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Risk factors for mortality in hospitalized COVID-19 patients across five waves in Pakistan

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This retrospective cohort study aims to describe the clinical characteristics and outcomes and assess risk factors for mortality across the epidemic waves in hospitalized COVID-19 patients in a major tertiary-care center in Pakistan. A total of 5368 patients with COVID-19, hospitalized between March 2020 and April 2022 were included. The median age was 58 years (IQR: 44–69), 41% were females, and the overall mortality was 12%. Comparative analysis of COVID-19 waves showed that the proportion of patients aged ≥ 60 years was highest during the post-wave 4 period (61.4%) and Wave 4 (Delta) (50%) ($p < 0.001$). Male predominance decreased from 65.2% in Wave 2 to 44.2% in Wave 5 (Omicron) ($p < 0.001$). Mortality rate was lowest at 9.4% in wave 5 and highest at 21.6% in the post-wave 4 period ($p = 0.041$). In multivariable analysis for risk factors of mortality, acute respiratory distress syndrome (ARDS) was most strongly associated with mortality (aOR 22.98, 95% CI 15.28–34.55, $p < 0.001$), followed by need for mechanical ventilation (aOR 6.81, 95% CI 5.13–9.05, $p < 0.001$). Other significant risk factors included acute kidney injury (aOR 3.05, 95% CI 2.38–3.91, $p < 0.001$), stroke (aOR 2.40, 95% CI 1.26–4.60, p = 0.008), pulmonary embolism (OR 2.07, 95% CI 1.28–3.35, $p = 0.003$), and age ≥ 60 years (aOR 2.45, 95% CI 1.95–3.09, $p < 0.001$). Enoxaparin use was associated with lower mortality odds (aOR 0.45, 95% CI 0.35–0.60, $p < 0.001$. Patients hospitalized during Wave 4 (aOR 2.22, 95% CI 1.39–3.56, $p < 0.001$) and the post-wave 4 period (aOR 2.82, 95% CI 1.37–5.80, $p = 0.005$) had higher mortality odds compared to other waves. The study identifies higher mortality risk in patients admitted in Delta wave and post-wave, aged ≥ 60 years, and with respiratory and renal complications, and lower risk with anticoagulation during COVID-19 waves.

Keywords COVID-19, Epidemic waves, Mortality, Mechanical ventilation

COVID-19 was declared a pandemic on 11th March, 2020 by World Health Organization (WHO)[1]. The impact of the pandemic was variable in low- and middle-income countries (LMICs) and was largely influenced by the healthcare infrastructure, epidemiology and government response. The WHO regions of Americas, Europe and South East Asia have experienced the highest cumulative total number of reported COVID-19 deaths[2]. At the country level, United States had the highest estimated cumulative confirmed deaths due to COVID-19 at 1.14 million, followed by the Brazil with 702,000 and India with 533,000 as of December 2023[3,4]. In Pakistan, more than 1.58 million confirmed cases of COVID-19 and over 30,000 fatalities have been reported between January 2020 and December 2023[5,6]. So far, there have been five recorded waves of COVID-19 in Pakistan. The first wave of COVID-19 was shown to have G, L, and S clade SARS-CoV-2 strains. The alpha variant was identified in Pakistan in January 2021. Between April and July 2021, the predominance shifted from Alpha to Delta variants, then between December and February 2022, from Delta to Omicron variants[7,8]. Several advancements have been made regarding COVID-19 prevention, diagnostic, and treatment procedures over this time period, including criteria for hospitalization and the introduction of COVID-19 immunization[9–11]. Pakistan started the vaccine roll out in February 2021 and a total of 333,085,477 doses of vaccine have been given as of 21 January 2023[5]. The national COVID-19 immunization coverage data has not been updated since November 2023 and an estimated 60% full

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vaccination rate has been reported[12]. A study by Mushtaq et al. reported better outcomes in younger patients, especially following vaccines with the majority receiving inactivated vaccines and Omicron variant infections[13].

