OXFORD

QJM: An International Journal of Medicine, 2023, 47–56

https://doi.org/10.1093/qjmed/hcac202
Advance Access Publication Date: 2 September 2022
Original paper

ORIGINAL PAPER

Vaccination saves lives: a real-time study of patients with chronic diseases and severe COVID-19 infection

A. Mukherjee[1,†], G. Kumar[1,†], A. Turuk[1], A. Bhalla[2], T.C. Bingi[3], P. Bhardwaj[4], T.D. Baruah[5], S. Mukherjee[6], A. Talukdar[7], Y. Ray[8], M. John[9], J.R. Khambholja[10], A.H. Patel[11], S. Bhuniya[12], R. Joshi[13], G.R. Menon[14], D. Sahu[14], V.V. Rao[14], B. Bhargava[1] and S. Panda[1], The NCRC Study Team[‡]

From the [1]Indian Council of Medical Research, New Delhi, India, [2]Postgraduate Institute of Medical Education & Research, Chandigarh, India, [3]Gandhi Medical College, Telangana, India, [4]All Indian Institute of Medical Sciences, Jodhpur, Rajasthan, India, [5]All Indian Institute of Medical Sciences, Raipur, Chhattisgarh, India, [6]College of Medicine, Sagore Dutta Hospital, Kolkata, West Bengal, India, [7]Medical College, Kolkata, West Bengal, India, [8]Infectious Disease and Beliaghata General Hospital, Kolkata, West Bengal, India, [9]Christian Medical College, Ludhiana, Punjab, India, [10]Smt. NHL, Municipal Medical College, Ahmedabad, Gujarat, India, [11]CIMS Hospital, Ahmedabad, Gujarat, India, [12]All India Institute of Medical Sciences, Bhubaneswar, Odisha, India, [13]All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India and [14]National Institute of Medical Statistics, Indian Council of Medical Research, Delhi, India

Address correspondence to Dr S. Panda, Indian Council of Medical Research, New Delhi, India. email: samiranpanda.hq@icmr.gov.in

[†]These authors contributed equally to this work.

[‡]The members of the NCRC Study Team are listed in Acknowledgements section.

Summary

Objectives: This study aims to describe the demographic and clinical profile and ascertain the determinants of outcome among hospitalized coronavirus disease 2019 (COVID-19) adult patients enrolled in the National Clinical Registry for COVID-19 (NCRC).

Methods: NCRC is an on-going data collection platform operational in 42 hospitals across India. Data of hospitalized COVID-19 patients enrolled in NCRC between 1st September 2020 to 26th October 2021 were examined.

Results: Analysis of 29 509 hospitalized, adult COVID-19 patients [mean (SD) age: 51.1 (16.2) year; male: 18 752 (63.6%)] showed that 15 678 (53.1%) had at least one comorbidity. Among 25 715 (87.1%) symptomatic patients, fever was the commonest symptom (72.3%) followed by shortness of breath (48.9%) and dry cough (45.5%). In-hospital mortality was 14.5% ($n = 3957$). Adjusted odds of dying were significantly higher in age group $\geq$60 years, males, with diabetes, chronic kidney diseases, chronic liver disease, malignancy and tuberculosis, presenting with dyspnoea and neurological symptoms. WHO ordinal scale 4 or above at admission carried the highest odds of dying [5.6 (95% CI: 4.6–7.0)]. Patients receiving one [OR: 0.5 (95% CI: 0.4–0.7)] or two doses of anti-SARS CoV-2 vaccine [OR: 0.4 (95% CI: 0.3–0.7)] were protected from in-hospital mortality.

Received: 4 July 2022; **Revised (in revised form):** 16 August 2022

Conclusions: WHO ordinal scale at admission is the most important independent predictor for in-hospital death in COVID-19 patients. Anti-SARS-CoV2 vaccination provides significant protection against mortality.

Introduction

Globally, and in India, the pandemic of SARS-CoV-2 has resulted in unprecedented morbidity and mortality with a detrimental effect on healthcare systems and economies. As a response to the pandemic, the 'National Clinical Registry for COVID-19' was initiated by the Indian Council of Medical Research (ICMR) in September 2020, with a broad objective to collect good quality, real-time data for evidence-based decision-making in clinical practice, public health program and policy.

Hospital mortality among coronavirus disease 2019 (COVID-19) patients has varied from 19% to 39% across various studies.[1–6] It has been observed that men, elderly (>60 years of age), and those with comorbidities such as asthma, chronic obstructive pulmonary disease, tuberculosis (TB), pneumonia, diabetes mellitus, hypertension, renal, hepatic and cardiac diseases and individuals with a history of smoking or substance use, history of kidney transplant are at higher risk of developing severe disease or progression to death. The factors associated with such outcomes have been varied; older age being consistent among many populations while others varied amongst studies.[1–8]

Indian investigations have reported an association of old age, presence of diabetes mellitus, presence of severe acute respiratory infection, raised inflammatory markers including interleukin-6, ferritin, lactate dehydrogenase and d-dimer with the progression of COVID and/or related in-hospital mortality.[9–12] Majority of these studies enrolled a small number of participants located at a single centre. Here, we present data from a large cohort of hospitalized COVID-19 patients from 42 hospitals across the country.

The aim of this analysis is to study the demographic profile, clinical characteristics, and outcomes among hospitalized COVID-19 adult patients, enrolled in the National Clinical Registry for COVID-19 (NCRC) and to ascertain the factors associated with predefined outcomes.

Methods

The National Clinical Registry for COVID-19 (NCRC) is a platform for on-going prospective data collection, developed and maintained by ICMR in collaboration with the Ministry of Health & Family Welfare (MOHFW), Government of India, All India Institute of Medical Sciences, New Delhi (AIIMS) and the ICMR-National Institute of Medical Statistics (NIMS). The structure and protocol of the registry are available in the public domain (https://www.icmr. gov.in/tab1ar1.html). A hub and spoke model has been adopted for this registry. In the beginning, an expression of intent was invited for participation in the registry network; willing hospitals were screened based on a site feasibility matrix. A steering committee with subject experts guides the conduct of the registry and suggests solutions to roadblocks, if any. A monitoring committee consisting of institutional principal investigators oversees the progress of the registry and explores newer ideas and initiatives, to keep the registry dynamic. The central implementation team at ICMR headquarters remains responsible for the overall execution of the project.

Across the network of NCRC, participating hospitals recruited consecutive in-patients, who had COVID-19 infection confirmed by real-time polymerase chain reaction, nucleic acid amplification test or rapid antigen test. Demographic, clinical and outcome data are collected in an on-going manner by the NCRC network. A dedicated team at the respective sites is responsible for data collection and data entry under the supervision of the institutional primary investigator and the central implementation team at ICMR. All the researchers were trained by the central implementation team at ICMR via an online platform. Regular refresher trainings are conducted in order to minimize errors and to address the gaps created by change of personnel in the teams.

