Original Article

Immediate cause and the role of multimorbidity in deaths associated with COVID 19 among hospitalized patients in a low resource district in Kerala India: A record-based case-control analysis

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Abstract

Introduction: Multimorbidity is the coexistence of two or more chronic medical conditions in a person. The study aims to investigate the immediate cause of death and risk factors of mortality including multimorbidity among patients hospitalized with SARS CoV2 infection in Kasaragod district in Kerala, India. **Methods:** A record-based case-control study was done using the hospital records and follow-up surveillance system of SARS-COV 2 patients admitted in the Kasaragod district. SARS-COV 2 patients who had expired during the study period from June to December 2020 and reported as COVID-19 deaths (N = 226) were the cases, and an equal number of hospital controls were the study participants. **Results:** The mean (SD) age of the cases and controls were found to be 64.6 (14.2) years and 61.5 (13.4) years, respectively. Covid pneumonia alone was reported as the cause of death in more than half (52%) of the study participants. This was followed by cardiovascular events (8.5%) and acute kidney injury (6.5%). Among individual comorbidities among people who expired, diabetes mellitus (53%) was the most common, followed by hypertension (46%) and cardiovascular diseases (23%). More than 50% were found to have multimorbidity. Logistic regression showed chronic kidney disease (CKD) (Adjusted odds ratio (AOR) = 2.18 (1.24–3.83)) and malignancy (AOR = 3.05 (1.27–7.32)) to be significantly associated with mortality as individual determinants. Hypertension–diabetes mellitus [AOR = 1.68 (1.02–2.76), P = 0.043] and hypertension–CKD [AOR = 3.49 (1.01–12.01), P = 0.48] dyads were multimorbidities significantly associated with mortality. **Conclusion:** Combinations of hypertension with diabetes mellitus and CKD were found to be significant determinants for mortality in hospitalized COVID-19 patients. Uniformity in death certification is required to understand the causes and contributors to death in COVID-19.

Keywords: Comorbidity, Covid-19, death certificate, India, mortality, multimorbidity

Introduction

The death rate in COVID-19 varies widely across geographies, influenced by diverse factors.[1] Scientific community has come a long way in addressing the threat of mortality through evidence-based treatment strategies to the rollout of vaccines.[2,3]

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Still, the pandemic imparts significant mortality among the elderly and debilitated, with the middle-aged population at substantial risk as well.[4] The role of age and comorbidities in COVID-19 deaths are well documented.[5,6] But data are scarce on the exact mechanism of death or immediate cause of death in COVID-19 patients from third-world countries. Medical Certification of Cause of Death, popularly known as the 'Death Certificate' issued by a medical practitioner, could be used to ascertain the cause of death. However, such certification is rarely complete, especially in low resource settings.[7,8]

Understanding determinants of mortality in regional granularity is essential in lowering mortality, especially in low- and middle-income countries (LMICs), where the existing health inequity has been profoundly widened by the COVID-19 pandemic. The WHO defines multimorbidity as 'being affected by two or more chronic health conditions in the same individual'.[9] Comorbidities like diabetes mellitus, hypertension and heart disease have been found to be poor prognostic indicators in people affected with Covid-19.[2,3,9] With multimorbidity being a major emerging threat, its effect on COVID-19 mortality in LMIC settings needs to be assessed. With a high burden of noncommunicable diseases (NCD), Kerala state in India offers a unique opportunity for understanding the role of comorbidities in such settings. Multimorbidity burden among productive age group individuals in Kerala is reported to be more than 45% in the age group of 30–69-year-old individuals.[10] COVID-19-affected individuals could develop severe complications in the presence of multimorbidity. However, this challenge has only been addressed minimally in Indian settings. With the contribution of NCD and cardiovascular diseases among total mortality reaching 72 and 37%, respectively, in Kerala, understanding the role of comorbidities in determining the prognosis in covid-19-affected patients is very pertinent.[11] Physical conditions like obesity have proven to be detrimental to recovery in hospitalized SARS CoV2-infected individuals.[12]

The present study proposes to scrutinize details of all patients who were found to be covid-19 positive and expired later in the Kasaragod district of Kerala, India. The third Covid-19 case in India appeared in the district in April 2020.[13] Multidimensional efforts were undertaken to reduce the cases and deaths in the Kasaragod district.[14] However, understanding the determinants of mortality in such resource-poor settings with a high burden of NCDs is essential for making region-specific policy decisions in the ongoing COVID-19 pandemic. The current study tries to identify the immediate causes and risk factors of deaths attributed to COVID-19. The data we provide will help primary care practitioners to understand the role of morbidity and multimorbidity in COVID-19 mortality and to prioritize COVID-19 patients seeking medical treatment.

Methods

Study design, setting and methods

The study was conducted as a record-based case-control study in the Kasaragod district of Kerala state in India. Study participants were selected from the hospital records of admitted COVID-19 patients to whom the follow-up clinical data were available until discharge from the hospital or till death. Discharged patients were followed for one month using the field surveillance system of the district.

