Original Article

Diabetes Mellitus and Other Comorbidities: Outcome among Covid-19 Patients in Kerala: A Retrospective Observational Study

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Abstract

Background: Covid-19 was declared by the WHO as a pandemic in 2020; India was also severely affected. Diabetes, a major lifestyle disorder, has seen its prevalence rate rising in developing countries. India is home to the world's second-largest population of diabetes. Several studies have reported greater severity and mortality of Covid-19 in diabetic patients. **Methodology:** This was a hospital-based retrospective study done in a rural-based medical college in Kerala State. Data was collected using a semi-structured proforma and analysis was performed using Statistical Package for Social Sciences software version 25. The study was part of the STS research program of the Indian Council of Medical Research (ICMR). **Results:** There were 567 patients in the study. Those with pre-existing diabetes had a worse outcome compared to those with newly detected diabetes. The presence of CKD was associated with a poor outcome. Patients admitted to the ICU, and those on assisted ventilation also had a lower survival rate; within the subgroup, those on non-invasive ventilation had a better outcome. **Conclusion:** Mortality in Covid-19 is multifactorial. Those with diabetes have a poor outcome. Comorbidities have been reported to confer a high mortality rate in Covid-19 but this was not so in our study (except for CKD). Variability in outcome with respect to comorbidities and better outcomes in those who were non-invasively ventilated calls for more research to establish the relationship between pre-existing conditions and severity of disease. The use of non-invasive ventilation could also provide succor to resource-limited communities.

Keywords: Comorbidities, Covid-19, diabetes mellitus, Kerala

Introduction

Covid-19 caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is primarily a respiratory disease, which was declared by the World Health Organization (WHO) as a global pandemic on March 11, 2020.[1] In May 2023, WHO declared that Covid-19 no longer constitutes a public health emergency of international concern (PHEIC).[2] In India, from 3 January 2020 to 16 August 2023, there have been 44,996,335 confirmed cases of Covid-19 with 531,922 deaths, reported to WHO, and is one of those countries which was severely affected.[3]

Diabetes which is a major lifestyle disorder and an established problem in the developed world has seen its prevalence rate rising sharply in developing countries. Diabetes has now become a global problem; its roots lie in the rapid socioeconomic transition with the urbanization of societies and industrialization. In India, the epidemic of diabetes continues to increase and is experiencing a shift in diabetes prevalence from urban to rural areas, from the affluent to the less privileged, and from older to younger people.[4] India is home to the world's second-largest population of diabetes (77 million).[5,6]

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Several studies including meta-analyses have reported greater severity and mortality of Covid-19 in people with diabetes than in those without.[7-9] In India too, a high prevalence of diabetes has been observed in hospitalized Covid-19 patients.[10,11] However, the outcomes have been conflicting; some studies have shown a poor outcome in those with diabetes[10,11] while others have not.[12]

It was in this context that this study was done to determine the association between diabetes mellitus (and other co-morbid illnesses) and outcomes in Covid-19 patients in Kerala.

Materials and Methods

This was a hospital based retrospective study done in a medical college in Kerala State. The study period was two years.

Data regarding the patients were obtained from the Medical Record Department (MRD) of the hospital with the permission of the medical superintendent. Adult (>18 years of age) patients hospitalized with Covid-19 infection in Ernakulam District of Kerala were included in the study. A diagnosis of Covid-19 was made when a patient tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) testing or antigen testing. Data were collected using a pre-tested, semi-structured questionnaire. Demographic data, co-morbidities, time of admission, time of death, testing, and treatment-related data were collected. The research was approved by the Institutional Ethics Committee (IEC) of the hospital (No: MOSC/IEC/616/2022).

The data collected were coded and entered in Microsoft Excel sheet which was re-checked and analyzed using Statistical Package for Social Sciences (SPSS) software version 25. Normality of data was checked using Kolmogorov–Smirnov test. Quantitative variables were summarized using median and interquartile range (IQR) as the data was not normally distributed. Categorical variables were represented using frequency and percentage. Mann–Whitney test was used to test the statistical significance of the difference between means of variables among different independent groups as the data was not normally distributed. Pearson Chi-square test and Fisher's exact test were used for comparing categorical variables between groups. Binary logistic regression was done to find out independent factors associated with survival. A *P*-value of <0.05 was considered statistically significant.

