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Original Article

Detrimental effect of diabetes and hypertension on the severity and mortality of COVID-19 infection: A multi-center case-control study from India



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ABSTRACT

Aims: This study aims to find a quantitative association between the presence of co-existing diabetes mellitus (DM) and/or hypertension (HTN) with COVID-19 infection severity and mortality.

Methods: A total of 813 patients with a positive COVID-19 were included. A case-control design was used to dissect the association between DM and HTN with COVID-19 severity and mortality.

Results: According to MOHFW guidelines, 535 (65.7%) patients had mild, 160 (19.7%) patients had moderate, and 118 (14.5%) patients had severe disease outcomes including mortality in 52 patients. Age, Neutrophil%, and Diabetes status were significantly associated with severe COVID-19 infection. After adjusting for age, patients with diabetes were 2.46 times more likely to have severe disease (Chi-squared = 18.89, p-value < 0.0001) and 2.11 times more likely to have a fatal outcome (Chi-squared = 6.04, p-value = 0.014). However, we did not find evidence for Hypertension modifying the COVID-19 outcomes in Diabetic patients.

Conclusion: COVID-19 severity and mortality both were significantly associated with the status of DM and its risk may not be modified by the presence of HTN.

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1. Introduction

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan City, Hubei Province of China. Because of its rapid spread to more than 200 countries all over the world WHO (World Health Organization)

declared the outbreak a public health emergency by January 30, 2020, making it a matter of serious international concern with more than 1 million deaths till date closing in on 2 million deaths with about 15% deaths in India [1].

It has been clinically observed that the presence of certain specific comorbidities was associated with an increased risk of severe infection and worsening of outcomes in COVID-19 patients, such as the development of severe ARDS (acute respiratory distress syndrome) and increased mortality. Among the patients who went on to develop ARDS, the most frequent comorbidities reported were hypertension (HTN) (27–30%), followed by diabetes mellitus (DM) (19%) and coronary artery disease (CAD) (6–8%) [2,3]. Diabetes is the most detrimental non-communicable disease in India that has unequivocally increased in the number of patients across each state over the years [4]. As of 2019, India is placed second worldwide with at least 77 million people (aged 20–79yrs.) living

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with diabetes [5]. Though gender differences are absent in the prevalence of diabetes— the etiology includes age, family history, sedentary lifestyle or low physical activity, obesity/BMI, income, and unemployment/retirement. For more than half the patients from metropolitan cities, the onset of diabetes occurs before the age of 50 years [6]. Uncontrolled DM has been found to make a person more susceptible to sepsis because of hyperglycemia, decreased immunity, small and large vessel vasculitis. Further, DM is comorbid with other diseases such as HTN, Cardiovascular disorders, and dyslipidemia. Hence, it is proposed that DM and its comorbidities are likely to contribute to a more severe form of COVID-19 infection [7,8]. Recent molecular studies have corroborated the clinical findings, showing that the SARS-Cov-2 virus can directly infect pancreatic cells [9].

Several studies have already emphasized that blood pressure (BP) control is of paramount importance in the management of COVID-19 infection [10]. It is also seen that HTN and cardiovascular diseases are found frequently in COVID-19 patients, with these patients often being on treatment with Angiotensin converting enzyme (ACE) inhibitors and Angiotensin receptor blockers (ARBs). Literature is contradictory on whether these medications cause increased susceptibility or are beneficial to patients with COVID-19 [11,12]. A few studies conducted in Wuhan have shown HTN as the most frequent co-morbidity in patients infected by COVID-19, ranging from 15% to 30% [13]. HTN causes end-organ damage that can result in ventricular hypertrophy and fibrosis, further increasing the susceptibility of the hypertensive heart in COVID-19 infection [14].

Given the plethora of information available about metabolic abnormalities in COVID-19 [15,16] similar studies on Indian cohorts are only beginning to emerge. A recent study on 401 and 325 COVID-19 patients from New Delhi [17] and Indore [18] respectively echoed the above findings reporting a significant association of DM and HTN in severe cases. In this study, we aim to test the reported associations of DM and HTN on the severity of COVID-19 infection in a larger multicentric cohort of Indian patients.

2. Methods

Study design: This is a retrospective study record-based that was conducted at a newly raised COVID-19 dedicated hospital under PM Cares fund in New Delhi, namely, Sardar Vallabh Bhai Patel COVID Hospital [19]. The study period was from July 13, 2020 to October 14, 2020.

