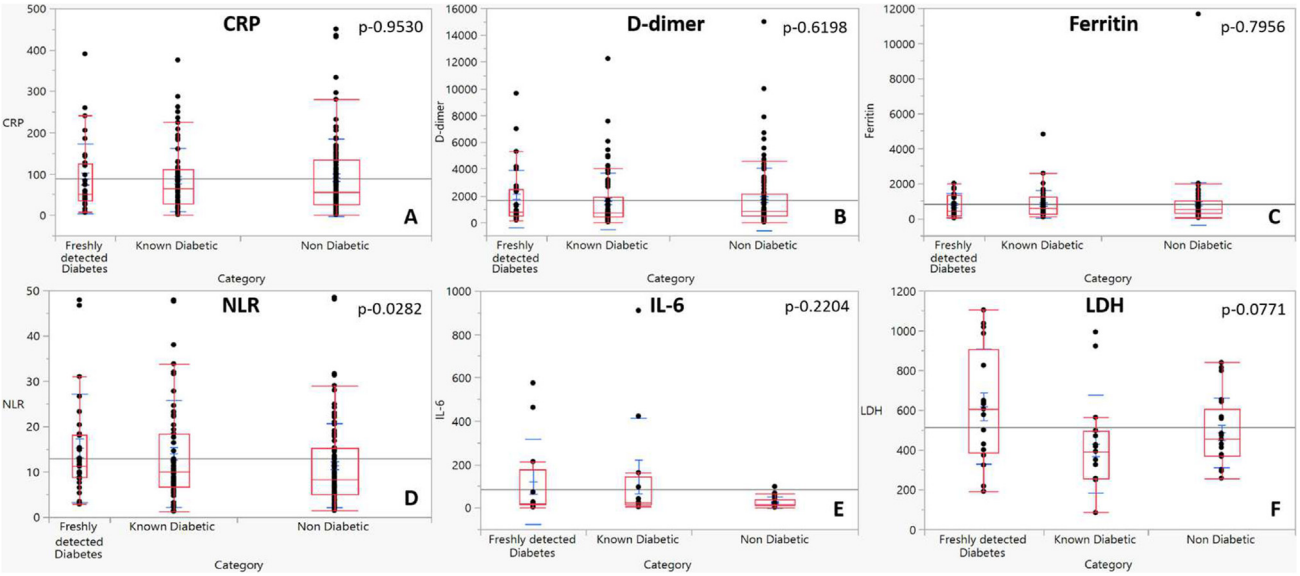

Fig. 2 – The difference in (A) CRP (B) D-dimer (C) serum ferritin (D) NLR (E) IL-6 and (F) LDH between non-diabetics, known diabetics and freshly detected diabetics. *CRP-C reactive protein(mg/L); D-dimer(ng/mL); serum ferritin(ng/mL); NLR- neutrophilic lymphocytic ratio; IL-6- interleukin 6(pg/ml); LDH- lactate dehydrogenase(IU/L).