Data are collected using a pre-structured case report form (CRF) and is entered into an electronic portal, which has been developed and is being maintained by the ICMR-NIMS, Delhi. The CRFs include socio-demographic information, symptom and comorbidity profile at the baseline, clinical examination findings at the time of admission and on alternate days during the course of hospital stay, results of laboratory investigations conducted as per the treating physician and the outcomes of the hospital stay.

The database platform is hosted on a secure server and is audited by the National Informatics Centre (NIC). Information contained in the database, the configuration of the information within the database, as well as the database itself are fully encrypted. Every client–server data transfer is encrypted through a valid certificate. Data loss is prevented by frequent backup runs.

Data analysis

Socio-demographic, clinical, laboratory and hospital outcome data were analysed; categorical data presented as frequency and proportions and continuous data as mean (standard deviation) or median (inter-quartile range), as appropriate. Logistic regression model was used to determine the factors associated with the outcome of the patients. For the purpose of outcome analysis, death was defined as death due to any cause of a COVID-19-positive patient occurring during hospital stay. Patients who were transferred to another hospital or left against medical advice were excluded from the outcome analyses, though their baseline characteristics were analysed. Age, gender, body mass index, pre-existing comorbidities, lag between symptom onset and admission, laboratory parameters at admission including lactate dehydrogenase (LDH), ferritin, d-dimer, C-reactive protein (CRP) and neutrophil to lymphocyte ratio (NLR), severity assessment by WHO ordinal scale[13] and status of anti-covid19 vaccination were used as explanatory variables in univariate analysis. Chi-square test, *t*-test or rank sum test was used to examine the association between explanatory variables and outcome, as appropriate. The variables with the significant association and those with known clinical or contextual importance were included in the multivariate logistic regression model. As laboratory values were available for a limited number of participants, separate models were used for each of the biomarkers. Data analysis was carried out using STATA v14 (College Station, TX, USA).

Ethical aspects

Approval was obtained from the Central Ethics Committee for Human Research at ICMR as well as from the respective Institutional Ethics Committee of each of the participating centres. Considering the observational nature of the registry, and the collection of anonymized data being done primarily from the routine case records of the patients, a waiver of consent was granted by the Ethics Committees.

Results

We present here an analysis of 29 509 hospitalized COVID-19 patients over the age of 18 years who were enrolled in NCRC from 1st September 2020 till 26th October 2021. The mean ± SD age of the study population was 51.1 ± 16.2 years; men (51.1 ± 16 years) being similar to that of women (51 ± 16.5 years). Almost three-fourth of the participants were at 40 years of age or above and two-thirds of the study participants in this group were men. The mean ± SD body mass index of the participants was 24.8 ± 4.1 kg/m^2, with one-third of the participants being within normal range, while over 64% were obese or overweight (Table 1). Four percent of the enrolled study participants were health care workers.

Of the 29 509 patients enrolled, 3794 (12.9%) were asymptomatic at the time of admission and were admitted due to conditions other than COVID-19 and later diagnosed to have COVID-19 or developed COVID-19 during the course of hospitalization. Among 25 715 (87.1%) patients who were admitted with symptoms, fever was the most common symptom (72.3%). Shortness of breath and dry cough was recorded in 48.9% and 45.5% of patients, respectively. Some of the other symptoms were fatigue (20.7%), cough with sputum (14.5%), sore throat (13.5%), muscle ache (12.3%) and headache (11.2%) (Supplementary Figure S1).

Median haemoglobin, leucocytes count, neutrophils and lymphocytes were largely within normal limits while the inflammatory markers were raised (Table 1).

No comorbidities were present in 13 831 (46.9%) patients; 15 678 (53.1%) participants had at least one comorbidity. Hypertension and diabetes mellitus were the commonest comorbidities reported among 32.4% and 26.2% of patients, respectively. Chronic cardiac disease and chronic kidney disease were present among 5.7% and 3.6% of the study participants, respectively. Other diseases including asthma, malignancy, chronic pulmonary disease, chronic liver disease, stroke, TB, chronic neurological disease, rheumatologic disease, autoimmune disease and haematological disorders, HIV infection, Hepatitis B and Hepatitis C infection were each reported in <2% of patients (Figure 1).

The most commonly used drugs were anticoagulants and steroids administered to 60.9% and 60% of patients, respectively. Doxycycline, ivermectin, remdesivir and azithromycin were the other commonly used drugs, while hydroxychloroquine, oseltavimir, favipiravir, IL-6 inhibitors including tocilizumab or itolizumab and convalescent plasma each was administered to <5% of patients. More than half of the admitted patients (15 922, 54%) required oxygen support during their hospital course, while 2307 (7.8%) required mechanical ventilation (Supplementary Table S1).

Figure 2 shows the monthly trend of selected therapies since the inception of the registry. A marked increase is noticeable in the use of steroid, oxygen supplementation and remdesivir in May 2021, coinciding with the second wave of the pandemic in India dominated by the delta variant of SARS-CoV-2 infection. The use of hydroxychloroquine considerably declined after September 2020, while the use of convalescent plasma has been low throughout.

Outcome data on death or discharge were available for 27 251 patients; 689 patients who left against medical advice and 1569 patients transferred to other hospitals were excluded from the outcome analysis. In-hospital deaths were reported in 3957 (14.5%) participants and 23 294 (85.5%) were discharged. The median duration (IQR) of hospital stay among the study participants was 7 (5–10) days; 7 (5–10) days among those discharged and 6 (2, 10) days among those who expired (P = <0.001). Out of the 3957 patients who expired, 3418 (86.4%) died within the first 14 days of hospital stay and 539 (13.6%) died after 14 days of hospital admission.