According to the clinical management system for COVID-19 in Kerala, asymptomatic cases were managed at home and domiciliary care centres, mildly symptomatic at COVID first-line treatment centres, moderate clinical symptoms at COVID second-line treatment centres and clinically severe cases or patients with significant risk factors were admitted to a COVID hospital.[15] Cases, for the current analysis, were defined as patients who were found to be SARS CoV2 positive either by real-time reverse transcriptase polymerase chain reaction (rRT-PCR), rapid antigen test (RAT) or Truenat™, admitted to a COVID hospital and expired during hospitalization or within 30 days of discharge due to complications attributed to COVID-19. All patients who had expired from June to December 2020 were recruited as cases. In total, 226 SARS CoV2 patients had expired during the study period, including five individuals who had passed away within a month of hospital discharge. The case group ($n = 226$) comprises all deaths among hospitalized patients attributed to COVID-19 in the Kasaragod district during the study period. The records were further verified to ascertain the cause of death and ICD codes.

Controls were patients who were found to be SARS CoV2 positive either by rRT-PCR, RAT or Truenat™, admitted to a COVID hospital and survived even after 30 days following discharge from the hospital. An equal number of controls ($N = 226$) were also recruited from the same hospital during the same time period of the hospital admission of the case to avoid bias associated with hospital care which may influence mortality. The controls were selected randomly from the line list of covid 19 patients who satisfied the inclusion criteria in the Kasaragod district. Age and gender were not matched to study the interaction between these variables and morbidities as the risk factors of mortality.

The cases and controls were from all three major government institutions in Kasaragod and Kannur districts, to which referrals were made. There were no major private institutions in Kasaragod or neighbouring districts to which severe COVID-19 cases were referred during the study period. During the study period, no death fulfilling the case definition occurred at home as every case was meticulously followed up at the ward level itself. Additionally, it was mandatory to test for Covid-19 in any deaths occurring at home, irrespective of symptoms. Such steps have ensured that all deaths due to COVID-19 have been captured by the health system.

Study tool and variables

The immediate cause of death and multimorbidity were the major study variables. WHO death certificate classifies causes of death as Immediate cause, antecedent cause and other significant contributors to death. The cause of death mentioned in the first

row of the WHO death certificate was considered the immediate cause of death in the study. The death certificates of the hospitals did not mention ICD codes. Hence, investigators assigned applicable ICD codes with the help of the treating physician after verifying the case records. Multiple ICD codes were used wherever appropriate. Subsequent rows of the death certificate mentioned the comorbidities suffered by the patient. In this study, they are considered contributors or risk factors of death and not the cause of death. Multimorbidity considered in this paper was caused by combinations of hypertension, diabetes mellitus, chronic kidney disease (CKD), cardiovascular disease, chronic liver disease, cerebrovascular accident, malignancy or psychiatric illness. All details were collected from the available records of the patient at the Covid District Programme Management and Support Unit (DPMSU) of Kasaragod district using a semistructured questionnaire. The patient's age and gender, socioeconomic details, comorbidities and addictions, duration of hospital admission, duration between symptom onset and hospital admission, details of admission including the type of institution, ICU admission, ventilator support and discharge/death were the variables used in the study. The status of patients 30 days after discharge from the hospital was verified by the field wing of DPMSU. The enrolment of control for every assigned case was done by nonmedical personnel from the complete list of surviving patients at the same institution during the same period.

Statistical analysis

The statistical analysis was done using SPSS 25.0.[16] Quantitative variables like age and duration of hospital stay are expressed as mean with standard deviation. Prevalence of comorbidities and multimorbidity are provided in percentages. In both case and control groups, diseases contributing to multimorbidity were depicted in pairwise comorbidity matrices. The odds ratio with confidence intervals has been estimated for all exposure variables. Two models were built using multiple logistic regression analysis to find out the determinants of mortality associated with SARS CoV2 infection. Comorbidities, along with the socioeconomic characteristics, were used as the exposure factors in the first model, whereas different combinations of multimorbidity were used as exposure variables in the second model. Four comorbidities with the lowest sample were not used for creating dyads. Individual comorbidities were not used as predictors in the second model because multimorbidity is nothing but these diseases in combination. A significance level of less than 0.2 was the initial criterion used to assign covariates to both models. The backward logistic regression method was employed to discard nonsignificant exposure variables. The maximum value of Nagelkerke *R* square with the minimum number of variables and significance of the model in the ANOVA table were the criteria used for finalizing the model.

Ethics clearance was obtained from the Institutional Human Ethics Committee of Government Medical College Kannur, Kerala (IHEC No: 121 A/2019/IEC/GMCK dated 24/04/2021). The study was based entirely on records, and the personal information of the individuals was not collected.