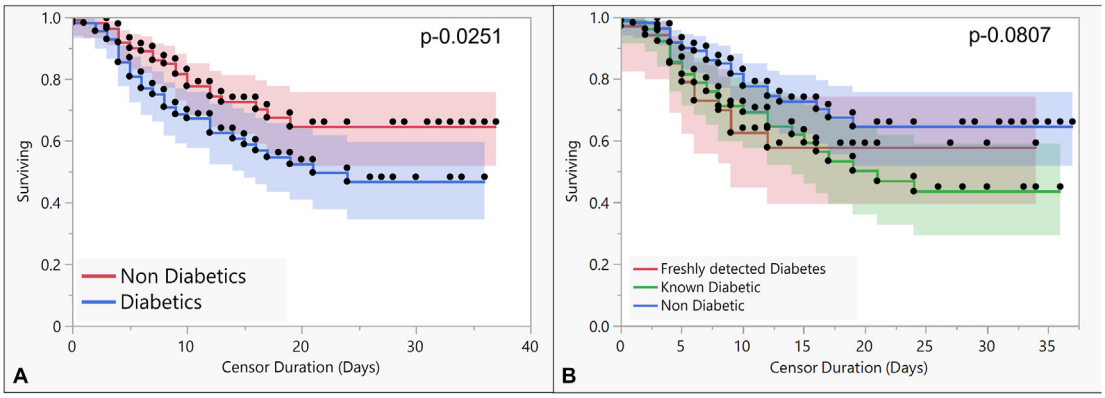

Fig. 3 – Kaplan–Meier curves for survival in (A) diabetics and non-diabetics and (B) non-diabetics, known diabetics and freshly detected diabetics.

are affected by DM.[19] In India's first and second wave of the COVID-19 pandemic, the elderly were preferentially affected.[20] Literature suggests a higher incidence of diabetes among the two earlier CoV pandemics, SARS beginning in 2002 and the Middle East respiratory syndrome (MERS) in 2012.[21] Literature from the past suggests DM (p-0·005) and ambient hyperglycemia (p-0·006) were independent predictors for overall outcomes in SARS.[22] Similarly, numerous studies have documented the relationship between DM and COVID-19 since its onset.[23,24]

In a case-controlled study (adjusted for age and gender), patients with DM infected with SARS-CoV-2 were shown to have a 5·29-fold higher risk of developing severe COVID-19 than ND (95% CI: 1·07–26·02).[25] All our diabetics and non-diabetics were known cases of severe COVID-19 infection; thus, our study cannot draw the above findings. In a study by Smith et al, the DM was seen in 62% of the admitted severe COVID-19 infection suggesting SARS-CoV-2 pathogenesis involves a novel interplay with glucose metabolism.[26] In comparison, DM was seen in only 38·37% amongst the admitted severe COVID in our study, and this low percentage could be attributed to the second wave affecting more young population than the elderly.

It is well documented in several studies that inflammatory and hypercoagulation status increase in COVID-19 cases as compared to non-COVID-19 respiratory illness, and the uncontrolled hyperglycemia status could aggravate this.[27,28] Sardu et al compared people with diabetes and non-diabetics amongst moderate COVID patients and showed that baseline IL-6/D-dimer levels were significantly higher in the hyperglycemic group than in the normoglycemic group ($p < 0·001$). Also, the levels persisted in remaining high during the hospitalization period.[29] People with diabetes had more inflammation, coagulation activation, myocardial/hepatic/renal injury among the COVID-19 infection compared to non-diabetics.[30] Similarly, a study carried out in China has shown

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that serum levels of inflammation-related biomarkers such as IL-6, C-reactive protein, serum ferritin, and coagulation index, D-dimer, were significantly higher ($p < 0{\cdot}01$) in diabetic patients compared with those without, suggesting that patients with diabetes are more susceptible to an inflammatory storm eventually leading to rapid deterioration of COVID-19.[31] A study by Shang et al found, that diabetic patients having COVID-19 infection have higher levels of neutrophils (p-0·014), C-reactive protein (p-0·008), procalcitonin ($p < 0{\cdot}01$), and D-dimer (p-0·033), and lower levels of lymphocytes (p-0·032) and albumin (p-0·035).[32] The same has been shown by a study in which there is a significant increase in these markers in the diabetic group compared to the non-diabetic group of COVID-19 patients without other comorbidities, indicating the independent impact of diabetes.[31] We found no difference in the inflammation (CRP, LDH, IL-6, ferritin) except NLR and coagulation activation (D-dimer) levels at baseline, probably due to stringent inclusion criteria of severe COVID cases with no representation of mild and moderate cases and 1:1 matching for age/gender. Also, we did not follow up these patients with weekly inflammatory markers due to the prevalent national management guidelines and resource constraints.[17] We also did not notice any cases of VTE amongst the study population, probably due to the proactive usage of the LMWH.