Table 1. Demographic, symptom and laboratory profile at the time of admission (n = 29 509)

Characteristic	Values
Age groups	
18–39 years	7742 (26.2)
40–59 years	11 664 (39.5)
60 year and above	10 103 (34.2)
Gender	
Male	18 752 (63.6)
Female	10 754 (36.4)
Transgender	3 (0.01)
Patients who had taken at least one dose of anti-SARS CoV-2 vaccine, n = 7438	909 (12.2)
BMI, kg/m^2, mean ± SD, n = 12 046[a]	24.8 ± 4.1
Underweight	361 (3)
Normal	3863 (32.1)
Overweight	2765 (22.9)
Obese	5057 (42)
Symptom onset to admission in days, Median (IQR)	4 (2–6)
Total bilirubin, mg/dl median (IQR), n = 15 091	0.6 (0.4–0.8)
Hemoglobin, g/dl (mean ± SD), n = 18 506	12.2 ± 2.2
WBC count (Cells/mm^3), median (IQR), n = 18 171	7400 (5200–11 000)
Neutrophils, %, median (IQR), n = 16 053	76.5 (65.5–85)
Lymphocytes, %, median (IQR), n = 15 971	17 (10–26.6)
Neutrophil to lymphocyte ratio (NLR), median (IQR), n = 15 942	4.4 (2.5–8.5)
Platelet count, 1000s/ml^3 median (IQR), n = 18 089	212 (158–278)
Ferritin, ng/ml, median (IQR), n = 7166	2059 (1019–3192)
LDH, IU/l, median (IQR), n = 8515	400 (265–649)
CRP, mg/dl, median (IQR), n = 9962	32 (7.7–90.3)
IL-6, pg/ml median (IQR), n = 2192	17 (5.8–53.3)
D-Dimer, mg/l, median (IQR), n = 8142	0.6 (0.3–1.9)
WHO ordinal scale on Day 1 of admission, = 26 909	
3	13 860 (51.5)
4	9864 (36.7)
5	2580 (9.6)
6	526 (2)
7	79 (0.3)

Values expressed in n (%) unless specified.
[a]Underweight: <18.5 kg/m^2, normal weight: 18.5–22.9 kg/m^2, overweight: 23–24.9 kg/m^2, obese: ≥25 kg/m^2. Ref: WHO Expert Consultation Group.[14]

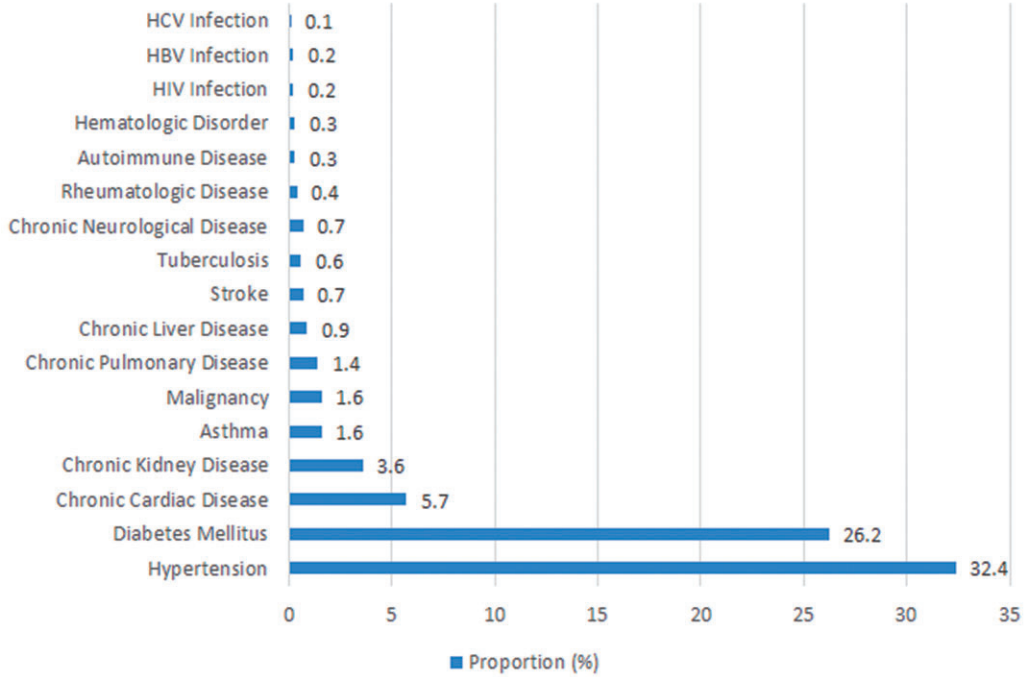

Figure 1. Comorbidity profile of patients, $n = 29\,509$. HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

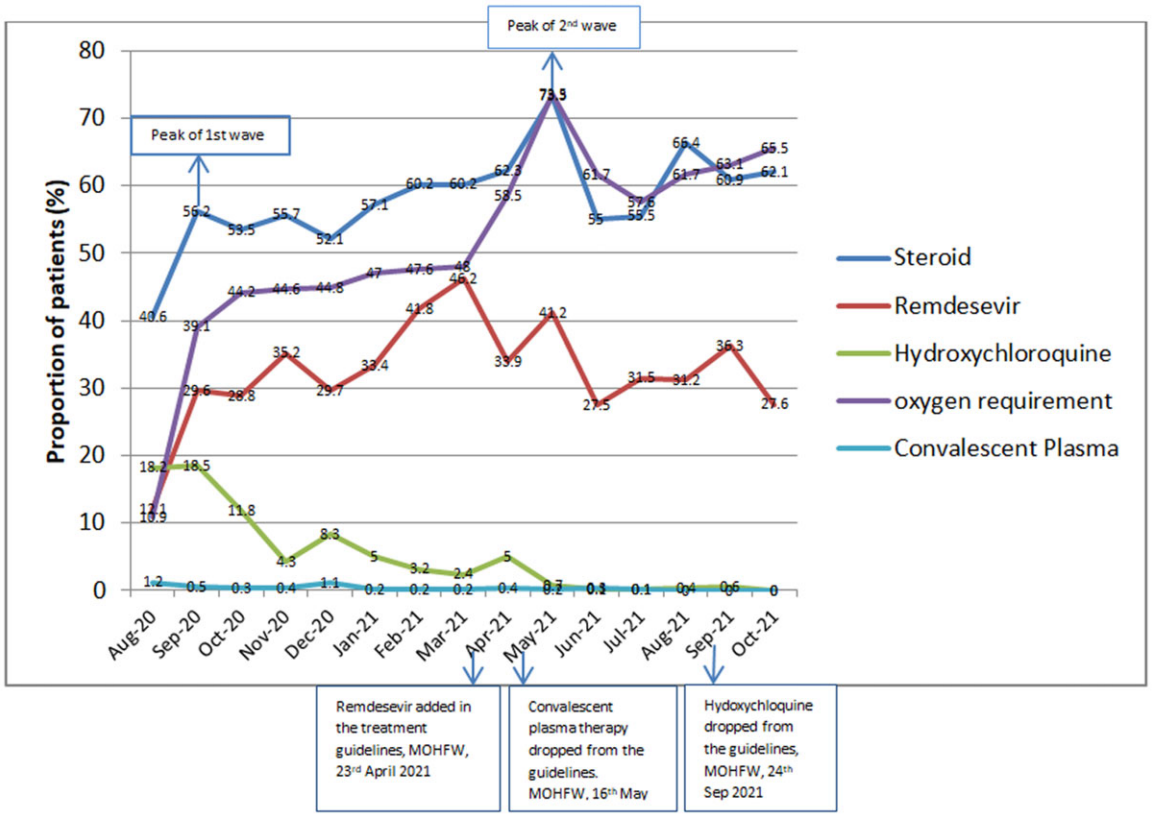

Figure 2. Trends of selected drugs and oxygen requirements.