Participants: All hospitalized COVID-19 cases with confirmed infection who were admitted at any of the participating centers between these periods, for treatment of COVID-19 infection diagnosed by a Rapid Antigen Test or RT-PCR on the nasal/throat swab sample were included. Patients of all age groups were included in the study. Data were retrieved from retrospectively maintained medical records including demographic data and clinical information.

Definitions and measures: The clinical classification for COVID-19 severity was defined according to the Ministry of Health and Family Welfare definition (MOHFW, Government of India). Mild cases are defined as “Patients with uncomplicated upper respiratory tract infection, may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, and without evidence of breathlessness or Hypoxia (normal saturation)”. Moderate cases are defined as patients with “Pneumonia with no signs of severe disease. Adolescent or adult with the presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO₂ <94% (range 90–94%) on room air, Respiratory Rate more or equal to 24 per minute. Child with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO₂ <94% (range 90–94%)

on room air, Respiratory Rate more or equal to 24 per minute.”. Severe cases are defined as patients with “Severe Pneumonia, Acute Respiratory Distress Syndrome, Sepsis or Septic shock. Adolescent or adult: with clinical signs of Pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO₂ <90% on room air. A child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO₂ <90%; severe respiratory distress (e.g., grunting, chest in-drawing); signs of pneumonia with any of the following danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions”. For a detailed description of specific conditions, please refer to the MoHFW website. Patients with a prior history of diabetes or HbA1c ≥ 6.5% [20] were classified as Diabetics (DM), however, the exact HbA1c were not available from the patient records. Patients with prior history of Hypertension were classified as Hypertensive (HTN).

All the hospitalized cases were followed up till discharge or death during COVID-19 illness. The primary criteria for discharge in mild/moderate hospitalized cases were the resolution of symptoms and a minimum stay of 10 days in the absence of follow-up RT-PCR negativity. At the time of discharge, the patients were advised to isolate themselves at home and self-monitor their health for further 7 days. Patients with severe infection were discharged only after clinical recovery and with a negative RT-PCR on repeat swab after resolution of symptoms. The study protocol was reviewed and approved by institutional ethics committees at both the participating centers. Consent waiver was granted given the retrospective nature of analysis and emergent nature of the pandemic. Confidentiality was maintained by the de-identification of data. All the data were analyzed at the cut-off date of October 14, 2020.

Statistical methods: JMP Pro version 15 was used for multivariate nominal logistic regression with Likelihood ratio tests to identify factors independently predicting disease severity and mortality. Univariate statistical analysis, Cochran-Mantel-Haenszel tests, and power calculations were done using open-source statistical software R Studio (running R version 4.0.3). In univariate analysis, categorical parameters underwent Fisher's exact test while continuous numerical parameters underwent Student's T-test. The Cochran-Mantel-Haenszel chi-square test was performed on partial two-by-two contingency tables. And a 'p' value of <0.05 was considered significant.

Power analysis: A posthoc sample size estimation was performed according to the Cochran-Mantel-Haenszel test. At the power of at least 90% with a significance level of 0.05 or less to detect an odds ratio (or theta) of 2 or more, assuming a 1:6 case-to-control ratio (as suggested by the prevailing statistics of severe cases in our dataset), the effective sample size calculated was 746. Therefore, at 813 patients our study is well powered.

3. Results

3.1. Baseline characteristics and overall statistics of COVID-19 outcomes in the cohort

The median age of 813 patients in our cohort was 49 years (4–91 years) with 254 females, 559 males. Based on MOHFW guidelines, 535 (65.7%) patients had mild, 160 (19.7%) patients had moderate, and 118 (14.5%) patients had severe disease outcomes including mortality in 52 patients. 63.1% of the patients had some form of comorbidities at the time of hospitalization with 29.2% patients suffering from DM and 27.3% of the patients suffering from HTN. Other notable comorbidities at the time of admission included Hypothyroidism (3.31%), Asthma (2.6%), COPD (2.45%), and chronic kidney disease (1.1%).