Varikasuvu et al in a pooled analysis found out that serum ferritin (SMD: 0·47 95% CI 0.17—0·77, $p = 0{\cdot}002$), CRP (SMD: 0·53 95% CI 0·20—0·86, $p = 0{\cdot}002$), IL-6 (SMD: 0·31 95% CI 0·09—0·52, $p = 0{\cdot}005$), fibrinogen (SMD: 0·31 95% CI 0·09—0.54, $p = 0{\cdot}007$), and D-dimer (SMD: 0·54 95% CI 0·16—0·91, $p = 0{\cdot}005$) levels are significantly elevated in diabetic patients as compared to non-diabetic counterparts with COVID-19.[33] The results of this AIIMS study were different from a pooled meta-analysis, lacking stringent inclusion criteria and analyzing patients of all categories of COVID-19 infection (not exclusively Severe COVID).

Poor fasting blood glucose ($\geq$ 11·1 mmol/L) (p-0·034) and glucocorticoid treatment (p-0·029) are associated with all-cause of mortality of severe COVID-19 amongst people with diabetes.[30] A retrospective study done in China by Li et al, has shown that in COVID-19 patients with diabetes, poorly non-diabetics led blood glucose (> 11 mmol/L) may be associated with poor outcomes.[34] The patients with FDD had higher HbA1C and FBG at admission, but the difference in the outcomes was not statistically different, probably owing to smaller numbers in the sub-group analysis.

The relation between the severity of diabetes (both in terms of HbA1C and duration of diabetes) and COVID outcomes has been published in the literature, wherein individuals with higher HbA1C and longer duration of diabetes were found to have higher mortality.[9,11,12] In our study, the mean HbA1C at admission was higher in individuals who succumbed to COVID vis-à-vis those who survived (9.0 vs. 7.89%, p-0.1456). But, we didn't elaborate on the relationship between HbA1C and outcomes, as we could perform HbA1C of only 93 patients at admission, whereas for the rest of the individuals, the reports were based on medical records (with few being more than a month old). We didn't systematically collect the duration of diabetes from all individuals at admission, as during the second wave of COVID, the history was sketchy and most of the patients were not accompanied by relatives for a good history, also, there was a lack of uniform availability of medical records.

In a pooled meta-analysis by Wu et al, the diabetic patients infected with COVID-19 had a 2·95-fold higher risk of fatality than ND.[25] A study in Italy concluded that plasma glucose levels at admission (p-0·015) and antidiabetic drugs might influence the survival of COVID-19 patients affected by type 2 diabetes.[35] Admission hyperglycemia, elevated d-dimer, and high HRCT score are potential risk factors for adverse outcomes and death.[34,36] Shang et al, demonstrated that the incidence of respiratory failure (p-0·022), acute cardiac injury ($p < 0{\cdot}01$), and death (p-0·001) in the diabetes group was significantly higher than that in the non-diabetes group.[32] Another study done by Chen et al, in China showed C-reactive protein might help identify patients with diabetes who are at greater risk of dying during hospitalization (p-0·043). Older patients with diabetes were prone to death related to COVID-19 (p-0·001). Attention needs to be paid to patients with diabetes and COVID-19 who use insulin (p-0·009).[37] Similar results were found in a meta-analysis study done in India, which showed that diabetic patients with COVID-19 are associated with a two-fold increase ($p < 0{\cdot}01$) in mortality and severity of COVID-19 compared to non-diabetics.[24] Our study corroborated with the findings from different other studies enumerated above in that the survival of patients with diabetes was inferior to those without diabetes in age and gender-independent fashion. To summarize the results, we found that DM is significantly associated with mortality in COVID-19 positive patients (p-0·0251).