Table 2 shows the association of baseline factors with in-hospital mortality in univariate analysis. Age ≥ 40 years, male gender, comorbidities such as diabetes mellitus, hypertension, chronic cardiac disease, chronic kidney disease, chronic liver disease, malignancy, stroke, and TB as well as respiratory (fast or difficult breathing) or neurological symptoms (altered

Table 2. Proportional mortality among hospitalized COVID-19 patients

Characteristic	Mortality (%)	Odds ratio (95% CI)	*P*-value[a]
Age			
18–39 years ($n = 7169$)	529 (7.4)	(Reference)	–
40–59 years ($n = 10\,760$)	1455 (13.5)	2 (1.8–2.2)	<0.001
60+ years ($n = 9322$)	1973 (21.2)	3.4 (3.0–3.7)	<0.001
Gender			
Male ($n = 17\,240$)	2613 (15.2)	1.2 (1.1–1.2)	<0.001
Female ($n = 10\,008$)	1344 (13.4)	(Reference)	–
Vaccinated with anti-SARS CoV-2 vaccine			
Unvaccinated ($n = 5964$)	1306 (21.9)	(Reference)	
Vaccinated with one dose ($n = 550$)	85 (15.5)	0.7 (0.5–0.8)	<0.001
Vaccinated with two doses ($n = 305$)	29 (9.5)	0.4 (0.3–0.6)	<0.001
Diabetes mellitus			
Yes ($n = 7126$)	1397 (19.6)	1.7 (1.6–1.8)	<0.001
No ($n = 20\,125$)	2560 (12.7)	(Reference)	
Hypertension			
Yes ($n = 8872$)	1686 (19)	1.7 (1.6–1.8)	<0.001
No ($n = 18\,379$)	2272 (12.4)	(Reference)	
Chronic cardiac disease			
Yes ($n = 1519$)	296 (19.5)	1.5 (1.3–1.7)	<0.001
No ($n = 25\,732$)	3661 (14.2)		
Chronic kidney disease			
Yes ($n = 934$)	323 (34.6)	3.3 (2.9–3.8)	<0.001
No ($n = 26\,317$)	3634 (13.8)	(Reference)	
Chronic liver disease			
Yes ($n = 250$)	80 (32)	2.8 (2.1–3.7)	<0.001
No ($n = 27\,001$)	3877 (14.4)	(Reference)	
Malignancy			
Yes ($n = 413$)	89 (21.6)	1.6 (1.3–2.1)	<0.001
No ($n = 26\,838$)	3868 (14.4)	(Reference)	
Stroke			
Yes ($n = 190$)	64 (33.7)	3.0 (2.2–4.1)	<0.001
No ($n = 27\,061$)	3893 (14.4)	(Reference)	
Tuberculosis			
Yes ($n = 169$)	41 (24.3)	1.9 (1.3–2.7)	<0.001
No ($n = 27\,082$)	3916 (14.5)	(Reference)	
Shortness of breath or fast breathing at admission			
Yes ($n = 11\,798$)	2772 (23.5)	3.7 (3.4–4.0)	<0.001
No ($n = 15\,453$)	1185 (7.7)	(Reference)	
Altered sensorium/seizures at admission			
Yes ($n = 412$)	185 (44.9)	5.0 (4.1–6.1)	<0.001
No ($n = 26\,839$)	3772 (14.1)	(Reference)	
Ordinal scale 4 or above at admission			
Yes ($n = 13\,860$)	3101 (26.3)	10.3 (9.2–11.4)	<0.001
No ($n = 13\,049$)	433 (3.4)	(Reference)	
BMI			
Underweight and normal ($n = 3944$)	387 (9.8)	(Reference)	–
Overweight and obese ($n = 7307$)	766 (10.5)	1.1 (0.9–1.2)	0.26

[a]*P*-values calculated by bivariate logistic regression.

sensorium or seizures) at presentation and WHO ordinal scale of 4 and above were associated with higher mortality. Receipt of at least one dose of anti-SARS CoV-2 vaccine was associated with lower mortality as compared to the unvaccinated patients [114 (13.3%) vs. 1306 (21.9%), $P < 0.001$]. Median concentrations of random blood sugar, NLR, LDH, interleukin-6 (IL-6), CRP and D-dimer were significantly higher among the patients who died as compared to those who were discharged from hospital (Table 3).

On sub-group analysis of patients with diabetes mellitus, malignancy, TB and those admitted with WHO ordinal scale 4 and above, mortality among vaccinated was significantly lower in each individual subgroup. Among patients with liver disease and kidney disease, though the mortality was lower among the vaccinated but the difference was not statistically significant (not shown in table).

Factors that were significantly associated with mortality in univariate analysis and those which had clinical relevance were considered in the multivariate logistic models. Odds of in-hospital mortality was significantly and independently higher among patients ≥40 years, male gender, with diabetes mellitus, chronic kidney diseases, chronic liver disease, malignancy and TB, and those who presented with dyspnoea or neurological symptoms, after being adjusted for other comorbidities such as

Table 3. Median laboratory parameters among patients who died and those who survived

Laboratory parameter	Median (IQR)	P-value[a]
Haemoglobin, g/dl		
Among those who died ($n = 2160$)	12 (10.1–13.4)	<0.001
Among survivors ($n = 15\,098$)	12.5 (11.1–13.8)	
Random blood sugar,		
Among those who died ($n = 980$)	180 (132–255)	<0.001
Among the survivors ($n = 7003$)	138 (105–228)	
Neutrophil–lymphocyte ratio		
Among those who died ($n = 1762$)	10.7 (6.1–19)	<0.001
Among survivors ($n = 13\,156$)	3.9 (2.3–7.3)	
LDH, IU/l		
Among those who died ($n = 1021$)	690.6 (458–959)	<0.001
Among survivors ($n = 6962$)	365 (248–575)	
IL-6, pg/ml		
Among those who died ($n = 347$)	59.2 (21–180)	<0.001
Among survivors ($n = 1711$)	13 (4.7–36.7)	
CRP, mg/dl		
Among those who died ($n = 1231$)	84.3 (39.6–141.8)	<0.001
Among survivors ($n = 8156$)	25.1 (6.1–78.6)	
D-dimer, mg/l		
Among those who died ($n = 1007$)	1.6 (0.7–5.9)	<0.001
Among survivors ($n = 6658$)	0.5 (0.3–1.4)	
Symptom onset to admission		
Among those who died ($n = 21\,382$)	4 (2–6)	0.54
Among survivors ($n = 3502$)	4 (2–6)	

[a]P-values calculated by rank sum test.