Results

The mean age of the population was 62.34 (±12.92). Majority of people belonged to the 51–60 age group (31.2%) closely followed by 61–70 age group (28.2%). Both together made up more than fifty percent of the population. Majority of the patients were males (62.3%) [Figure 1].

488 (86.1%) patients had pre-existing diabetes. In 31 (5.5%) diabetes was newly detected (diagnosed for the first time). 48 (8.5%) patients were free from diabetes. 525 (92.6%) patients had other comorbidities too. Hypertension (52.9%) was the most common comorbidity followed by Ischemic Heart Disease (IHD) (16.4%) and Chronic Kidney Disease (CKD) (16.2%) [Table 1].

The mean hospital stay was 8.91 (±7.90) days. 226 (39.9%) patients required Intensive Care Unit (ICU) care and the mean duration of ICU stay was 6.48 (±6.64) days. 57 percent of the patients required oxygen. However, only 26.3% patients required some form of assisted ventilation. Of those who required assisted ventilation 61.7 percent could be managed by non-invasive ventilation; only 38.3 percent required invasive ventilation [Table 2].

In our study, patients admitted to the ICU had significantly reduced survival rates of 65% compared to 96.5% for those not admitted ($P < 0.001$, Chi-square test), with non-survivors exhibiting a markedly prolonged average ICU stay of 8.44 ± 8.79 days relative to the 5.43 ± 4.86 days observed in survivors ($P = 0.013$, Mann–Whitney test). Patients with newly detected diabetes exhibited a survival rate of 96.8%, in contrast to the 83.4% among those with pre-existing diabetes ($P = 0.044$, Fisher's exact test). The presence of CKD correlated with a decreased survival rate of 76.1%, as opposed to 85.5% without the condition ($P = 0.025$, Chi-square test). Oxygen requirement

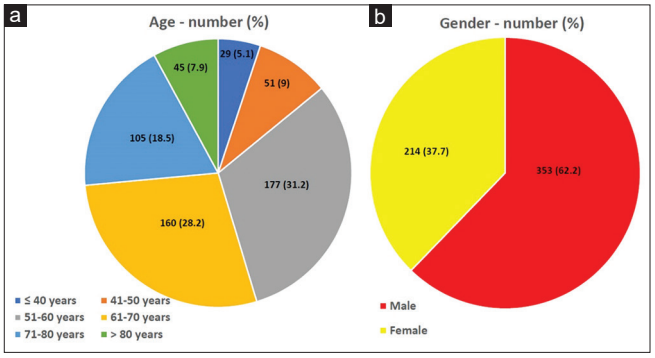

Figure 1: Demographic data: (a) Age and (b) Gender

Table 1: Diabetes and other comorbidities

Comorbidities	No (%)
Diabetes-no (%)	
Pre-existing	488 (86.1)
Newly detected	31 (5.5)
Nil	48 (8.5)
Comorbidities-no (%)	
Yes	525 (92.6)
No	42 (7.4)
Median (IQR)	2 (1-3)
Comorbidities-no (%)	
Hypertension	300 (52.9)
Ischemic Heart Disease (IHD)	93 (16.4)
Chronic Kidney Disease (CKD)	92 (16.2)
Cerebrovascular Accident (CVA)	32 (5.6)
Chronic Obstructive Pulmonary Disease (COPD)	21 (3.7)
Chronic Liver Disease (CLD)	20 (3.5)
Malignancy	6 (1.1)

was a significant predictor of survival; patients requiring oxygen showed a survival rate of 74.3%, while those not needing it stood at 96.7% ($P < 0.001$, Chi-square test). Assisted ventilation emerged as another critical factor: those requiring it had a 62.4% survival rate, contrasting the 91.6% among those who did not. Notably, within the subgroup of those on assisted ventilation, individuals on invasive ventilation had a significantly lower survival rate (21.1%) compared to those on non-invasive ventilation (88%; $P < 0.001$, Chi-square test) [Table 3].

The factors associated with survival by multivariate analysis included no oxygen requirement, no assisted ventilation, and not getting admitted in the ICU [Table 4].