In our study, there was no significant difference in laboratory/radiological parameters and outcomes compared to the subgroups of FDD and KD. A study done in China by Zhang et al, has also shown similar results for both groups.[38]

There are many future implications of our study; since India has a higher prevalence of diabetes, and diabetes can lead to severe COVID-19 infection, its prevention in people with diabetes is vital. First certainly, diabetic patients should be educated well about extra precautions and preventive measures like social distancing, wearing a face mask, and hand hygiene to protect themselves from coronavirus infection. Second, there should be increased vigilance in the outpatient clinics of diabetes for COVID-19, and the threshold for testing for this infection in diabetic patients should be lowered.

Strengths and limitations

To the best of our knowledge, this is the first large age/gender-matched study (n-226) on the independent influence of diabetes on the severity and outcomes of COVID-19 in India. In addition, we also studied the prevalence of diabetes among COVID-19 patients. Second, we compared the wide array of laboratory severity markers and high radiological evaluation at admission to study the impact of diabetics vs. non-diabetics in differentiating severity markers amongst clinically diagnosed severe COVID cases. Thirdly, despite real-world resource-constrained settings, we attained the complete outcome data through teleconsultation, including patients discharged against medical advice or referred to other hospitals. The

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major limitations of our study were the lack of information on the obesity indices (BMI, weight, waist-hip ratio). The HbA1C at admission reflecting the glycemic non-diabetics among the KD was not available for analysis. A hospital-based study from a COVID care center (CCC) catering only for severe COVID cases was a selection bias. Also, the interaction of the comorbidities on the overall outcomes was not studied.

Conclusion

The mortality is significantly higher in severe COVID patients with diabetes when compared to non-diabetics in age/gender-matched study population despite strict glycemic non-diabetics based on basal-bolus insulin regimens. There was no difference in the CT score, inflammatory or coagulation markers at admission among the diabetics or non-diabetics. Also, there was no significant difference in outcomes or laboratory/radiological markers between freshly detected and known diabetics on subgroup analysis.

Disclosure of competing interest

The authors have none to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mjafi.2022.06.010.

REFERENCES

1. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol*. 2019;17:181–192.
2. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed: Atenei Parmensis*. 2020;91:157.
3. Organisation WHO. *COVID Dashboard*. 2021.
4. Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity*. 2020;28:1195–1199.
5. Wu ZH, Tang Y, Cheng Q. Diabetes increases the mortality of patients with COVID-19: a meta-analysis. *Acta Diabetol*. 2021;58:139–144.
6. Saeedi P, Petersohn I, Salpea P, et al. *Global and Regional Diabetes Prevalence Estimates for 2019 and Projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas*. 9th ed. vol. 157. Diabetes Research and Clinical Practice; 2019.
7. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol*. 2020;8:782–792.
8. Corona G, Pizzocaro A, Vena W, et al. Diabetes is most important cause for mortality in COVID-19 hospitalized patients: systematic review and meta-analysis. *Rev Endocr Metab Disord*. 2021;22:275–296.
9. Klein SJ, Mayerhöfer T, Fries D, Preuß Hernández C, Joannidis M. Elevated HbA1c remains a predominant finding in severe COVID-19 and may be associated with increased mortality in patients requiring mechanical ventilation. *Crit Care*. 2021;25:1–4.
10. Zhang Y, Li H, Zhang J, et al. The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: a single-centre, retrospective, observational study in Wuhan. *Diabetes Obes Metabol*. 2020;22:1443–1454.
11. Unluguzel Ustun G, Keskin A, Aci R, Arslanbek Erdem M, Ari M. Association between Hb A1c and severity of COVID-19 patients. *Hemoglobin*. 2021;45:124–128.
12. Merzon E, Green I, Shpigelman M, et al. Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes. *Diabetes Metab Res Rev*. 2021;37, e3398.
13. Chen J, Wu C, Wang X, Yu J, Sun Z. The impact of COVID-19 on blood glucose: a systematic review and meta-analysis. *Front Endocrinol*. 2020:732.
14. Organisation WH. *COVID-19 Clinical Management: Living Guidance*. 2021:81.
15. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. *Diabetes Care*. 2018;41:S13–s27.
16. Gupta Y, Goyal A, Kubihal S, Golla KK, Tandon N. A guidance on diagnosis and management of hyperglycemia at COVID care facilities in India. *Diabetes Metabol Syndr*. 2021;15:407–413.
17. AIIMS/ICMR-COVID-19 National Task Force/Joint Monitoring Group (Dte.GHS) Ministry of Health & Family Welfare GoI. *Clinical Guidance for Management of Adult COVID-19 Patients*. 2021:1.
18. Government of India MoHaFW. *Clinical Management Protocol for COVID-19*. 2021:22.
19. Jain A, Paranjape S. Prevalence of type 2 diabetes mellitus in elderly in a primary care facility: an ideal facility. *Indian J Endocrinol Metab*. 2013;17:S318–S322.
20. Chen Y, Klein SL, Garibaldi BT, et al. Aging in COVID-19: vulnerability, immunity and intervention. *Ageing Res Rev*. 2021;65:101205.
21. Bloomgarden ZT. Diabetes and COVID-19. *J Diabetes*. 2020;12:347–348.
22. Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med*. 2006;23:623–628.
23. Al-Salameh A, Lanoix JP, Bennis Y, et al. Characteristics and outcomes of COVID-19 in hospitalized patients with and without diabetes. *Diabetes Metab Res Rev*. 2021;37, e3388.
24. Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metabol Syndr*. 2020;14:535–545.
25. Wu J, Zhang J, Sun X, et al. Influence of diabetes mellitus on the severity and fatality of SARS-CoV-2 (COVID-19) infection. *Diabetes Obes Metabol*. 2020;22:1907–1914.
26. Smith SM, Boppana A, Traupman JA, et al. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. *J Med Virol*. 2021;93:409–415.