3.2. Effect of comorbidities and blood cell counts on COVID-19 outcomes

For 573 out of the 813 patients, we also had data for blood parameters such as Hemoglobin levels, red blood cell counts, Platelet counts, Lymphocyte percentage, Monocyte percentage, and Neutrophil percentage. In a univariate analysis (Table 1), we found that Old age (61.9 ± 13.5 vs 45.1 ± 17.5 , p -value < 0.0001), higher prevalence of DM (52.9% vs 25.1%, p -value < 0.0001), higher prevalence of HTN (42.9% vs 24.8%, p -value < 0.0001), lower Hemoglobin levels (12.06 ± 2.3 vs 12.75 ± 2 , p -value = 0.0037), lower Lymphocyte percentage (14.14 ± 10.3 vs 31.66 ± 111.5 , p -value = 0.001), lower Monocyte percentage (5.7 ± 5.8 vs 8.25 ± 4.2 , p -value < 0.0001), and higher Neutrophil percentage (78.4 ± 13.2 vs 62.6 ± 12.9 , p -value < 0.0001) were significantly associated with COVID-19 severity.

Further, to isolate the independent effect of the above parameters we performed a Nominal multivariate analysis and found that three factors associated with patient severity (Table 2) namely Age 60 years or more (OR = 3.52, 95% CI = 2.03–6.12, p -value < 0.0001), DM (OR = 2.15, 95% CI = 1.2–3.85, p -value = 0.0105) and Neutrophil percentage (OR = 1.11, 95% CI = 1.08–1.15, p -value = 0.015). While Nominal multivariate analysis only found Age 60 years or more (OR = 6.48, 95% CI = 3.04–13.8, p -value < 0.0001) to be significantly associated with patient mortality (Table 3).

3.3. Dissecting the effects of major comorbidities diabetes on COVID-19 outcomes

Since the data for the blood parameters was not available for all the patients, we argued that in order to dissect the accurate association of DM we must perform an orthogonal analysis with all the patient data. We proceeded to use Cochran-Mantel-Haenszel chi-squared test while accounting for Age as a co-founder on the COVID-19 outcome. For this, we calculated partial two-by-two contingency tables of patient severity and mortality in the context of the major comorbidities correcting for Age as a cofounder (Table 4). We found that patients with DM had a significantly higher association with severe COVID-19 (OR = 2.46, 95% CI = 1.62–3.72, Chi-squared = 18.89, p -value < 0.0001) and COVID-19 mortality (OR = 2.11, 95% CI = 1.14–3.54, Chi-squared = 6.04, p -value = 0.014). Previous studies have shown that DM and HTN may interact to determine COVID-19 severity²⁴. However, among patients with DM ($n = 238$), we did not find a significant association between HTN and COVID-19 severity (95% OR = 1.08, CI = 0.58–2.02, Chi-squared = 0.0093, p -value = 0.92) or mortality (95% OR = 0.896, CI = 0.39–2.05, Chi-squared = 0.0023, p -value = 0.962). Therefore, the presence of HTN does not exacerbate the severity of COVID-19 in patients suffering from DM, suggesting that the two comorbidities do not interact.

Table 1
Univariate analysis of different comorbidities and blood parameters on COVID19 severity ($n = 118$; severe cases represent severe COVID-19 infection as defined by MoHFW or patient mortality).

Parameter	Severe and Dead patients ($n = 118$)	Mild and Moderate patients ($n = 695$)	P-value
Gender	72.3% Males	68.2% Males	0.39
Diabetics (DM)	52.9%	25.1%	3.8×10^{-9}
Hypertension (HTN)	42.9%	24.8%	8.71×10^{-5}
Any comorbidity	84.9%	59.4%	3.02×10^{-8}
Age	61.9 ± 13.5	45.1 ± 17.5	1.34×10^{-24}
Hemoglobin	12.06 ± 2.3	12.75 ± 2	0.0037
Lymphocyte%	14.14 ± 10.4	31.66 ± 111.54	1.02×10^{-3}
Monocyte%	5.71 ± 5.86	8.25 ± 4.16	2.2×10^{-5}
Neutrophil%	78.4 ± 13.2	62.6 ± 12.9	2.75×10^{-23}
RBC counts	$4.35 \pm 0.78 \times 10^6/\text{mL}$	$4.48 \pm 2 \times 10^6/\text{mL}$	0.277
Platelet counts	$14.65 \pm 48.9 \times 10^3/\text{mL}$	$14.18 \pm 55.19 \times 10^3/\text{mL}$	0.933

