Analysis of trimodal pattern of mortality among hospitalized COVID-19 patients- Lessons from tertiary care hospital

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Abstract

Background and Aims: Many patients with COVID-19 become critically ill and requireICU admission. Risk factors associated with mortality have been studied, but this study provides insight regarding disease progression and hence help to plan rescue strategies to improve patient outcome.

Material and Methods: This retrospective, observational study included all patients with diagnosis of COVID-19 from March1 to June30,2021 who died in hospital.

Results: During the study period, 1600 patients were admitted, with 1138 (71%) needing ICU care. There were 346 (21.6%) deaths, distributed as 15.8%(n = 55) within 48h of admission, 46.2%(n = 160) in next 10 days, and 37.8%(n = 131) thereafter. This trimodal mortality pattern of distribution was similar to polytrauma patients. Patients were divided into categories according to time duration from admission to death. In our cohort, 235 (14.7%) patients required mechanical ventilation, with a mortality of 85.4%(n = 201). Tachypnea was significantly ($P < 0.001$) associated with death at all times; however, hypotension was associated with early death and low oxygen saturation with poor outcome upto 10 days ($P < 0.001$). Refractory hypoxia was cause of death in all three groups, while other causes in group II were AKI (28%), sepsis (18%), and MODS (10%). Group III patients had different causes of mortality, including barotrauma (9%), pulmonary thromboembolism (8%), refractory hypercarbia (12%), MODS (13%), AKI (10%), sepsis (7%), and cardiac events (6%).

Conclusion: While physiological dearrangements are associated with rapid progression and early death, complications related to hyper-coagulable state, lung injury, and organ failure lead to death later. Providing quality care to a high volume of patients is a challenge for all, but posthoc analysis such as air crash investigation can help find out potential areas of improvement and contribute to better outcomes and mortality reduction.

Keywords: Causes of mortality, COVID-19, mortality, ordinal scale, trimodal peak

Since the outbreak in December 2019 in China, coronavirus disease2019 (COVID-19) has affected millions of people around the world.[1] Epidemiological studies showed that 6%–10% of patients developed acute hypoxemic respiratory failure due to diffuse lung injury and COVID-19 related acute respiratory distress syndrome (C-ARDS).,[2,3] Yang et al.[4]

compared case-fatality rate (CFR) and rate ratios for patients with comorbidities and concluded that the older population had a higher CFR, but the young population with comorbidity should also be considered as a vulnerable group. Bairwa et al.[5] in their retrospective analysis of severely ill patients with C-ARDS suggested close monitoring of biochemical and

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hematological parameters as a clinical indicator for potential progression to critical illness.

C-ARDS develops in 40%–96% of patients admitted to the intensive care unit (ICU).[6] There are regional and institutional differences in the incidence of invasive mechanical ventilation (IMV) for these patients, ranging from 16% to 78%, but is invariably associated with high mortality (upto 97%).[7,8] This wide variation in outcomes has many literature gaps and needs further investigation to be clearly understood. The high fatality rate reported from low- and middle-income countries (LMICs) suggests that they contribute a much greater share of COVID-19 deaths.[9] It is not presently known whether this difference in deaths in LMICs is driven by erroneous reporting; geographical variation; differences in infection patterns, age, and comorbidities in the underlying populations; variation in treatment protocols; or training of health care workers in the management of crisis situation.

On literature search, to the best of our knowledge, this is the first and one of the largest studies from India to evaluate the causes of mortality with respect to the timeline of disease course for patients who had demise within the hospital. This study may provide insight regarding disease progression and plan rescue preventive and therapeutic strategies. Hence, recognition of factors both in patients as well as in the system may help in improving management strategies; allocation plans for potentially scarce resources, such as oxygen, ventilators, and therapeutics; improving patient outcome; and reducing mortality. It may also guide discussions with patients and families regarding the prognosis of the disease.

Material and Methods

This retrospective observational study was approved by the institutional ethics committee of the hospital (IEC No. 2020015), which waived the requirement for individual patient consent for participation. All consecutive adult patients (>18 years) with confirmed diagnosis of SARS-CoV-2 infection (polymerase chain reaction testing of the nasopharyngeal sample or tracheal aspirate), from March to June 2021, who died in the hospital were enrolled in the study.

Data including demographic, clinical characteristics, comorbidities, radiological and laboratory findings were extracted from the institutional electronic medical records system by two physicians. Data regarding triage vitals, medical treatment including the need for IMV and renal replacement therapy, disease progression and complications with time and length of stay and outcomes including discharge, and mortality

were extracted by manual screening of patient records. All parameters were rechecked for accuracy independently by two physicians, and any discrepancy was resolved by a third senior physician before the final analysis.