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27. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-Related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. *Thromb Haemostasis*. 2020;120:998–1000.
28. Di Micco P, Russo V, Carannante N, et al. Clotting factors in COVID-19: epidemiological association and prognostic values in different clinical presentations in an Italian cohort. *J Clin Med*. 2020;9.
29. Sardu C, D'Onofrio N, Balestrieri ML, et al. Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control? *Diabetes Care*. 2020;43:1408–1415.
30. Xu Z, Wang Z, Wang S, et al. The impact of type 2 diabetes and its management on the prognosis of patients with severe COVID-19. *J Diabetes*. 2020;12:909–918.
31. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020, e3319.
32. Shang J, Wang Q, Zhang H, et al. The relationship between diabetes mellitus and COVID-19 prognosis: a retrospective cohort study in Wuhan, China. *Am J Med*. 2021;134:e6–e14.
33. Varikasuvu SR, Varshney S, Dutt N. Markers of coagulation dysfunction and inflammation in diabetic and non-diabetic COVID-19. *J Thromb Thrombolysis*. 2021;51:941–946.
34. Li Y, Han X, Alwalid O, et al. Baseline characteristics and risk factors for short-term outcomes in 132 COVID-19 patients with diabetes in Wuhan China: a retrospective study. *Diabetes Res Clin Pract*. 2020;166:108299.
35. Mirani M, Favacchio G, Carrone F, et al. Impact of comorbidities and glycemia at admission and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes with COVID-19: a case series from an academic hospital in Lombardy, Italy. *Diabetes Care*. 2020;43:3042–3049.
36. Yanamandra U, Shobhit S, Paul D, et al. Relationship of computed tomography severity score with patient characteristics and survival in hypoxemic COVID-19 patients. *Cureus*. 2022;14: e22847.
37. Chen Y, Yang D, Cheng B, et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. *Diabetes Care*. 2020;43:1399–1407.
38. Zhang Y, Li H, Zhang J, et al. The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: a single-centre, retrospective, observational study in Wuhan. *Diabetes Obes Metabol*. 2020;22:1443–1454.

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