4. Discussion

Results from our multivariate analysis on 573 patients, found that Age, Neutrophil percentage, and DM status were most associated with COVID-19 severity. Further, results from the Cochran-Mantel-Haenszel test on the entire cohort of 813 patients, while controlling for age as a confounder, confirmed findings from previous analyses and meta-analyses [14–27] that DM is a significant contributor to COVID-19 severity and mortality. Our results agree with the meta-analysis Kumar et al. showing that DM was associated with a significant increase in COVID-19 severity (OR of 2.75) and mortality (OR of 1.90) [25] with similar Odds-ratios. We are also in line with results about the association of DM with COVID-19 outcomes from recent studies on smaller Indian cohorts [17,18]. They also found that out of the total admissions for COVID-19, 27.8% were diabetic. A metanalysis by Singh et al. showed that 11.5% of COVID-19 patients were diabetic and that there was a significant increase in the risk of severe COVID-19 (Risk ratio of 2.11) compared with patients without co-morbidities [28]. These results are further supported by the observation. HbA1c among COVID-19 patients with DM requiring admission was high (8.23 ± 2.03) indicating uncontrolled DM. In addition to DM, the high/growing prevalence of impaired glucose tolerance (IGT), especially in people below the age of 40 years [6] suggests the possibility of latent DM-like symptoms (similar to those of type 2 DM) which may also lead to complications in COVID-19 infection. Studies have shown that at-admission hyperglycemia in COVID-19 patients with or without diabetes has been associated with poorer outcomes when compared with patients with normoglycemia [28]. A retrospective study conducted by Zhu et al. on COVID-19 patients with diabetes stratified on the basis of glycemic control showed that poorly controlled blood glucose of >180 mg/dl had significantly higher levels of poor prognostic biochemical and hematological markers as well as an increased severity and mortality in patients with COVID-19 [29]. Another retrospective study by Bode et al. showed that among COVID-19 patients with diabetes (HbA1c >6.5%) and uncontrolled hyperglycemia who were not previously diagnosed with diabetes (HbA1c <6.5%), the latter showed a significantly higher percentage of deaths [30]. This suggests that any cause of poorly controlled blood glucose levels such as diabetes or stress hyperglycemia in the setting of acute illness are associated with significantly higher levels of poor prognostic biochemical markers as well as an increased severity and mortality in patients with COVID-19 [31].

It is interesting to note from a study done in china that in severe COVID-19 patients the biochemical and hematological markers for severe COVID-19 were significantly higher in diabetics when compared with non-diabetic. There was also a significant increase in neutrophils, D-dimer, ferritin, CRP, Procalcitonin, Creatinine and decrease in Lymphocytes count in diabetics when compared with non-diabetic COVID-19 patients [32].

Table 2
Multivariate logistic regression of parameters to predict Patient severity, DM = Diabetes mellitus, HTN=Hypertension = red blood cell-R = logistic regression.

Source	Estimate	L-R		Unit Odds ratio (OR)	
		Chi-square	Prob > Chi Sq	OR	OR Range
Gender	-0.23	2.27	0.132	1.59	0.865–2.93
DM (1 = present)	-0.38	6.55	0.0105	2.15	1.2–3.85
HTN (1 = present)	0.06	0.143	0.705	0.88	0.47–1.67
Hemoglobin	-0.097	1.687	0.194	0.91	0.785–1.05
Neutrophil %	0.106	5.94	0.0148	1.12	1.076–1.149
Lymphocyte %	0.0009	0.01	0.919	1	0.988–1.014
Monocyte %	0.0395	0.752	0.386	1.04	0.965–1.122
RBC	0.055	0.643	0.422	1.057	0.944–1.182
Platelet count	0.00037	0.02	0.89	1	0.995–1.005
Age (60 or more)	-0.63	19.94	<0.0001	3.52	2.03–6.12

Table 3
Multivariate logistic regression of parameters to predict Patient mortality, DM = Diabetes mellitus, HTN=Hypertension = red blood cell-R = logistic regression.