Discussion

The Covid-19 pandemic has raged globally stretching the global healthcare system to its limits. The virus does not distinguish between the rich and the poor. The healthcare facilities and capabilities of developing nations are starkly different from those of richer nations; hence, the challenges they faced were often unfathomable. India faced the dual threat of a huge disease burden with a modest health infrastructure. With this fact in mind, we went about documenting the cases of Covid-19 in our tertiary care facility. In this study, we have addressed the issue of diabetes and other co-morbidities of our patients with Covid-19 and its impact on the overall prognosis of the patients in terms of mortality.

In our study, we found that those with pre-existing diabetes had a worse outcome compared to those with newly detected diabetes. This finding of ours is in agreement with most other studies from our country and around the world. In a meta-analysis done by Ashish Kumar *et al.*,[13] diabetes in patients with Covid-19 was associated with a two-fold increase in mortality as well as severity of Covid-19 when compared to non-diabetics. In a multi-center study from another part of the country Covid-19, severity and mortality both were significantly associated with the status of diabetes mellitus.[11] In a pooled analysis related to disease severity and mortality by Seshadri Reddy Varikasuvu *et al.*,[14] Covid-19 patients with diabetes had a significantly higher risk of disease severity and associated mortality outcomes. In other studies from around the globe too, diabetes was associated with a poor outcome in Covid-19 patients.[15-17] Hyperglycemia is known to cause increased viral proliferation in Covid-19.[18] Worsening of hyperglycemia also induces inflammation, endothelial dysfunction, and thrombosis via the generation of oxidative stress, enhancing the dysregulation of glucose metabolism and hypercoagulability further.[19] This in turn can lead to multiorgan failure and increased mortality rates.

The presence of CKD was associated with a poor outcome as opposed to those without. Other co-morbidities like hypertension, IHD, CVD, COPD, CLD, and malignancy did not alter the outcome in our study. These findings are in stark contrast to studies from other parts of the world. In a meta-analysis done by E H Taylor *et al.*,[20] hypertension, cardiovascular disease, respiratory disease, renal disease, and malignancy were associated with mortality. In a cohort study on Covid-19 mortality and

Table 2: Treatment details

Duration of hospital stay-days	
Mean±SD	8.91±7.90
Median (IQR)	7 (4-11)
Admitted in ICU-no (%)	
Yes	226 (39.9)
No	341 (60.1)
Duration of ICU stay-days (*n*=226)	
Mean±SD	6.48±6.64
Median (IQR)	4 (2-8)
Oxygen requirement-no (%)	
Yes	323 (57)
No	244 (43)
Assisted ventilation-no (%)	
Yes	149 (26.3)
No	418 (73.7)
Type of assisted ventilation-no (%) (*n*=149)	
Invasive	57 (38.3)
Non-invasive	92 (61.7)

Table 3: Factors associated with survival

Variable	Survival at discharge		*P*
	Yes (*n*=476) *n* (%)	No (*n*=91) *n* (%)	
Admitted in ICU			
Yes	147 (65)	79 (35)	<0.001*,#
No	329 (96.5)	12 (3.5)	
Duration of ICU stay	*n*=147	*n*=79	
Mean±SD	5.43±4.86	8.44±8.79	
Median (IQR)	4 (2-6)	5 (3-12)	0.013*,$
Diabetes			
Newly detected	30 (96.8)	1 (3.2)	0.044*,@
Pre-existing	407 (83.4)	81 (16.6)	
CKD			
Yes	70 (76.1)	22 (23.9)	0.025*,#
No	406 (85.5)	69 (14.5)	
Oxygen requirement			
Yes	240 (74.3)	83 (25.7)	<0.001*,#
No	236 (96.7)	8 (3.3)	
Assisted ventilation			
Yes	93 (62.4)	56 (37.6)	<0.001*,#
No	383 (91.6)	35 (8.4)	
Type of assisted ventilation	*n*=93	*n*=56	
Invasive	12 (21.1)	45 (78.9)	<0.001*,#
Non-invasive	81 (88)	11 (12)	

*Statistically significant, @Fisher's exact test, #Chi-square test, $Mann–Whitney test