Results

Demography, clinical severity and the course of illness

There were 3032 COVID-19 deaths in Kerala among hospitalized patients during the study period and deaths in Kasaragod contributed 7.5% of the total deaths in the state. Among the 226 cases and 226 controls enrolled, details regarding comorbidities were available in the hospital records for 200 cases and 225 controls. Majority of patients (56.5%) who succumbed to death were aged more than 65 years in comparison to the 43.8% in the control arm. Most of the study participants were aged 45 and above (93% Vs 90.3%), with more males in both groups (68% Vs 62%). The mean (SD) age of cases and controls were found to be 64.6 (14.2) and 61.5 (13.4) years, respectively.

All cases (100%) were severely symptomatic (pneumonia plus one of the following signs: respiratory rate ≥30 breaths/min, severe respiratory distress or SpO2 ≤90% on room air) at some time during the course of their illness as expected, while 42% of the controls were also severely symptomatic. A mean (SD) duration of 2.56 (3.2) days was taken for the expired individuals to reach the diagnosis of COVID-19 from the start of their symptoms. It took 9.6 h on average for them to initiate hospital care, and they spent a mean (SD) of 6.3 (7) days from hospitalization to death. The mean (SD) durations taken by the control group were 2.11 (1.9) days for diagnosis, 1.3 (0.8) days for hospitalization and 15 (6.7) days for discharge from hospital. Time from onset of symptoms to confirmation of diagnosis and proportion of individuals requiring some form of ventilation support were similar among both groups. However, time duration between confirmation of diagnosis and hospital admission was significantly higher among controls ($p < 0.001$).

Individuals with two or more comorbidities were classified as having multimorbidity. More than 50% of the cases and 40% of the controls were found to have multimorbidity. Among individual comorbidities, diabetes mellitus (53% Vs 52%) was most common, followed by hypertension (46% Vs 45.3%) and cardiovascular diseases (23% Vs 28%) in both groups [Table 1].

The immediate cause of death

The causes of mortality were scrutinized to understand the clinical diagnosis at the time of death and to assess the manner of reporting deaths associated with COVID-19. The International Classification of Diseases (ICD-10) codes for diagnoses are also provided. Covid pneumonia alone was reported as cause of death in more than half (52%) of the study participants. Along with other diseases, COVID-19 pneumonia contributed to two-thirds (64%) of COVID-19-associated deaths. Cardio-vascular events (8.5%) and acute kidney injury (6.5%) were the next two major causes. Sepsis and encephalopathies were also present. Details regarding the immediate cause of death are given in Table 2.

Table 1: Baseline characteristics of study participants

Variables	Cases *n*=200 *n* (%)/ mean (SD)	Controls *n*=225 *n* (%)/ mean (SD)
Demographic factors		
Age in years		
Less than 45	14 (7%)	22 (9.3%)
45–54	20 (10%)	38 (17%)
55–64	53 (26.5%)	66 (29.5%)
65–74	69 (34.5%)	62 (27.7%)
75 and above	44 (22%)	36 (16.1%)
Gender		
Male	136 (68%)	139 (62%)
Female	64 (32%)	86 (38%)
Clinical severity and duration		
Experience of clinical severity during treatment		
Mild to moderately symptomatic	0	130 (58%)
Severely symptomatic	200 (100)	95 (42%)
Use of invasive or noninvasive ventilation at the time of admission (oxygen mask, noninvasive or invasive ventilation)	98 (49%)	95 (42%)
Time duration between onset of symptom to confirmation of diagnosis (in days)	2.56 (3.2)	2.11 (1.9)
Time duration between confirmation of diagnosis and hospital admission (in days)	0.4 (1.1)	1.3 (0.8)
Time duration hospital admission and Hospital discharge/death (in days)	6.3 (7)	15 (6.7)
Comorbidities		
Multimorbidity	101 (50.5%)	91 (40.4%)
Hypertension	92 (46%)	102 (45.3%)
Diabetes mellitus	106 (53%)	117 (52%)
Chronic kidney disease (CKD)	40 (20%)	24 (10.7%)
Cardio vascular disease (CVD)	46 (23%)	63 (28%)
Cerebro vascular accident (CVA)	10 (5%)	7 (3.1%)
Malignancy	19 (9.5%)	8 (3.6%)
Chronic liver disease (CLD)	13 (6.5%)	6 (2.7%)
Psychiatric illness	5 (2.5%)	6 (2.7%)

Co-morbidities and multimorbidity

The combination of diabetes and hypertension was the most common pair of multimorbidity among both cases (34%) and controls (27%). Combinations of CKD and CVD also contributed to high numbers of multimorbidity in the study groups. The number of people simultaneously suffering from three or more comorbidities was 46 and 43, respectively, among cases and controls.(23% Vs 19%). The proportion of individuals with three co-morbidities was 19 and 14.7%. The most common three-disease combinations were diabetes and hypertension with CVD or CKD. The prevalence of multimorbidity dyads among cases and controls is shown in Figures 1 and 2.

Univariate analysis revealed that multimorbidity is significantly associated with COVID-19 mortality [OR = 1.5 (1.02–2.2), P = 0.038]. There were statistically significant associations for CKD and malignancy with COVID-19 mortality.