Table 4. Adjusted odds ratio for determinants of hospital deaths using logistic regression

	Model 1 ($n = 6159$) Odds ratio (95% CI)
Age categories	
18–39 years	(Reference)
40–59 years	1.3 (1.1–1.6)
60 years and above	1.9 (1.6–2.3)
Gender (male)	1.3 (1.1–1.5)
Vaccinated with anti-SARS CoV-2 vaccine	
One dose	0.5 (0.4–0.7)
Two doses	0.4 (0.3–0.7)
Diabetes mellitus	1.4 (1.2–1.6)
Hypertension	0.9 (0.8–1.1)
Chronic cardiac disease	0.8 (0.6–1.0)
Chronic kidney disease	2.8 (2.0–3.7)
Chronic liver disease	2.4 (1.1–5.2)
Malignancy	1.9 (1.2–3.2)
Stroke	1.0 (0.5–2.3)
Tuberculosis	3.0 (1.5–6.1)
Shortness of breath or fast breathing	1.3 (1.1–1.5)
Altered sensorium/seizures	3.6 (2.4–5.4)
WHO ordinal scale 4 and above at admission	5.6 (4.6–7.0)

hypertension, chronic cardiac disease, stroke, severity at admission (WHO ordinal scale) and vaccination status. WHO ordinal scale being 4 and above at admission carried the highest odds of dying [5.6 (95% CI: 4.6, 7.0)]. Patients vaccinated with one and two doses of anti-SARS CoV-2 vaccine had significantly lower odds of dying [OR: 0.5 (95% CI: 0.4–0.7) for one dose and OR: 0.4 (95% CI: 0.3–0.7) for two doses] (Table 4).

Data available for various baseline laboratory parameters at baseline were limited (as described in Table 3). Hence, separate models were tested for each of these parameters. The odds ratio for all biomarkers including haemoglobin, LDH, IL-6 and CRP were statistically significant, but marginally over 1. The odds of death increased by 1.1 for each unit rise in baseline values of NLR and D-dimer separately [OR: 1.1 95% CI: 1.1–1.1] after adjusting for age, comorbidities and severity of the illness at admission. The logistic regression models (Model 2–8) that included laboratory values are presented in Supplementary Table S2. The area under the curve for ROC (AUC ROC) for NLR was 0.79 (95% CI: 0.78–0.80) and for D-dimer was 0.7 (0.68–0.71) (Supplementary Figure S2). Considering the optimal cut-off for NLR as 6.67, both the sensitivity and specificity to classify in-hospital death was 72%; a cut-off of 0.82 mg/l for baseline D-Dimer had a sensitivity and specificity 71% and 65%, respectively.

Discussion

Our study includes data from 29 509 hospitalized COVID-19 patients from 42 hospitals across the country. Apart from the often cited factors such as diabetes mellitus, male gender and advanced age, our study highlighted the association of other comorbidities such as chronic kidney disease, chronic liver disease, malignancy and TB with increased in-hospital mortality of COVID-19 patients in Indian settings. The importance of anti-SARS-CoV-2 vaccination in protecting against mortality was also evident from our analysis.

More than half of our study participants had at least one co-morbidity, most common being hypertension and diabetes mellitus. The proportion of COVID-19 in-patients having hypertension is similar to the overall population level frequency of hypertension recorded among adult Indians.[15] On the contrary, proportion of diabetics seem to be much higher in this cohort than the national average.[16] Multiple studies have confirmed that following SARS-CoV-2 infection, diabetics are more likely to be hospitalized as compared to non-diabetics, especially if there is poor glycaemic control.[17] Diabetes causes an inhibition in neutrophil chemotaxis, phagocytosis and intracellular destruction of microbes, thus offering efficient virus entry and decreased viral clearance.[18]

In our study, patients above 40 years of age had 1.3 times higher adjusted odds of dying than the younger patients, which increased to 2.1 times with advanced age $\geq$ 60 years. Advanced age, especially $\geq$ 60 years, is an established independent risk factor for dying in COVID-19 patients, as shown in various studies across multiple countries since the onset of the pandemic.[19,20] However, the working age population above 40 years of age also have been deeply affected as shown in our investigation. It would be prudent to include them in all preventive measures and triaging strategies for severity. Age-standardized mortalities for COVID-19 in India, analysed from the Integrated Disease Surveillance Programme special surveillance data, showed that along with the elderly above 60 years of age, the age group of 45–59 years were also affected.[21] This could be partly explained by the fact that forced expiratory volume is generally seen to decline after the age of 30–40 years.[22] Additionally, older age group is known to have a higher prevalence of chronic diseases, which could further attenuate the already dysregulated immune response.

Studies from various parts of India and the world have reported comorbidities in various combinations to be associated with in-patient mortality in COVID-19 patients.[23–27] Along with the more recognized risk factors such as diabetes mellitus, chronic kidney disease and malignancy, our investigation unearthed the independent association of chronic liver disease with higher odds of dying among COVID-19 in-patients. Another retrospective analysis from a single centre in South India linked chronic liver disease with in-hospital mortality of Covid-19 patients.[28] Increased systemic inflammation, immune dysfunction, coagulopathy and intestine dysbiosis are the hypothesized mechanisms. Important to note in this context is that, the pandemic has been associated with poor eating habits and increased alcohol intake, which might lead to an increase in the severity of liver diseases.[8,29,30]

The presence of TB (on-treatment TB) was an important factor associated with higher in-hospital mortality in our cohort. This finding carries a significant relevance in a high TB burden country like India. Increased severity and mortality have been reported in COVID-19 patients with TB in two meta-analyses which included only 26 and 34 Indian patients, respectively.[31,32] Our study provides more robust supportive evidence for the association of present TB status with COVID-19 mortality.