The primary outcome was in-hospital mortality with no time frame set for this outcome. Admission criteria to the ICU included oxygen requirements >6–8 L/min to reach SpO_2 ≥90%–92% (non-rebreathing mask, NIV, HFNC, mechanical ventilator), respiratory rate ≥30/min, lung infiltrate >50%, acute organ dysfunction as vasopressor support, urine output <150 mL in 6h, confused/drowsy state and patients at high risk for clinical deterioration.

Patients were assessed using World Health Organization (WHO) COVID-19 disease severity scale.[10] The 8-point WHO ordinal scale classifies patients from ambulatory stage to hospitalization with mild to moderate disease to severe disease with intubation and mechanical ventilation and signs of organ failure till death. Three physicians in consensus considered the cause of death by using standard criteria: Berlin criteria 2012 was used to define acute respiratory distress syndrome (ARDS) in intubated patients. Non-intubated patients were assumed to have ARDS and die of hypoxemic respiratory failure if they were receiving oxygen support via high-flow nasal cannula or noninvasive mechanical ventilation with PEEP >5 cmH_2O at the time of death.[11] The diagnosis of acute kidney injury (AKI) was made following the standard KDIGO criteria that included an increase in serum creatinine by >0.3mg/dL in 48 h or a decrease in urine output of <0.5mL/kg/h for 6–12 h.[12] Multiorgan dysfunction syndrome (MODS) was defined by clinical or laboratory failure of two or more systems as stated by the SOFA score, which included individual scores of any system ≥1.[13] Diagnosis of sepsis was based on International Consensus Definition for Sepsis and Septic Shock 2018. Secondary infection was diagnosed when patients showed symptoms or signs of pneumonia or bacteremia and positive culture of new pathogen obtained from the lower respiratory tract or blood samples. Barotraumas was defined as evidence of pneumothorax on chest radiograph or pneumomediastinum on CT images or subcutaneous emphysema in clinical records. Acute pulmonary embolism was diagnosed by CT imaging or clinical diagnosis along with elevated D-dimers and transthoracic echocardiography in case the patient was too sick to be transferred for imaging. Acute cardiac injury was defined as a rise in serum levels of cardiac biomarkers above the 99th percentile of the upper reference limit or evidence of new abnormalities in electrocardiography and echocardiography.

For comparison of the baseline status of this cohort, an age-based propensity dataset was created of patients infected

with the SARS-2 virus who were discharged from the hospital during the same time period.

Statistical analysis

Data regarding continuous variables were described in terms of range; interquartile range, mean ± standard deviation, median, and categorical variables were described as frequencies (number of cases) and relative frequencies (percentages). A comparison of quantitative variables between the study groups was done using ANOVA. For comparing categorical data, Chi-square ($\chi2$) test was performed and Fischer's exact test was used when the expected frequency was <5. To determine the risk factors associated with mortality, the odds ratio was calculated. $P < 0.05$ was considered statistically significant. All statistical calculations were done using Statistical Package for the Social Science 21version (SPSS Inc., Chicago, IL, USA) for Microsoft Windows.

Results

During the study period, 1600 patients were admitted with COVID-19 and1138 (71%) needed ICU admission. There had been 1106 (69.2%) discharges, 346 (21.6%) deaths, and 148 (9.2%) were still admitted in the hospital at the time of analysis. Among those who had been discharged, 104 (30.5%) patients had moderate to severe disease, and 240 (69.7%) had severe disease, while among the deceased, all had severe disease.

Of the 346 patients who died, 32 (9%) died within 24h, another 23 (7%) by 48h, 21 (6%) by 72h, and 20 (6%) by day4, 22 (6%) by day5, and 29 (9%) by day6. The elaborative description of mortality each day depicted peaks at day 1, day 7, and day20, showing trimodal peak distribution as in trauma [Figure 1]. There were 15.8% (n = 55) deaths occurring within first 48 h of admission, 46.2%(n = 160) in next 10 days, and 37.8% (n = 131) deaths thereafter. To analyze the risk factors affecting this trimodal mortality pattern, patients were divided into categories according to the time period from admission to death. Group I included patients who died within 48 h of admission, GroupII included those who died within 3–10 days of admission to the hospital, and group III included patients who died in hospital thereafter.

Among 346 patients, 65%(225) were males. The median age of the deceased was 62 years (range: 18–99 years, IQR: 42.5–69.5), and the mortality rate increased with increasing age. Age distribution of patients showed that 49% of the total deaths occurred in the age group of more than 60 years, and maximum mortality in this group occurred <48 h [Table 1]. However, there was no statistically significant relationship between age and peak time to mortality.
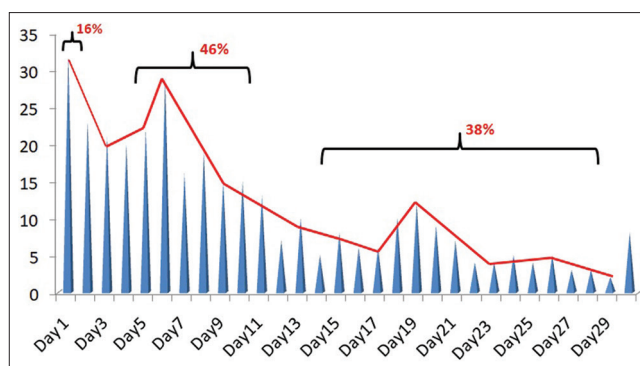
Figure 1: Distribution of mortality with time. The graph shows the number of deaths each day among 346 expired patients during the second wave of COVID-19. The mortality trends show a trimodal distribution with 16% of deaths occurring within 2 days of admission, 46% within 10 days, and 38% later on