A rapid rise in cases and deaths was observed in most LMICs in the earlier waves of COVID-19 infection. Resources were limited, healthcare facilities were overwhelmed, and there were critical shortages of personal protective equipment (PPE) and ventilators[14]. The clinical manifestations and outcomes of hospitalized COVID-19 patients have been variably reported from the earlier phase of the pandemic from LMICs including Pakistan[15]. There have been significant epidemiological differences including lower mortality despite a greater prevalence of comorbidities and increased incidence of hospital-acquired infections in Pakistan compared to developed countries. However, there is a scarcity of data that describes factors associated with mortality in hospitalized COVID-19 patients across different waves; particularly from low- and middle-income countries; because of varying capacities for the detection and management of patients, along with lack of reliability in data collected[16]. Moreover, the data reported from these countries have accounted for one or two waves[17,18]. This constitutes a major gap in the literature as the world seeks to understand the pandemic for better future preparedness[19].

Multiple resurgences have occurred globally despite numerous efforts to combat COVID-19, portraying varying degrees of effectiveness in containing SARS-CoV-2 infection. Understanding the risk factors for mortality due to COVID-19 across the different waves from LMICs is important because it guides the adaptation of medical resources to manage patients given the likelihood of future resurgences of this and other similar viruses and their variants. This study aims to describe the risk factors associated with mortality among hospitalized COVID-19 patients across all five waves of COVID-19 in Pakistan.

Methods

Study design and patients

A retrospective cohort study was conducted on patients hospitalized with COVID-19 between March 2020 and April 2022 at a tertiary care center in Karachi, Pakistan. The inclusion criteria were all hospitalized patients greater than or equal to 18 years of age with a positive test for SARS-CoV-2. We excluded readmissions and only the first episode of COVID-19 was included in this study. We examined our hospital's digital health information capture technologies and collected structured data to build a COVID-19 Registry. Apart from age, gender and comorbidities, data was collected on outcome variables comprising in-hospital mortality and length of hospital stay, laboratory parameters at the time of hospitalization, management and complications. The dataset captured the entire hospital admission of each patient. The follow-up time was from the date of admission to the date of discharge or death for each patient. The length of hospital stay was defined as the total number of days admitted to the hospital. The outcome of interest was in-hospital mortality defined as death during hospitalization.

Study setting

The study was conducted at the Aga Khan University Hospital, a 750-bed academic medical tertiary care center that received the first patient of COVID-19. It's one of 3 institutes in the country to have been accredited by the Joint Commission International. The Aga Khan University Hospital (AKUH) has played an important role in Pakistan's COVID-19 response and distinguished itself from all other hospitals in the country by being the first to acquire testing capacity and developing a specialized testing zone, establishing dedicated COVID-19 patient care units and implementing stringent infection control procedures. Moreover, with its existing team of trained infectious disease and critical care intensivists, our hospital was a leader in developing training programmes for capacity building in other hospitals, both public and private, and outreach facilities[20].

Definition of COVID-19 epidemic waves

According to studies, a COVID-19 wave is characterized by the transition from a stable number of daily SARS-CoV-2-positive tests to a rising number of positive test results, followed by a peak and subsequent fall in daily positive test findings. The end of a wave is defined as the day when the number of daily SARS-CoV-2-positive test results decreased after a peak and stabilised[21,22]. Pakistan experience five distinct epidemic waves[6,23]. COVID-19 epidemic waves in Pakistan were defined as follows based on prior published work by Nasir et al[8]. which considers the dates experienced within the country as well as the Province of Sindh where our center is located and the associated variants of concern: (i) First wave (Wave 1) Pre-Variants of concern (VOCs) March to July 2020; (ii) Second wave (Wave 2) Pre-VOCs October 2020 to January 2021; (iii) Third wave (Wave 3) Alpha variant April 2021 to May 2021; (iv) Fourth wave (Wave 4) Delta variant July 2021 to September 2021; and (v) Fifth wave (Wave 5) Omicron variant December 2021 to February 2022. The period in between waves was defined as the respective post-wave period following the wave (Fig. 1).