The presence of CKD and malignancy were found to be significant contributors to COVID-19-associated deaths. CLD [AOR = 2.55 (0.98–3.83), P = 0.07] was also retained in the model because it got a borderline significance of 0.07. Types of multimorbidity were used as covariates in the second model to avoid multicollinearity. hypertension–diabetes mellitus combination and hypertension-CKD combination were found to be significant contributors to deaths [Table 3].

Discussion

The National seroprevalence surveys by the Indian Council of Medical Research revealed that among all Indian States, Kerala got the best-reporting fidelity of COVID-19 infections during the period of the current study.[17] Better fidelity in reporting infections may be a strength of the study setting. Most of the deaths occurred among elderly echoing large scale studies from other settings.[4] It could be noted that the average time to take a definitive treatment for COVID-19 in a COVID hospital was less than three days. It is very low and might have been attributed to lower mortality rates.[18] Moreover, the patients who expired took almost an additional day to start treatment compared to the control group, which was statistically significant. Hospital stay was found to be longer in individuals who have survived rather than those who expired and among those with multimorbidity as in other settings as well.[19,20]

Many of the diagnoses overlapped with at least one other cooccurring event that was a plausible chain of an event

Table 2: Documented cause of death from hospital records

Cause of Death	ICD-10 codes	Frequency (%) *n*=200
COVID-19 Pneumonia	U07.1, J12.82	112 (56%)
COVID-19 Pneumonia + Respiratory failure	U07.1, J96.00	6 (3%)
Cardiac Arrest/CAD/ACS/Acute MI/Anterior wall MI/STEMI/NSTEMI	I46.9, I25.10, I21.9	17 (8.5%)
COVID-19 Pneumonia + CAD	U07.1, J12.82, I25.10	3 (1.5%)
Sepsis+MODS	A41.9, R65.20, U07.1	3 (1.5%)
COVID-19 Pneumonia + Sepsis	U07.1, J12.82, A41.9	2 (1%)
COVID-19 Pneumonia + ARDS + Sepsis + MODS	A41.9, R65.20, U07.1, J80	3 (1.5%)
CVA	I63.9	2 (1%)
Malignancy	C80.1	5 (2.5%)
COVID-19 Pneumonia + Metabolic encephalopathy	U07.1, J12.82, G93.41	4 (2%)
Hepatic encephalopathy	K72.91	3 (1.5%)
Expired after discharge following COVID-19 (Exact cause of death unknown)	R99	5 (2.5%)
Acute kidney injury	S37.0	13 (6.5%)
COVID-19 Pneumonia + Chronic kidney disease	U07.1, J12.82, N18	5 (2.5%)
Acute on chronic kidney disease	N18.9	2 (1%)
Acute kidney injury + CAD	N18.9, I25.10	1 (0.5%)
Hepatorenal syndrome	K76.7	1 (0.5%)
CAD + COPD	I25.10, J44.9	1 (0.5%)
CLD + COPD	K76.9, J44.9	1 (0.5%)
CVA + AKI	I63.9, N18.9	1 (0.5%)
COVID-19 Pneumonia + Interstitial Lung Disease	U07.1, J12.82, J84.9	1 (0.5%)
COVID-19 Pneumonia + CVA	U07.1, J12.82, I63.9	1 (0.5%)
COVID-19 Pneumonia + CKD + Malignancy	U07.1, J12.82, N18, C80.1	1 (0.5%)
COVID-19 Pneumonia + CVA + CAD	U07.1, J12.82, I63.9, I25.10	1 (0.5%)
COVID-19 Pneumonia + AKI + Hypoxic Encephalopathy	U07.1, J12.82, N18.9,	1 (0.5%)
CKD + (Metabolic+Hepatic) encephalopathy	N18, G93.41, K72.91	1 (0.5%)
Severe head injury + Brainstem damage	S09.90XA	1 (0.5%)
Others		3 (1.5%)
Total		200

CAD – Coronary artery disease; ACS – Acute coronary syndrome, STEMI – ST-elevation myocardial infarction; NSTEMI – Non-ST elevation myocardial infarction; MODS – Multiorgan dysfunction syndrome; ARDS – Acute respiratory distress syndrome; COPD – Chronic obstructive pulmonary disease; CLD – Chronic liver disease; CVA – Cerebrovascular accidents; AKI – Acute kidney injury; CKD – Chronic kidney disease