Source	Estimate	L-R		Unit Odds ratio (OR)	
		Chi Square	Prob > Chi Sq	OR	OR Range
Gender	-0.27	1.69	0.194	1.704	0.754–3.848
DM (1 = present)	-0.37	3.49	0.062	2.09	0.963–4.545
HTN (1 = present)	0.34	2.54	0.11	0.51	0.22–1.17
Hemoglobin	-0.101	0.96	0.32	0.903	0.74–1.10
Neutrophil %	0.08	2.93	0.087	1.08	1.039–1.13
Lymphocyte %	0.00007	0.009	0.9225	1	0.988–1.013
Monocyte %	-0.009	0.022	0.882	0.99	0.876–1.12
RBC	0.051	0.237	0.6262	1.052	0.893–1.23
Platelet count	-0.011	4.18	0.041	0.988	0.97–1.007
Age (60 or more)	-0.93	25.9	<0.0001	6.488	3.045–13.826

Table 4
Partial two-by-two contingency tables used for Cochran-Mantel-Haenszel chi-square test in order to dissect the association of Diabetes with COVID-19 patient severity (severe cases represent severe COVID-19 infection as defined by MoHFW or patient mortality) and mortality.

All patients (n = 813)					
	Below 60 years		Age 60 years and above		
	Not Diabetic	Diabetic	Not Diabetic	Diabetic	
Not Severe	425	107	95	68	
Severe case	23	25	32	37	
Survivors	446	121	106	87	
Mortality	2	11	21	18	
Only diabetic patients (n=238)					
	Below 60 years		Age 60 years and above		
	Not Hypertensive	Hypertensive	Not Hypertensive	Hypertensive	
Not Severe	64	43	18	50	
Severe case	13	12	11	26	
Survivors	71	50	23	64	
Mortality	6	5	6	12	

Furthermore, we also find that in our cohort, the percentage of patients with DM was more in line with previous studies in India from Indore and New Delhi at about 25–30%, rather than on the cohort from Jaipur that reported much lower values of about 5% [33,34]. Another study from India reported that out of deceased cases nearly 50.5% had preexisting comorbidities [34]. However, unlike previous studies on a cohort of Indian patients¹⁷ and cohort of non-Indian patients [35,36] showing that HTN was also associated with increased COVID-19 severity and mortality, we did not find HTN to be associated with COVID-19 severity or to modify the risk of COVID-19 outcome in patients with DM.

To the best of our knowledge, ours is the first Indian study finding a significant association between high Neutrophil% with the severity of COVID-19 confirming previous findings in other similar

cohort-based studies from Asia [37]. Our results represent currently one of the largest cohorts of COVID-19 patients in India at more than 800 patients. Since this was a retrospective record-based study, we lost a significant amount of data due to digitization. Going forward, we hope that an effort is made to achieve optimal glycemic control in diabetic patients to prevent increased severity and mortality due to COVID-19. Telemedicine is also a promising alternative to conventional hospital appointments for diabetic patients to access healthcare facilities especially in these trying times.

Limitations: The exact interaction between COVID-19, DM, and HTN that leads to the worsening of COVID-19 need to be studied further at the molecular level. It has been suggested that the link between HTN, DM, and SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE-2) that is believed to be one of the co-receptors

that are used by the SARS-CoV-2 to infect cells [38] Higher levels of ACE-2 have been reported in patients with DM and/or HTN as compared to healthy individuals which may aid in the natural pathogenesis of the diseases. Hence, many DM and/or HTN patients are on ACE-1 inhibitors or angiotensin-receptor antagonists. Hence, if there were effects due to medication it would alleviate the symptoms of the disease in these patients rather than enhance these. However, this is a limitation of our study as we did not control for medications taken in our analysis due to insufficient information regarding the same. Further, several other parameters that have been previously shown to be associated with COVID-19 outcome such as obesity, inflammation markers were not considered. Further, we do not have information about new-onset hyperglycemia and were not able to comment on its association with the COVID-19 outcome.

Presentation at a meeting

NIL.

Specific authors contribution

SKJ and IG designed the study. SKJ, PG, SNS, SKV, RNH, SSB, PSM and SS Collected and Curated the data. SKJ and IG performed data analysis. SKJ, PG, SNS, PSM, IG, SS contributed in writing the Manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the ARMED FORCES MEDICAL COLLEGE, PUNE, which waived the need for obtaining informed consent (IEC S. No: IEC/2020/325 2020-10-30). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Declaration of competing interest

The authors have no conflict of interest.

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