Statistical analysis

For continuous variables such as age and length of hospital stay, median and interquartile range were reported, and percentages were reported for categorical variables such as sex and comorbid conditions in each wave. Pearson's Chi-square test was performed to compare the proportions of the categorical variables and one-way ANOVA was used for comparison of the continuous variables throughout the waves and post-waves. Logistic regression analysis was performed to evaluate the risk factors for in-hospital mortality including the effect of waves and post-wave periods. Multivariable logistic regression analysis was performed adjusting for age, sex, comorbid conditions, treatment, and other covariates which were selected based on biological plausibility, previous studies, and statistical significance ($p < 0.1$) in univariable analysis. Interactions were assessed pairwise by the inclusion of product terms for all variables remaining in the final multivariable model. The results were provided as adjusted odds ratios (a OR) and 95% confidence intervals (CI). All statistical analyses were performed in Stata statistical software (version 17.0, StataCorp, College Station, TX).

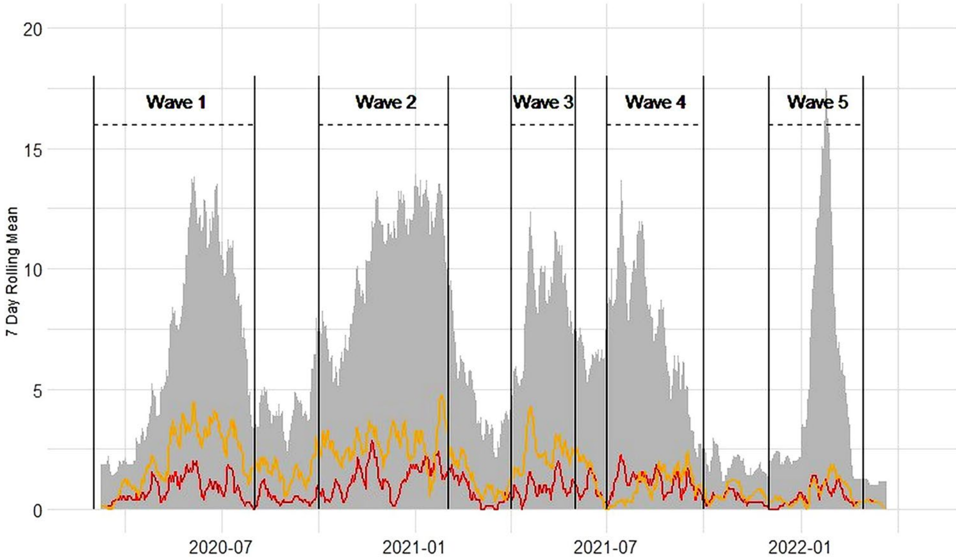

Fig. 1. 7-day moving average of COVID-19 hospital admissions, in-hospital deaths (red), and mechanical ventilation (yellow) in Aga Khan University Hospital Karachi, Pakistan from March 2020, to April 2022.

Ethics approval

The study received approval from the Aga Khan University (AKU) Ethics Review Committee (ERC) (Reference number: 2020-3650; 2023-3650). The study was performed in accordance with the Declaration of Helsinki. The data was collected retrospectively and was fully anonymized so the requirement for informed consent was waived by ERC.

Results

Overall, a total of 5368 patients with PCR and/or SARS-CoV-2 Antigen test confirmed diagnosis of COVID-19 were hospitalized between March 2020 and April 2022. The median age of the entire cohort was 58 years (IQR: 44–69) and 41% were females. The highest number of hospital admissions was during Wave 2 (n = 1422). The overall mortality was 12%.

Comparison of COVID-19 waves

The proportion of patients aged ≥ 60 years was highest during the post-wave 4 period at 61.4% followed by Wave 4 (Delta wave) 50% compared with all other waves ($p < 0.001$). A decline in male predominance was observed over time, from 65.2% in Wave 2 to 44.2% in Wave 5 ($p < 0.001$). Among the co-morbid conditions, the prevalence of diabetes mellitus ($p < 0.001$) and hypertension ($p = 0.001$) fluctuated across waves with the highest proportion observed during the post-wave 4 period compared with other waves. Amongst treatment strategies, corticosteroid use increased significantly in Wave 2 (85.79%) and declined in Wave 5 (54.91%) in comparison with other waves ($p < 0.001$). Remdesivir utilization was highest 64.4% in post-wave 4 period and lowest at 36.6% in Wave 5 ($p < 0.001$) in comparison with other waves. Complications such as ARDS were highest (22.3%) in Wave 1 ($p < 0.001$) while acute kidney injury was notably highest (50%) in Wave 5 ($p < 0.001$) compared with all other waves. Mortality rates varied across waves, ranging from 9.4 to 21.6% ($p = 0.041$), with the highest rate observed during the post-wave 4 period. The median length of stay was longest during Wave 1 and post-wave 1 period (5 days) compared with other waves ($p < 0.001$) (Table 1).