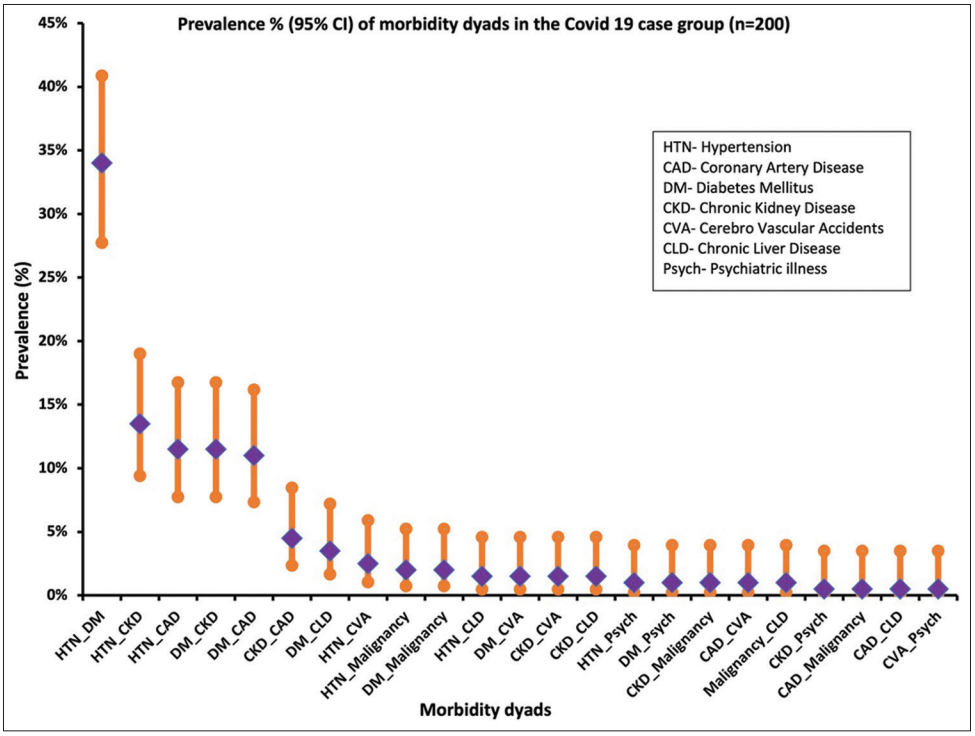

Figure 1: Multi-morbidity Burden among cases

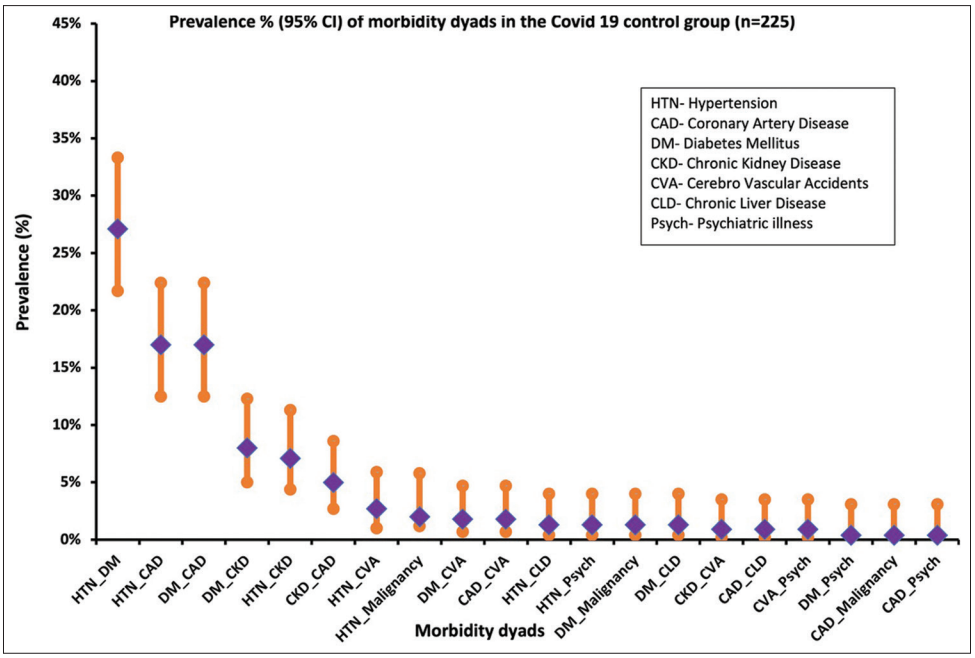

Figure 2: Multi-morbidity Burden among Controls

Table 3: Univariate analysis and binomial logistic regression for finding factors associated with COVID-19 mortality