Table 4: Factors associated with survival-multivariate analysis

Variable	OR	95% CI for OR	*P*
No oxygen requirement	4.32	1.41-13.20	0.010*
No assisted ventilation	2.41	1.34-4.34	0.003*
Not admitted in ICU	11.18	4.85-25.75	<0.001*

*Statistically significant

associated risk factors, cardiovascular disease, hypertension were independently associated with Covid-19 mortality.[21] In a study conducted in India based on the factors associated with mortality among moderate and severe patients with Covid-19, patients with two or more comorbidities had 2.25 times the risk of death.[22] In a meta-analysis to evaluate the impact of various comorbidities on serious events, the presence of hypertension, cardiovascular disease, COPD, and Chronic Kidney Disease had significant association in patients with Covid-19 showing poorer outcomes.[23] Individuals with CKD are at higher risk of severe disease due to their chronic immunosuppression, which may result from pharmacological treatments, or due to the inflammatory state of kidney disease and uremia.[24]

In our study those who required oxygen had a poor outcome, the logical explanation being, the more severe the lung involvement, the more the need for oxygen support. This finding was similar to other studies from around the world. In a study conducted in France, independent risk factors like oxygen requirement were associated with mortality.[25] In a study conducted in Italy, patients who required a high fraction of inspired oxygen were associated with mortality.[15] Assisted ventilation was another critical factor that was associated with outcome; those requiring it had a lower survival rate compared to those who did not. Notably, within the subgroup of those on assisted ventilation, individuals on invasive ventilation had a significantly lower survival rate compared to those on non-invasive ventilation. Similar studies with subgroup analysis of assisted ventilation in Covid-19 are rare in indexed literature. In a study done by Yongli Yan *et al.*,[26] patients with diabetes receiving mechanical ventilation had higher mortality. In a meta-analysis based on case fatality rates of patients with Covid-19, patients requiring invasive mechanical ventilation showed a significant association with mortality.[27]

In our study, patients admitted to the ICU had significantly reduced survival rates compared to those not admitted with non-survivors exhibiting a markedly prolonged average ICU stay. Similar findings have been reported from other parts of the world too.[15,28]

The main objective of this study was to study the association between diabetes mellitus (and other co-morbid illnesses) and outcomes in Covid-19 patients in Kerala. Hence, factors like oxygen requirement assisted ventilation and ICU care which are measures undertaken to sustain life in critically ill are at best secondary observations and not necessarily factors that have a direct bearing on the outcome in Covid-19 patients; they merely point to the severity of illness by virtue of requiring the highest level of life-sustaining critical care. Among diabetes mellitus (and other chronic comorbidities like hypertension, IHD, CKD, CVD, COPD, CLD, and malignancy), diabetes mellitus and CKD were associated with a poor outcome.

This study was not without limitations. This was a single center study. The presence of comorbidities was ascertained from the medical records and whether these comorbidities were well controlled was not recorded at the time of admission. Information regarding the severity of illness and the use of immunosuppressants was also incomplete in the available records. Data regarding vaccination against Covid-19 was inadequate, and hence, this factor could not be analyzed. As new mutants of the virus emerge, the efficacy of existing vaccines to offer the same level of protection will also be of concern[29-31] and likewise research will have to focus on this aspect of vaccination too.

Conclusion

Mortality in Covid-19 is multifactorial. In our study, those with diabetes had a poor outcome. Except for CKD, the presence of other chronic comorbidities like hypertension, IHD, CVD, COPD, CLD, and malignancy did not alter the outcome of the patient in the study. Those requiring oxygen support, those requiring ICU care, and those requiring assisted ventilation had a bad outcome; these can be considered as proxy indicators of severe Covid-19 infection. Notably among those on assisted ventilation, outcome was better on those who were on non-invasive ventilation. Variability in outcome with respect to comorbidities and better outcome in those who were non-invasively ventilated (in comparison with those who were invasively ventilated) points to the need for more research to establish the relationship between pre-existing conditions and severity of disease. Research on the use of non-invasive ventilation and its use could also provide succor to resource-limited communities. It need not be further emphasized, that patients need to be made aware of the importance of adequate control of diabetes mellitus and regular follow-up to reduce/decrease the progression of CKD.

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Conflicts of interest

There are no conflicts of interest.

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