Factors associated with mortality and the effect of waves

Several factors were found to be significantly associated with mortality on multivariable logistic regression analysis. Acute respiratory distress syndrome (ARDS) was significantly associated with mortality (a OR 22.98, 95% CI 15.28–34.55, $p < 0.001$), followed by mechanical ventilation (a OR 6.81, 95% CI 5.13–9.05, $p < 0.001$). A significant interaction between ARDS and ventilation was observed suggesting a complex relationship between these 2 variables (a OR 0.21, 95% CI 0.13–0.0.35) whereby their combined effect is less than the multiplicative product of their individual effects on mortality in hospitalized COVID-19 patients. Furthermore, other complications which were significantly associated with mortality included acute kidney injury (a OR 3.05, 95% CI 2.38–3.91, $p < 0.001$), stroke (a OR 2.40, 95% CI 1.26–4.60, $p = 0.008$), and pulmonary embolism (OR 2.07, 95% CI 1.28–3.35, $p = 0.003$). Advanced age (> = 60 years) (a OR 2.45, 95% CI 1.95–3.09, $p < 0.001$) was also associated with an increased risk of death. Notably, enoxaparin use was associated with lower odds of mortality (a OR 0.45, 95% CI 0.35–0.60, $p < 0.001$), suggesting a potential protective effect while steroid use did not confer any mortality benefit (a OR 4.14, 95% CI 2.59–6.62, p < 0.001) reflecting increased severity of illness in patients who received steroids. Patients hospitalized during Wave 4 (Delta wave) (a OR 2.22, 95% CI 1.39–3.56, $p < 0.001$) and