Univariate analysis to find factors associated with mortality				
Variable	**Cases *n*=200 (%)**	**Controls *n*=225 (%)**	**Odds ratio (95% confidence interval)**	***P****
Hypertension	92 (46%)	102 (45.3%)	1.03 (0.7–1.5)	0.89
Diabetes mellitus	106 (53%)	117 (52%)	1.04 (0.7–1.5)	0.84
Chronic kidney disease (CKD)	40 (20%)	24 (10.7%)	2.09 (1.2–3.6)	0.007
Cardio vascular disease (CVD)	46 (23%)	63 (28%)	0.77 (0.5–1.2)	0.24
Cerebro vascular accident (CVA)	10 (5%)	7 (3.1%)	1.64 (0.6–4.4)	0.32
Malignancy	19 (9.5%)	8 (3.6%)	2.85 (1.2–6.7)	0.01
Chronic liver disease (CLD)	13 (6.5%)	6 (2.7%)	2.54 (0.9–6.8)	0.06
Psychiatric illness	5 (2.5%)	6 (2.7%)	0.94 (0.3–3.1)	0.72
Multimorbidity	101 (50.5%)	91 (40.4%)	1.5 (1.02–2.2)	0.038
Binomial Logistic Regression analysis for finding predictors of mortality				
Model 1 – Only single diseases as predictor variables				
Variable	**Adjusted Odd's Ratio (95% confidence interval)**			***P***
Chronic kidney disease	2.18 (1.24–3.83)			0.007
Malignancy	3.05 (1.27–7.32)			0.013
Chronic liver disease	2.55 (0.98–7.0)			0.07
P value of model is 0.009, Cox & Snell *R* Square=0.047, Nagelkerke *R* Square=0.062				
Model 2 – Two disease (multimorbidity) combinations as predictor variables				
Variable	**Adjusted odd's ratio (95% confidence interval)**			***P***
Hypertension & diabetes mellitus	1.68 (1.02–2.76)			0.043
Hypertension & chronic kidney disease	3.49 (1.01–12.01)			0.048
P value of model is 0.013, Cox & Snell *R* Square=0.033, Nagelkerke *R* Square=0.044				

or a significant contributing condition, similar to death certificate-based studies conducted by the CDC USA.[21] Meticulous adherence to ICD codes during death certification is essential for understanding the immediate and distal determinants of mortality in any disease. But we noticed that no differentiation has been made between the immediate and antecedent causes during the death certification process of these COVID-19 patients which was a stumbling block in understanding the immediate causes of death.

A high burden of comorbidities and organ damage has been reported in expired patients from the initial days of the pandemic itself.[22] Most of the deaths in the present study have been certified as covid pneumonia depending on the clinical, laboratory and radiological findings. However, histopathological analysis during autopsies in other settings has revealed inconsistent findings like pulmonary embolism, alveolar haemorrhage and vasculitis indicating the need for detailed pathological analysis in at least a subset of the subjects.[23] Apart from Covid pneumonia,

various acute organ injuries were found to be the causes of death. Acute kidney and lung injuries were found to be relevant causes echoing similar findings from a large meta-analysis.[24] However, the causes of acute kidney injury could range from prerenal azotemia to thrombotic microangiopathies depending on individual patients, geographical regions and length of hospital stay.[25] Acute cardiac injury, which is a significant risk factor,[24] was found to be mentioned in various forms like acute coronary syndrome, coronary artery disease, acute myocardial disease and likewise. Comorbidities like hypertension,[26,27] diabetes mellitus,[3,28] CVD,[5,29] CKD,[5] CLD[30,31] and malignancy[32] are also implicated in increased mortality across various settings. CKD and malignancy were significantly more among high-risk individuals, even adjusting for other comorbidities, as was seen from a retrospective cohort study conducted in similar resource-limited settings in Bangladesh.[32] Risk of mortality among CLD patients was also significant in univariate analysis. The risk of ventilation did not vary between the study groups, contrary to findings from the meta-analysis.[5]

The study explores the role of multimorbidity in COVID-19 mortality which is a minimally documented domain in India. A study conducted in Brazil found a significant association between covid 19 mortality and multimorbidity (defined as more than one morbidity) with aOR 3.63 (3.16-4.17).[33] Combinations of hypertension with diabetes mellitus and CKD were found to be significant multimorbidity in COVID 19-related deaths in our study. The occurrence of CKD with hypertension (HTN) as the significant multimorbidity dyad in the present study could be due to the higher prevalence of hypertension (35%) in the state of Kerala compared to diabetes (20%).[34] Chudasama *et al.*[35] developed a multimorbidity index to analyse the association between severe SARS CoV2 infection (indicated by hospitalization or death) and multimorbidity to find the combination of HTN and stroke, diabetes and HTN, CKD and HTN as the most prevalent multimorbidity combination associated with severe illness and the highest risk was for CKD with DM (4.93 [95% CI 3.36, 7.22]). Similarly, a Columbian study analysing 1488 Covid deaths determined the combination of hypertension and diabetes as the most prevalent morbidity dyad across all age groups and higher prevalence of morbidities as the age increases except for obesity which was fatal in young age groups.[36]

The high burden of NCDs was flagged to be a significant risk factor for Kerala from the initial days of the pandemic itself. Robust reverse quarantine mechanisms for protecting the elderly and those with comorbidities were implemented comprehensively at the grass-root levels.[37,38] Such measures could have prevented the excess deaths due to these common NCDs leading to an unidentifiable difference in mortality in this study. The lack of a significant association with individual diseases like diabetes mellitus and hypertension could also have been due to the broad spectrum of presentation from mild to severe illness. The present study was not designed to capture the effect of mild diabetes or hypertension on COVID-19, as most of these patients would have remained at home without getting hospitalized. However, individuals with malignancies and CKDs tend to be hospitalized immediately when diagnosed with COVID-19.