Severity of illness at admission as evident by presenting complaints of respiratory or neurological symptoms and WHO ordinal scale 4 or above had higher odds of dying in our registry participants. Similar observations have been reported from a few single-centre studies from India, where majority of non-survivors required early oxygen supplementation (oxygen requirement is at WHO ordinal scale 4 and above).[23,24]

The baseline laboratory markers including neutrophil–lymphocyte ratio (NLR), LDH, D-Dimer, IL-6 and CRP were higher among the non-survivors, though on multivariate analysis, the odds ratio was marginally above one with minimal clinical relevance, except for NLR and D-dimer. Previous studies have shown that raised biomarkers such as IL-6, CRP, LDH and NLR are associated with higher mortality.[33–36] Considering these markers are non-specific indicators of inflammation, the baseline values of IL-6, CRP or LDH seem to offer limited benefit in the meaningful prediction of mortality. NLR being a readily available marker can be used to prognosticate outcomes at admission as can D-Dimer. However, guidelines for clinical management from other countries have also stated that there is no consensus in the evidence supporting the use of any of the inflammatory markers or D-dimer at baseline to stratify the risk and decide therapeutics.[37]

Importantly, the current study underlined the protection provided by COVID-19 vaccination against in-hospital mortality. COVID-19 vaccine, irrespective of the type, reduced the odds of dying by 50% with one dose and by 60% with two doses. Other smaller, single-centre studies from both South and North India have demonstrated the effectiveness of COVID-19 vaccination in reducing mortality.[38,39] These findings along with mathematical modelling based projections[40] underscore the key role of vaccine in mitigating the impact of the COVID-19 pandemic and managing the burden it poses on the healthcare system.

Limitations

As this was a record-based study in hospitals maintaining paper-based records, the identification of symptoms, comorbidities, complications and laboratory parameters relied on the accuracy of the records maintained. Secondly, the patients who were transferred to other institutes or who had left against medical advice were not followed up and could not be included in mortality analysis as their outcomes were unknown.

Strengths

The current analysis from the National Clinical Registry for COVID-19, to the best of our knowledge, is the largest widely representative study to examine the association of demographic, clinical characteristics, and laboratory parameters with mortality among hospitalized COVID-19 patients in India. These data capture information from various geographical zones of India involving multiple centres.

Conclusion

The current investigation highlights the importance of age $\geq$ 40 years and comorbidities like chronic liver disease, and TB as predictors of in-patient mortality along with the oft-reported risk factors such as male gender, diabetes mellitus, chronic kidney disease, and baseline severity of illness. WHO ordinal scale 4 and above was an important independent factor associated with in-patient mortality. Interestingly, the baseline values of CRP, IL-6 and LDH offered little help in predicting the outcome, though NLR and D-dimer can be used to classify in-hospital outcomes with a sensitivity and specificity ranging from 65% to 72%. On an encouraging note, vaccination against COVID-19 clearly lowered the risk of dying from the disease and featured as an important tool in the armamentarium in our fight against the COVID-19 pandemic.

Supplementary material

Supplementary material is available at *QJMED* online.

Authors' contributions

S.P. is the guarantor. Study design, data analysis, data interpretation and manuscript writing team: A.M., G.K., A.T., A.B., T.C.B., P.B., T.D.B., S.M., A.T., Y.R., M.J., J.R.K., A.H.P., S.B., R.J., G.R.M., D.S., V.V.R., B.B., S.P. and A.A. Monitoring and conduct of the study: A.M., G.K., A.T., L.K.S., P.M. and Y.P. Patient enrolment, conduct of study, clinical care and data collection: A.B., T.C.B., P.B., T.D.B., S.M., A.T., Y.R., M.J., J.R.K., A.H.P., S.B., R.J., G.D.P., V.S., K.S., R.M., V.S.A., M.A.M., D.K., S.S., S.M., P.K.K., A.K., A.S., A.P., S.C., M.D., T.M., S.C., B.B., S.R.P., D.M., S.C., A.A., D.V., M.T., N.S., M.P., S.M., A.D., K.Y.L., M.R., C.G.S., U.K.O., R.R.J., A.K., A.P., A.S., M.P., L.S., M.R., A.D.S., L.K., P.P., N.D., S.D., J.S., A.M., L.P., J.P.S., S.S., V.K.K., A.K., N.Y., R.U., S.S., A.S., N.N.S., N.M.S., K.R., H.P., P.R.M., M.K.P., S.S., A.K., M.P., M.A., D.P., V.S., S.A., R.C., M.R., N.D., B.K.G., B.K., J.G., S.B., A.A., M.S., N.F., S.P., V.N., S.C., S.M., S.K.S., S.T., P.L., H.D., A.G., V.K., N.S., R.V., A.P., M.P.K., A.B.R., N.K., R.K., K.M., Y.S.R., A.M., J.C., M.C., R.K.B., M.A.M., S.K., P.S., S.G. and A.H.

Acknowledgements

P. Mishra[1], Y. Panchal[1], L.K. Sharma[2], A. Agarwal[3], G.D. Puri[4], V. Suri[4], K. Singla[4], R. Mesipogu[5], V.S. Aedula[5], M.A. Mohiuddin[5], D. Kumar[6], S. Saurabh[6], S. Misra[6], P.K. Kannauje[7], A. Kumar[7], A. Shukla[7], A. Pal[8], S. Chakraborty[8], M. Dutta[8], T. Mondal[9], S. Chakravorty[9], B. Bhattacharjee[9], S.R. Paul[10], D. Majumder[10], S. Chatterjee[10], A. Abraham[11], D. Varghese[11], M. Thomas[11], N. Shah[12], M. Patel[12], S. Madan[12], A. Desai[13], M.L. Kala Yadhav[14], R. Madhumathi[14], G.S.

Chetna[14], U.K. Ojha[15], R.R. Jha[15], A. Kumar[15], A. Pathak[16], A. Sharma[16], M. Purohit[16], L. Sarangi[17], M. Rath[17], A.D. Shah[18], L. Kumar[18], P. Patel[18], N. Dulhani[19], S. Dube[20], J. Shrivastava[20], A. Mittal[20], L. Patnaik[21], J.P. Sahoo[21], S. Sharma[21], V.K. Katyal[22], A. Katyal[22], N. Yadav[22], R. Upadhyay[23], S. Srivastava[23], A. Srivastava[23], N.N. Suthar[24], N.M. Shah[24], K. Rajvansh[24], H. Purohit[24], P.R. Mohapatra[25], M.K. Panigrahi[24], S. Saigal[26], A. Khurana[26], M. Panchal[27], M. Anderpa[27], D. Patel[27], V. Salgar[28], S. Algur[28], R. Choudhury[29], M. Rao[29], D. Nithya[29], B.K. Gupta[30], B. Kumar[30], J. Gupta[30], S. Bhandari[31], A. Agrawal[31], M. Shameem[32], N. Fatima[32], S. Pala[33], V. Nongpiur[33], S. Chatterji[34], S. Mukherjee[34], S.K. Shivnitwar[35], S. Tripathy[35], P. Lokhande[35], H. Dandu[36], A. Gupta[36], V. Kumar[36], N. Sharma[37], R. Vohra[37], A. Paliwal[37], M. Pavan Kumar[38], A. Bikshapathi Rao[38], N. Kikon[39], R. Kikon[40], K. Manohar[41], Y. Sathyanarayana Raju[41], A. Madharia[42], J. Chakravarty[43], M. Chaubey[43], R.K. Bandaru[44], M. Ali Mirza[44], S. Kataria[45], P. Sharma[45], S. Ghosh[46] and A. Hazra[46]