	Wave 1	Post-wave 1	Wave 2	Post-wave 2	Wave 3	Post-wave 3	Wave 4	Post-wave 4	Wave 5	Post-wave 5	*p* value
Duration	Mar to July 2020	Aug to Sept 2020	Oct 2020 to Jan 2021	Feb to Mar 2021	April to May 2021	June 2021	July to Sept 2021	Oct to Nov 2021	Dec 2021 to Feb 2022	March to Apr 2022	
Variants	Pre VOC		Pre VOC		Alpha		Delta		Omicron		
Total N = 5368	N = 1064	N = 291	N = 1422	N = 316	N = 601	N = 223	n = 780	N = 101	N = 550	N = 20	
Demographics											
Median age in years (IQR)	54 (40–65)	57(47–68)	59 (48–69)	63 (50–71.5)	59 (48–69)	56 (39–66)	60 (41–70)	65 (50–73)	58 (32–72)	62 (27–77.5)	< 0.001
Age group											< 0.001
> = 60 years	405	133	699	177	290	102	395	62	267	11	
	38.06%	45.7%	49.16%	56.01%	48.25%	45.74%	50.64%	61.39%	48.55%	55%	
Sex											< 0.001
Male	661	182	927	201	362	133	389	52	243	11	
	62.12%	62.54%	65.19%	63.61%	60.23%	59.64%	49.87%	51.49%	44.18%	55%	
Comorbid conditions											
Diabetes mellitus	409	118	622	136	267	101	318	46	180	6	< 0.001
	38.44%	40.55%	43.74%	43.04%	44.43%	45.29%	40.77%	45.54%	32.73%	30%	
Hypertension	453	120	720	162	291	103	346	54	241	7	0.001
	42.58%	41.24%	50.63%	51.27%	48.42%	46.19%	44.36%	53.47%	43.82%	35%	
Chronic kidney disease	102	29	173	34	62	21	88	8	70	2	0.525
	9.59%	9.97%	12.17%	10.76%	10.32%	9.42%	11.28%	7.92%	12.73%	10%	
Coronary artery disease	68	16	89	17	12	4	15	4	29	1	< 0.001
	6.39%	5.5%	6.26%	5.38%	2%	1.79%	1.92%	3.96%	5.27%	5%	
Chronic liver disease	24	6	18	5	8	5	16	3	18	0	0.212
	2.26%	2.06%	1.27%	1.58%	1.33%	2.24%	2.05%	2.97%	3.27%	0%	
Management											
Corticosteroids	736	242	1220	276	484	171	547	79	302	12	< 0.001
	69.17%	83.16%	85.79%	87.34%	80.53%	76.68%	70.13%	78.22%	54.91%	60%	
Remdesivir	78	121	735	194	359	127	408	65	201	9	< 0.001
	7.33%	41.58%	51.69%	61.39%	59.73%	56.95%	52.31%	64.36%	36.55%	45%	
Tocilizumab	145	75	113	25	53	20	63	4	9	0	< 0.001
	13.63%	25.77%	7.95%	7.91%	8.82%	8.97%	8.08%	3.96%	1.64%	0%	
Enoxaparin	582	216	1034	224	446	144	491	63	174	5	< 0.001
	54.7%	74.23%	72.71%	70.89%	74.21%	64.57%	62.95%	62.38%	31.64%	25%	
Non-invasive mechanical ventilation	279	90	318	76	146	43	80	26	51	3	< 0.001
	26.22%	30.93%	22.36%	24.05%	24.29%	19.28%	10.26%	25.74%	9.27%	15%	
Invasive mechanical ventilation	110	29	77	13	47	11	31	8	20	0	< 0.001
	10.34%	9.97%	5.41%	4.11%	7.82%	4.93%	3.97%	7.92%	3.64%	0%	
Complications											
ARDS	237	43	170	31	66	17	83	5	34	0	< 0.001
	22.27%	14.78%	11.95%	9.81%	10.98%	7.62%	10.64%	4.95%	6.18%	0%	
Acute kidney injury	385	85	428	92	154	53	240	33	275	8	< 0.001
	36.18%	29.21%	30.1%	29.11%	25.62%	23.77%	30.77%	32.67%	50%	40%	
Pulmonary embolism	11	5	34	9	23	11	18	3	13	0	0.01
	1.03%	1.72%	2.39%	2.85%	3.83%	4.93%	2.31%	2.97%	2.36%	0%	
Myocardial infarction	88	22	99	21	45	11	65	9	59	0	0.134
	8.27%	7.56%	6.96%	6.65%	7.49%	4.93%	8.33%	8.91%	10.73%	0%	
Stroke	17	9	21	2	4	2	14	2	20	1	0.004
	1.6%	3.09%	1.48%	0.63%	0.67%	0.9%	1.79%	1.98%	3.64%	5%	
Lactic acidosis	81	18	89	27	30	17	61	8	30	2	0.334
	7.61%	6.19%	6.26%	8.54%	4.99%	7.62%	7.82%	7.92%	5.45%	10%	
Hospital acquired pneumonia	793	220	1234	292	293	11	28	12	17	2	< 0.001
	74.53%	75.6%	86.78%	92.41%	48.75%	4.93%	3.59%	11.88%	3.09%	10%	
Outcomes											
Death	117	27	159	40	58	24	103	19	45	3	0.041
	11.99%	10.89%	12.34%	14.29%	10.92%	12.24%	14.69%	21.59%	9.39%	18.75%	
Median length of stay in days (IQR)	5 (3–9)	5 (2–8)	4 (2–7)	4 (2–8)	4 (2–7)	4 (2–8)	3 (2–7)	3 (2–6)	3 (2–4)	4 (2–6)	< 0.001

Table 1. Clinical characteristics across the epidemic waves.

the post-wave 4 period (a OR 2.82, 95% CI 1.37–5.80, $p = 0.005$) had higher odds of mortality compared with all other waves and post-wave periods. (Table 2).

Discussion

Our study describes the largest cohort of hospitalized COVID-19 patients from Pakistan across five COVID-19 epidemic waves spanning March 2020 to April 2022. It provides insights from a low- and middle-income country where the treatment resources were limited, and an inactivated vaccine was methodically rolled out in the population through an organized, concerted effort by the Government.