Our study also reports one-third of the survivors reporting post covid symptoms within one month of hospital discharge. This is less than a meta-analysis reporting 63.2, 71.9 and 45.9% post-COVID-19 symptoms at 30, 60 or ≥ 90 days after onset/hospitalization.[39] The need for periodic monitoring and evaluation of these post covid individuals assumes a higher priority.

Strengths and Limitations

Temporal matching of cases and controls was done to reduce the unidentified effects of any virus strain differences that might have occurred during the pandemic. The recruitment of cases and controls from all three major institutions to which patients are referred from the district improved the generalizability of the study and reduced potential biases. Meticulous follow-up of patients with decentralized tracking and testing system has ensured that unidentified deaths were minimal or negligible during the phase of the pandemic when study was conducted. But the sample size of the study may not be sufficient to estimate the risk of less frequent morbidities as the study was more focused on the combination of morbidities rather than individual morbidities. The findings cannot be generalized to all COVID-19 patients, as a majority of patients with mild symptoms would never have been hospitalized. Comparison of baseline details of 26 excluded cases (due to absence of comorbidity data) showed no significant difference from the 200 cases included in the analysis. Hence, they could be considered missing at random with only minimal effect on the overall study.

Impact of the study

Understanding the determinants of mortality is a crucial step in reducing mortality due to SARS CoV2 by identifying high-risk patients. As co-morbidity pattern varies across populations, understanding the immediate cause of death and multimorbidity burden among those infected with SARS CoV2 in Indian settings will be essential for making policy decisions. With occurrence of periodic COVID-19 waves and multiple rounds of Covid-19 vaccinations, it is essential that the exact causes of death are captured so as to aid clinicians in prioritizing their patients.

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Conflicts of interest

There are no conflicts of interest.

References

1. Lim ZJ, Subramaniam A, Ponnapa Reddy M, Blecher G, Kadam U, Afroz A, *et al.* Case fatality rates for patients with covid-19 requiring invasive mechanical ventilation. A meta-analysis. Am J Respir Crit Care Med 2021;203:54–66.
2. Chidambaram V, Tun NL, Haque WZ, Majella MG, Sivakumar RK, Kumar A, *et al.* Factors associated with disease severity and mortality among patients with COVID-19: A systematic review and meta-analysis. PLoS One 2020;15:e0241541.
3. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, *et al.* Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes Metab Syndr 2020;14:535–45.
4. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: Systematic review, meta-analysis, and public policy implications. Eur J Epidemiol 2020;35:1123–38.
5. Nandy K, Salunke A, Pathak SK, Pandey A, Doctor C, Puj K, *et al.* Coronavirus disease (COVID-19): A systematic review and meta-analysis to evaluate the impact of various comorbidities on serious events. Diabetes Metab Syndr 2020;14:1017–25.
6. Russell CD, Lone NI, Baillie JK. Comorbidities, multimorbidity and COVID-19. Nat Med 2023;29:334–43.
7. MCCD_Report-2018.pdf. Available from: https://censusindia.gov.in/2011-Documents/mccd_Report1/MCCD_Report-2018.pdf. [Last accessed on 6 Nov 2021].
8. Nyondo T, Msigwa G, Cobos D, Kabadi G, Macha T, Karugendo E, *et al.* Improving quality of medical certification of causes of death in health facilities in Tanzania 2014–2019. BMC Health Serv Res 2021;21:214.
9. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression. J Renin Angiotensin Aldosterone Syst 2020;21:1470320320926899.
10. C R, Jeemon P. Prevalence and patterns of multi-morbidity in the productive age group of 30-69 years: A cross-sectional study in Pathanamthitta District, Kerala. Wellcome Open Res 2020;5:233.
11. India State-Level Disease Burden Initiative Collaborators. Nations within a nation: Variations in epidemiological transition across the states of India, 1990-2016 in the Global Burden of Disease Study. Lancet 2017;390:2437–60.
12. Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, *et al.* Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: A rapid systematic review and meta-analysis. PLoS One 2020;15:e0233147.
13. Vaman RS, Valamparampil MJ, Ramdas AV, Manoj AT, Varghese B, Joseph F. A confirmed case of COVID-19 among the first three from Kerala, India. Indian J Med Res 2020;151:493–4.
14. Vaman RS, Valamparambil MJ, V RA, T MA, Varghese B, Joseph F. Development of a district level multifaceted first-response strategy to COVID-19 in a resource limited setting in Kerala, India. Int J Community Med Public Health 2020;7:3735–9.
15. Guidelines-Treatment-Protocol-April-2021-merged.pdf. Available from: https://dhs.kerala.gov.in/wp-content/uploads/2021/04/Guidelines-Treatment-Protocol-April-2021-merged.pdf. [Last accessed on 2021 Nov 14].
16. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp; 2017.
17. Centre advises States to conduct State-specific Sero Surveys in consultation with ICMR to generate district-level data on sero-prevalence. Ministry of Health and Family Welfare. 2021. Available from: https://pib.gov.in/pib.gov.in/Pressreleaseshare.aspx?PRID=1739902. [Last accessed on 2021 Aug 29].
18. Faes C, Abrams S, Van Beckhoven D, Meyfroidt G, Vlieghe E, Hens N. Time between symptom onset, hospitalisation and recovery or death: Statistical analysis of Belgian COVID-19 patients. Int J Environ Res Public Health 2020;17:7560.
19. Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, B. Pearson CA, *et al.* COVID-19 length of hospital stay: A systematic review and data synthesis. BMC Med 2020;18:270.
20. Thiruvengadam G, Lakshmi M, Ramanujam R. A study of factors affecting the length of hospital stay of covid-19 patients by cox-proportional hazard model in a South Indian tertiary care hospital. J Prim Care Community Health 2021;12:21501327211000230.
21. Gundlapalli AV, Lavery AM, Boehmer TK, Beach MJ, Walke HT, Sutton PD, *et al.* Death certificate-based ICD-10 diagnosis codes for COVID-19 mortality surveillance-United States, January-December 2020. MMWR Morb Mortal Wkly Rep 2021;70:523–7.
22. Zhang B, Zhou X, Qiu Y, Song Y, Feng F, Feng J, *et al.* Clinical characteristics of 82 cases of death from COVID-19. PLoS One 2020;15:e0235458.
23. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, *et al.* Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology 2020;77:198–209.
24. Wu T, Zuo Z, Kang S, Jiang L, Luo X, Xia Z, *et al.* Multi-organ dysfunction in patients with coviD-19: A systematic review and meta-analysis. Aging Dis 2020;11:874–94.
25. Ng JH, Bijol V, Sparks MA, Sise ME, Izzedine H, Jhaveri KD. Pathophysiology and Pathology of Acute Kidney Injury in Patients With COVID-19. Adv Chronic Kidney Dis 2020;27:365–76.
26. Liang X, Shi L, Wang Y, Xiao W, Duan G, Yang H, *et al.* The association of hypertension with the severity and mortality of COVID-19 patients: Evidence based on adjusted effect estimates. J Infect 2020;81:e44–7.
27. Mubarik S, Liu X, Eshak ES, Liu K, Liu Q, Wang F, *et al.* The Association of hypertension with the severity of and mortality from the covid-19 in the early stage of the epidemic in Wuhan, China: A multicenter retrospective cohort study. Front Med (Lausanne) 2021;8:623608.
28. Hui Y, Li Y, Tong X, Wang Z, Mao X, Huang L, *et al.* The risk factors for mortality of diabetic patients with severe COVID-19: A retrospective study of 167 severe COVID-19 cases in Wuhan. PLoS One 2020;15:e0243602.
29. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: From basic mechanisms to clinical perspectives. Nat Rev Cardiol 2020;17:543–58.
30. Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, *et al.* Outcomes following SARS-CoV-2