[1]National Institute of Medical Statistics, Indian Council of Medical Research, Delhi, India
[2]Indian Council of Medical Research, New Delhi, India,
[3]Medstar Health, Baltimore, MD, USA,
[4]Postgraduate Institute of Medical Education & Research, Chandigarh, India,
[5]Gandhi Medical College, Telangana, India,
[6]All Indian Institute of Medical Sciences, Jodhpur, Rajasthan, India,
[7]All Indian Institute of Medical Sciences, Raipur, Chhattisgarh, India,
[8]College of Medicine, Sagore Dutta Hospital, Kolkata, West Bengal, India,
[9]Medical College, Kolkata, West Bengal, India,
[10]Infectious Disease and Beliaghata Hospital, Kolkata, West Bengal, India,
[11]Christian Medical College, Ludhiana, Punjab, India,
[12]CIMS Hospital, Ahmedabad, India,
[13]National Institute Of Mental Health and Neurosciences, Bangalore, Karnataka, India,
[14]Bowring & Lady Curzon Medical College & Research Institute, Bangalore, Karnataka, India,
[15]Shaheed Nirmal Mahato Medical College, Dhanbad, Jharkhand, India,
[16]RD Gardi Medical College, Ujjain, Madhya Pradesh, India,
[17]Hi Tech Medical College and Hospital, Bhubaneswar, India,
[18]Dhiraj Hospital & Sumandeep Vidyapeeth, Vadodara, Ahmedabad, India,
[19]Late BRK Memorial Medical College, Jagdalpur, Chhattisgarh, India,
[20]Gandhi Medical College, Bhopal, Madhya Pradesh, India,
[21]Institute of Medical Sciences & SUM Hospital, Siksha 'O' Anusandhan deemed to be University, Bhubaneswar, India,
[22]Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India,
[23]Government Institute of Medical Sciences, Noida, Uttar Pradesh, India,
[24]Smt. NHL, Municipal Medical College, Ahmedabad, Gujarat, India,
[25]All India Institute of Medical Sciences, Bhubaneswar, India,
[26]All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India,
[27]GMERS Medical College Himmatnagar, Gujarat, India,
[28]Gulbarga Institute of Medical Sciences, Kalburagi, Karnataka, India,
[29]St. Johns Medical College, Bengaluru, Karnataka, India,
[30] S.P. Medical College, Bikaner, Rajasthan, India,
[31]SMS Medical College, Jaipur, Rajasthan, India,
[32]JN Medical College Aligarh Muslim University, Aligarh, Uttar Pradesh, India,
[33]North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya, India,
[34]Tata Medical Centre, Kolkata, West Bengal, India,
[35]Dr D Y Patil Medical College Hospital and Research Centre, Pune, Maharashtra, India,
[36]King George Medical University, Lucknow, Uttar Pradesh, India,
[37]Mahatma Gandhi Medical College, Jaipur, Rajasthan, India,
[38]Kakatiya Medical College, MGM Hospital Warangal, Telangana, India,
[39]Department of Health & Family Welfare, Government of Nagaland, Nagaland, India,
[40]Community Health Initiative, Nagaland, India,
[41]Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, India,
[42]ESI Hospital and Gayatri Hospital, Raipur, Chhattisgarh, India,
[43]Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India,
[44]ESIC Medical College, Sanathnagar, Hyderabad, India,
[45]Medanta-The Medicity, Gurugram, Haryana, India **and**
[46]Institute of Postgraduate Medical Education & Research, Kolkata, West Bengal, India

Funding

The study was supported by the Indian Council of Medical Research, New Delhi.

Conflict of interest: A.M., G.K., A.T., L.K.S. and S.P. are employed by the Indian Council of Medical Research, the funding source of the study. A.A. was employed by the Indian Council of Medical Research at the beginning of the study. No other author has declared any conflict of interest.

References

1. Becerra-Muñoz VM, Núñez-Gil IJ, Eid CM, García Aguado M, Romero R, Huang J, *et al.* Clinical profile and predictors of in-hospital mortality among older patients hospitalised for COVID-19. *Age Ageing* 2021; **50**:326–34.
2. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with in-hospital mortality in a US National Sample of Patients with COVID-19. *JAMA Netw Open* 2020; **3**: e2029058.
3. Gray WK, Navaratnam AV, Day J, Babu P, Mackinnon S, Adelaja I, *et al.* Variability in COVID-19 in-hospital mortality rates between National Health Service trusts and regions in England: a national observational study for the Getting It Right First Time Programme. *EClinicalMedicine* 2021; **35**: 100859.