Furthermore, it also provides a unique insight into the clinical course of COVID-19 patients hospitalized during the post-wave periods. Our study found significant changes in patient demographics across COVID-19 waves with a progressively increasing elderly population (highest in Wave 4 and post-wave 4 period) and a decrease in male predominance (lowest in Wave 5). Studies from other LMICs such as Iran and Zambia have reported a peaking of median age till Wave 4 with a subsequent decline in age in Wave 5[21,24]. However, we observed that there was only a modest decline in median age between Wave 4 and Wave 5 (60 years vs. 58 years). This is similar to a study from US reporting greater incidence of hospitalization among elderly in Wave 5[25]. Conversely, studies from Spain and Slovenia have reported hospitalizations among young and adolescent patients during the Omicron Wave[26,27]. These differences could be due to the increased transmissibility of the variant coupled with variability in vaccination uptake and types of vaccines received in the different countries[28,29]. Our study found a ratio reversal in male to female ratio between the initial 4 Waves and the 5th (Omicron) wave. While it was similarly reported from Iran[30], there was conflicting data from US[25]. This could be due to gender disparity in vaccine coverage which is reportedly lesser coverage among women as well as vaccine accessibility in LMICs[31].

Our study found an overall mortality of 12% and the mortality rate varied significantly across waves and post-wave periods, ranging from 9.4 to 21.59%, with the highest rate observed during the post-wave 4 period. Upon evaluating the effect of waves and post-wave periods on mortality, a significant association was found between Wave 4 and the post-wave 4 period. In-hospital mortality has been variably reported from different parts of the world with most of the data available from the first year of the pandemic. Among the high-income countries, in-hospital mortality reported from the US ranged between 13.2 and 24.5%[32] and 25% from England[33] during the first two waves of the pandemic in the period between 2020 and 2021. The in-hospital mortality rates were reportedly higher from Latin America (24%)[34] as well as from low-middle income countries such as Iran (20%)[35]. Our center was the first to report an in-hospital mortality of 13% from Pakistan from the first wave of pandemic[36] and the current study also corroborates that finding of 12%, which is comparatively lower than other countries. One possible explanation could be the early use of corticosteroids, which were given to 69% of the hospitalized patients during Wave 1 in our cohort, although guidelines for use by WHO came in September 2020[37], prior to the beginning of the second wave in the country. Although there is a trend towards higher mortality in patients who received steroids in our study, it is indicative of the severity of illness necessitating the use of steroids in these patients.

Parameters	Adjusted odds ratio	95% confidence interval	*p* value
Age > = 60 years	2.45	1.95–3.09	< 0.001
Steroids use	4.14	2.59–6.62	< 0.001
Enoxaparin use	0.45	0.35–0.60	< 0.001
ARDS	22.98	15.28–34.55	< 0.001
Acute kidney injury	3.05	2.38–3.91	< 0.001
Pulmonary embolism	2.07	1.28–3.35	0.003
Stroke	2.4	1.26–4.60	0.008
Mechanical ventilation	6.81	5.13–9.05	< 0.001
Effect of each wave			
Wave 5 (Omicron)	Reference		
Wave 1 (Pre-VOC)	0.8	0.50–1.28	0.352
Post-wave 1	0.81	0.44–1.50	0.508
Wave 2 (Pre-VOC)	1.1	0.71–1.72	0.67
Post-wave 2	1.35	0.76–2.38	0.302
Wave 3 (Alpha)	0.95	0.57–1.60	0.851
Post wave 3	1.66	0.86–3.19	0.13
Wave 4 (Delta)	2.22	1.39–3.56	0.001
Post-wave 4	2.82	1.37–5.80	0.005
Post-wave 5	3.94	0.92–16.90	0.065
Mechanical ventilation * ARDS	0.21	0.13–0.35	< 0.001

Table 2. Multivariable logistic regression analysis showing the factors associated with mortality including effect of each wave. *CI* Confidence Interval, *ARDS* Acute Respiratory Distress Syndrome. Reference categories are omitted for binary variables. Pre-VOC = Pre- Variants of Concern. Interaction term (Mechanical Ventilation*ARDS).