infection in patients with chronic liver disease: An international registry study. J Hepatol 2021;74:567–77.

31. Dorjee K, Kim H, Bonomo E, Dolma R. Prevalence and predictors of death and severe disease in patients hospitalized due to COVID-19: A comprehensive systematic review and meta-analysis of 77 studies and 38,000 patients. PLoS One 2020;15:e0243191.
32. Islam MZ, Riaz BK, Islam ANMS, Khanam F, Akhter J, Choudhury R, *et al.* Risk factors associated with morbidity and mortality outcomes of COVID-19 patients on the 28th day of the disease course: A retrospective cohort study in Bangladesh. Epidemiol Infect 2020;148:e263.
33. Mascarello KC, Vieira ACBC, Souza ASS de, Marcarini WD, Barauna VG, Maciel ELN. COVID-19 hospitalization and death and relationship with social determinants of health and morbidities in Espírito Santo State, Brazil: A cross-sectional study. Epidemiol Serv Saude 2021;30:e2020919.
34. Sarma PS, Sadanandan R, Thulaseedharan JV, Soman B, Srinivasan K, Varma RP, *et al.* Prevalence of risk factors of non-communicable diseases in Kerala, India: Results of a cross-sectional study. BMJ Open 2019;9:e027880.
35. Chudasama YV, Zaccardi F, Gillies CL, Razieh C, Yates T, Kloecker DE, *et al.* Patterns of multimorbidity and risk of severe SARS-CoV-2 infection: An observational study in the U.K. BMC Infect Dis 2021;21:908.
36. Fernández-Niño JA, Guerra-Gómez JA, Idrovo AJ. Multimorbidity patterns among COVID-19 deaths: Proposal for the construction of etiological models. Rev Panam Salud Publica 2020;44:e166.
37. Menon JC, Rakesh P, John D, Thachathodiyl R, Banerjee A. What was right about Kerala's response to the COVID-19 pandemic? BMJ Glob Health 2020;5:e003212.
38. Raveendran AV, Jayadevan R. Reverse quarantine and COVID-19. Diabetes Metab Syndr 2020;14:1323–5.
39. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Florencio LL, Cuadrado ML, Plaza-Manzano G, *et al.* Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. Eur J Intern Med 2021;92:55–70.