4. Khamis F, Memish Z, Bahrani MA, Dowaiki SA, Pandak N, Bolushi ZA, *et al.* Prevalence and predictors of in-hospital mortality of patients hospitalized with COVID-19 infection. *J Infect Public Health* 2021; **14**:759–65.
5. Ruscica M, Macchi C, Iodice S, Tersalvi G, Rota I, Ghidini S, et al Prognostic parameters of in-hospital mortality in COVID-19 patients—an Italian experience. *Eur J Clin Invest* 2021; **51**.
6. Sarfaraz S, Shaikh Q, Saleem SG, Rahim A, Herekar FF, Junejo S, *et al.* Determinants of in-hospital mortality in COVID-19; a prospective cohort study from Pakistan. *PLoS One* 2021; **16**: e0251754.
7. Galiero R, Pafundi PC, Simeon V, Rinaldi L, Perrella A, Vetrano E, *et al.*; on behalf of COVOCA Study Group. Impact of chronic liver disease upon admission on COVID-19 in-hospital mortality: findings from COVOCA study. *PLoS One* 2020; **15**:e0243700.
8. Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, *et al.* High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020; **73**:1063–71.
9. Mammen JJ, Kumar S, Thomas L, Kumar G, Zachariah A, Jeyaseelan L, *et al.* Factors associated with mortality among moderate and severe patients with COVID-19 in India: a secondary analysis of a randomised controlled trial. *BMJ Open* 2021; **11**:e050571.
10. Zodpey SP, Negandhi H, Kamal VK, Bhatnagar T, Ganeshkumar P, Athavale A, *et al.* Determinants of severity among hospitalised COVID-19 patients: hospital-based case-control study, India, 2020. *PLoS One* 2021; **16**:e0261529.
11. Agarwal N, Biswas B, Lohani P. Epidemiological determinants of COVID-19 infection and mortality: A study among patients presenting with severe acute respiratory illness during the pandemic in Bihar, India. *Niger Postgrad Med J*. 2020; **27**:293–301.
12. Mishra V, Burma AD, Das SK, Parivallal MB, Amudhan S, Rao GN. COVID-19-hospitalized patients in Karnataka: survival and stay characteristics. *Indian J Public Health* 2020; **64**:221–4.
13. Rubio-Rivas M, Mora-Luján JM, Formiga F, Arévalo-Cañas C, Lebrón Ramos JM, Villalba García MV, *et al.* WHO Ordinal Scale and Inflammation Risk Categories in COVID-19. Comparative Study of the Severity Scales. *J Gen Intern Med*. 2022; **37**:1980–7.
14. WHO Expert Consultation Group. Appropriate body mass index for Asian populations and its implications for policy and intervention strategies. *Lancet Public Health* 2004; **363**: 157–63.
15. Ramakrishnan S, Zachariah G, Gupta K, Shivkumar Rao J, Mohanan PP, Venugopal K, *et al.* Prevalence of hypertension among Indian adults: Results from the great India blood pressure survey. *Indian Heart J*. 2019; **71**:309–13.
16. Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, *et al.* Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR-INDIAB population-based cross-sectional study. *Lancet Diabetes Endocrinol*. 2017; **5**:585–96.
17. Hamer M, Gale CR, Batty GD. Diabetes, glycaemic control, and risk of COVID-19 hospitalisation: Population-based, prospective cohort study. *Metabolism*. 2020; **112**:154344.
18. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol - Endocrinol Metab*. 2020; **318**:E736–41.
19. Kang SJ, Jung SI. Age-Related Morbidity and Mortality among Patients with COVID-19. *Infect Chemother*. 2020; **52**:154–64.
20. O'Driscoll M, Ribeiro Dos Santos G, Wang L, Cummings DAT, Azman AS, Paireau J, *et al.* Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature*. 2021; **590**:140–5.
21. Azarudeen MJ, Aroskar K, Kurup KK, Dikid T, Chauhan H, Jain SK, *et al.* Comparing COVID-19 mortality across selected states in India: The role of age structure. *Clin Epidemiol Glob Health*. 2021; **12**:100877.
22. Kerstjens HA, Rijcken B, Schouten JP, Postma DS. Decline of FEV1 by age and smoking status: facts, figures, and fallacies. *Thorax*. 1997; **52**:820–7.
23. Barman Roy D, Gupta V, Tomar S, Gupta G, Biswas A, Ranjan P, *et al.* Epidemiology and Risk Factors of COVID-19-Related Mortality. *Cureus*. 2021; **13**(12):e20072.
24. Padmaprakash KV, Vardhan V, Thareja S, Muthukrishnan J, Raman N, Ashta KK, *et al.* Clinical characteristics and clinical predictors of mortality in hospitalised patients of COVID 19: An Indian study. *Med J Armed Forces India*. 2021; **77(Suppl 2)**: S319–32.
25. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. *Int Urol Nephrol*. 2020; **52**:1193–4.
26. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, *et al.* OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature*. 2020; **584**: 430–6.
27. Ozturk S, Turgutalp K, Arici M, Odabas AR, Altiparmak MR, Aydin Z, *et al.* Mortality analysis of COVID-19 infection in chronic kidney disease, haemodialysis and renal transplant patients compared with patients without kidney disease: a nationwide analysis from Turkey. *Nephrol Dial Transplant*. 2020; **35**:2083–95.
28. Saithanyamurthi HV, Munirathinam M, Ananthavadivelu M. Prevalence of liver injury in 445 patients with Corona Virus Disease-19-Single-centre experience from southern India. *Indian J Gastroenterol*. 2021; **40**:303–8.
29. Wang Q, Davis PB, Xu R. COVID-19 risk, disparities and outcomes in patients with chronic liver disease in the United States. *EClinicalMedicine*. 2020; **31**:100688.
30. Marjot T, Webb GJ, Barritt AS, Moon AM, Stamataki Z, Wong VW, *et al.* COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol*. 2021;1–17.
31. Aggarwal AN, Agarwal R, Dhooria S, Prasad KT, Sehgal IS, Muthu V. Active pulmonary tuberculosis and coronavirus disease 2019: A systematic review and meta-analysis. *PLoS ONE*. 2021; **16**:e0259006.
32. Song W-M, Zhao J-Y, Zhang Q-Y, Liu S-Q, Zhu X-H, An Q-Q, *et al.* COVID-19 and Tuberculosis Coinfection: An Overview of Case Reports/Case Series and Meta-Analysis. *Front Med*. 2021; **8**:657006.
33. Yan L, Zhang HT, Goncalves J, *et al.* An interpretable mortality prediction model for COVID-19 patients. *Nat Mach Intell*. 2021; **2**:283–8.
34. El-Shabrawy M, Alsadik ME, El-Shafei M, Abdelmoaty AA, Alazzouni AS, Esawy MM, *et al.* Interleukin-6 and C-reactive protein/albumin ratio as predictors of COVID-19 severity and mortality. *Egypt J Bronchol*. 2021; **15**:5.
35. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, *et al.* An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med*. 2020; **26**:1636–43.
36. Ahmeidi AA, Musa A, Ahmed HS, Elahmar AA, Goota RB, Ahmed IA, *et al.* Inflammatory markers as predictors of mortality in COVID-19 infection. *Afr J Lab Med*. 2020; **9**:1298.
37. Hospitalized Adults: Therapeutic Management [Internet]. COVID-19 Treatment Guidelines. [cited 2022 Sep 9]. Available from: https://www.covid19treatmentguidelines.nih.gov/man

agement/clinical-management-of-adults/hospitalized-adults–therapeutic-management/
38. Abhilash KP. COVID-19 vaccines: Hope on the horizon with doubts. *Curr Med Issues* 2021; **19**:67–9.
39. Muthukrishnan J, Vardhan V, Mangalesh S, Koley M, Shankar S, Yadav AK, *et al*. Vaccination status and COVID-19 related mortality: A hospital based cross sectional study. *Med J Armed Forces India*. 2021; **77(Suppl 2)**: S278–82.
40. Mandal S, Arinaminpathy N, Bhargava B, Panda S. India's pragmatic vaccination strategy against COVID-19: a mathematical modelling-based analysis. *BMJ Open*. 2021; **11**:e048874.