Among the waves and post-wave periods, the highest in-hospital mortality (15%) was reported during the fourth wave (Delta) and 21% which was the post-wave period of the same in our study. The majority of the countries across the world reported high all-cause and in-hospital mortality with the delta variant inCOVID-19 but South Asia was most affected by this wave. Pakistan saw a sharp increase in the number of cases during the Delta wave accompanied by a rise in mortality rates[38].This was similarly reported from neighboring countries such as Bangladesh, Iran and India[39–41]. In the study from Iran, delta surge was associated with a comparatively greater risk of death from alpha surge and this was attributed to a high number of hospitalisations, a shortage of hospital beds, ICU spaces, and medical supplies, poor nutritional status of hospitalised patients, and a lack of intensivist physicians or specialised nurses in the ICU. Moreover, a recent study from Cameroon also showed higher mortality with Delta compared to all other variants[42].

Although high income countries also experienced rise in cases of COVID-19 during delta period, less severe diseases and low mortality rate were reported from countries with high vaccine coverage[43]. In studies from US, comparatively higher mortality was observed in patients during delta wave as opposed to omicron wave and it was attributed to better vaccination uptake prior to omicron wave[4445]}. A recent large cohort study from England reported declining crude COVID-19-related death rates across all the 5 waves though there was slight increase in death rates during delta wave in population subgroups[22]. Pakistan had rolled out COVID-19 in-activated vaccine among healthcare workers in February and in general population in March 2021. However, it grappled with vaccine hesitancy in early phases coinciding with delta surge, which could potentially be one of the reasons for increased disease severity and high mortality during that time period[46]. Whether the type of vaccine could have been the reason has been subject to debate but a study conducted in Pakistan did not find any differences in mortality due to vaccine type[47]. Rather, higher risk of death was reported among those who were unvaccinated regardless of type of variants in another study[13]. Fewer studies have evaluated post-wave periods because of differences in the patterns of waves observed in different parts of the world[18,48]. Our finding of highest mortality during post-wave period could be due to lesser hospitalizations during that period and higher proportion of elderly patients. This may have implications for early recognition and management of patients during post-wave periods which may be affected during periods of low transmission.

Our study found that the in-hospital mortality was lowest (9%) during the fifth wave (Omicron) in our study. This is similarly reported from both LMICs and HICs countries[49,50]. However, higher mortality rates during the Omicron wave were reported from Australia[51]. The number of deaths reported from US due to COVID-19 far exceeded the other high income countries and surpassed deaths seen in the Delta wave early in the Omicron wave with comparatively higher all-cause mortality especially in the Northeastern States but in-hospital deaths have subsequently continued to decline as per CDC[52]. Studies from sub-Saharan Africa reported a comparatively higher mortality during the Delta wave when compared with the Omicron wave but it was significantly lower than the first wave[53]. The differences in mortality are likely due to differences in the timing and type of vaccine rollouts which were non-MRNA vaccines in most LMICs compared to HICs and availability of therapeutics such as the monoclonal antibodies.

Among the risk factors for mortality; our study found a significant association of ARDS and mechanical ventilation with in-hospital mortality. Furthermore, we found that there was a significant interaction between these two variables though the Odds Ratio suggested that their combined effect is less than their individual effects. This could be due to the influence of other treatments as well as the timing of ventilation which was not captured in this study[54]. This has been similarly reported globally particularly from LMICs. According to a systematic review, patients with COVID-19 who received IMV in the LMIC subgroup had statistically greater mortality rates than those in the HIC subgroup highlighting the need for investment in resources and capacity building in this area[55]. Our study also found a significant association of in-hospital mortality with thrombotic complications such as stroke and pulmonary embolism. This has been similarly reported in other studies[56]. A large study from Northern Italy reported an increase in deaths due to pulmonary embolism alongside cerebrovascular disease[57]. Acute kidney injury was also an independent predictor of mortality in our cohort. In a systematic review, a pooled risk ratio of 4.6 was reported suggesting increased risk of death in COVID-19 patients with AKI[58]. It has been consistently associated with mortality both during early as well as later phase of the pandemic[59]. Moreover, advanced age has been similarly associated with mortality globally and this has been consistent across different waves. In a systematic review of studies from Europe, increased in-hospital mortality was observed in patients with COPD, arrhythmia, IHD, heart failure, cancer, renal disease, liver disease, obesity, and diabetes after adjusting for age and gender[60]. Among treatment options, the only one found to have a protective association with in-hospital mortality was enoxaparin use. Studies have shown variable results with use of Enoxaparin on COVID-19 outcomes. While one study from Italy did not observe an mortality benefit with its use[61], another large multicenter COVID-19 Registry from Italy reported considerable reduction in mortality rates in patients greater than 59 years of age when treated with Enoxaparin and other antithrombotic medications[62]. Hence current WHO guidelines give conditional recommendation for prophylactic use of antithrombotic medications in hospitalized COVID-19 patients[9].

As opposed to HICs, diabetes was not independently associated with higher mortality in hospitalized patients in our study as well as from Bangladesh[39] although there was a trend towards higher mortality in univariate analysis in Wave 1 and Wave 5. This is likely due to higher overall prevalence of Diabetes Mellitus in South Asia and a small effect size could have been missed due to lack of sufficient statistical power. Moreover, there may have been variability in glycemic control which has not been accounted for in the analysis and is a limitation of the study. Furthermore, sex differences were also not observed unlike US and Europe as well as sub-saharan Africa where male sex was predisposed to increased mortality[63]. These differences may be reflective of the gender differences in health seeking behaviour in our country[64]. Our study found a longer length of stay during Wave 1 and post-Wave 1 period which could only be a reflection of our hospital policy of keeping patients in the hospital till PCR was negative in the initial phase of the pandemic when little was known about the disease.

Strengths and limitations

Our study findings allow for a comprehensive understanding of patient demographics, disease course, management and outcomes and provides important information on critical COVID-19 that can help to optimize resource allocation. It has been conducted in a major tertiary care center with diagnostic capabilities for complex conditions and coupled with the large sample size, it offers accurate insight into the mortality due to COVID-19 over the five waves as well as the post-wave periods experienced in the country. The addition of post-wave periods provides an assessment of clinical course and outcomes in periods of low transmission which is unique as the majority of the studies have focused on waves only. Furthermore, our study employs a novel approach of using longitudinally maintained digitalized clinical data in a resource-constrained setting. Our study has several limitations. Firstly, as a single-center study in a large tertiary care hospital, and despite the diverse population presenting to the center, it may not be generalizable due to variations in healthcare infrastructure across the country because our hospital had set protocols in place and was manned by full-time infectious diseases and critical care physicians. Furthermore, the study is limited by data completeness in terms of lack of data on symptoms of the disease and vaccination status of individual patients as the apparent differences in outcomes across waves might be partly due to varying vaccination rates rather than solely virus variants or treatment changes. Finally, as the infection became milder in subsequent waves, fewer patients were admitted, and a greater proportion of patients were not admitted for COVID; therefore, these data cannot be used to assess the overall impact of the infection on the community.

Conclusion

The study identifies higher mortality risk in patients admitted in Delta wave and post-wave, aged ≥ 60 years, and with respiratory and renal complications, and lower risk with anticoagulation during COVID-19 waves.

These findings serve to fill an important gap in literature and have implications for resource allocation in future resurgences of COVID-19 in LMICs.

Data availability

All data relevant to the study are included in the article.

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Author contributions
N.N, F.K, A.L, Z.S, A.H were involved with Study Conceptualization. N.N, S.T, A.A, C.F.S, A.K, N.K. were involved with study implementation and management; N.N., S.T., S.F.M., A.M., were involved in writing the first draft of manuscript; S.F.M., N.N., B.J., I.K. K.H, S.B, assisted in data collection; N.N., S.T, A.A, C.F.S, N.K were involved in data analysis and curation; A.H, Z.S, A.L, S.F.M, B.J, F.K were involved in study supervision. All authors have read, contributed to and approved the final draft of the manuscript.

Competing interests
The authors declare no competing interests.

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