At least one associated comorbidity was present in 332 (95.9%) deceased patients. We analyzed Charlson's comorbidity index (CCI) for all discharged and expired patients. In our cohort, patients were equally distributed among various CCI categories as 15% and 11.2% had a CCI of 0, 30% and 25% had CCI of 1–2, 33% and 35% had CCI equal to 3–4, and 21% and 28% had CCI of 5 or more in the discharge and expired groups, respectively.[14] Increased odds for mortality as compared to discharge were present for all comorbid conditions except hypertension and malignancy [Table 1]. To evaluate the risk factors influencing the time of mortality, demographic characteristics and comorbid conditions of discharged patients were compared to three mortality groups. Our results showed that chronic kidney disease was significantly associated ($P = 0.005$) with mortality upto 10 days (groups I and II), and obesity was significantly ($P = 0.003$) associated with late mortality (group III), as shown in Table 1.

Further, 70%(241) of patients in the mortality group had severe disease on presentation, among which 188 (78%) were on high oxygen support, 21 (38%) in group I, 81 (51%) in group II, and 86 (66%) in group III. In our cohort, 235 (14.7%) patients required invasive mechanical ventilation, with a high mortality of 85.4%(n = 201), and among these, 49 (22%) patients were on ventilator at admission [Figure 2]. The median time to ventilation was 4.5 days (IQR: 3–5 days) in the deceased group and 5.5 days in the discharge group. The median duration of mechanical ventilation was 5.6 days (IQR: 2–8 days) in the deceased group and 10.8 days (IQR: 6–17 days) in the discharge group. Of all the ventilated patients, 34 (14.6%) were successfully extubated and percutaneous tracheostomy was performed in 30 patients forweaning from the ventilator.

Do not resuscitate (DNR)/do not intubate (DNI) orders were in place for 17 patients (7%) on admission, either due

Table 1: Demographic characteristics and comorbid conditions of expired patients compared to age-based propensity dataset of discharged patients

Characteristics	Discharge n=344 (%)		Total death n=346		OR (95% CI)	Groups according to time of death					
						0-2 days n=55 n (%)		3-10 days n=160 n (%)		10 days n=131 n (%)	
Demographics											
Males	226	(66%)	225	(65%)	0.91 (.7-1.3)	39	(71%)	105	(65%)	81	(62%)
Age groups											
<40 years	43	(12%)	44	(12.7%)	0.8 (0.5-1.4)	6	(11%)	24	(15%)	14	(11%)
40-60 years	133	(39%)	121	(35%)	1.0 (0.6-1.6)	15	(27%)	48	(30%)	58	(45%)
>60 years	169	(49%)	181	(52.3%)		34	(62%)	89	(55%)	58	(45%)
Co-morbid conditions Diabetes	171	(50%)	189	(55%)	1.2 (0.9-1.6)	34	62%	89	55%	66	51%
Hypertension	137	(40%)	130	(37.5%)	0.91 (.7-1.2)	15	27%	60	37%	55	42%
Coronary Artery Disease	29	(8%)	39	(11.2%)	1.3 (0.8-2.2)	8	15%	20	12%	11	8%
Congestive Heart Failure	1	(0%)	2	(0%)	2 (1.1-4.5)	1	2%	0	0%	1	1%
Chronic Kidney Disease	20	(6%)	41	(12%)	2 (1.2-3.8)	9*	16%	2 *	14%	10	8%
Chronic Liver Disease	11	(3%)	14	(4%)	1.5 (0.5-2.8)	1	2%	6	4%	7	5%
Obesity	16	(5%)	34	(10%)	2.2 (1.2-4.4)	3	5%	15	9%	16*	12%
COAD	1	(0%)	2	(0%)	2.1 (1.2-2.5)	1	2%	1	1%	0	0%
Asthma	2	(1%)	4	(1%)	2 (1.7-3.3)	1	2%	2	1%	1	1%
Malignancy	2	1 (%)	2	(0%)	0.9 (0.6-1.2)	0	0%	2	1%	0	0%
Charlson's Comorbidity Index (CCI)											
0	53	(16%)	39	(11.2%)		4	7%	18	11%	17	13%
1 or 2	106	(30%)	86	(25%)		13	26%	36	23%	37	28%
3 or 4	115	(33%)	123	(35.5%)		21	37%	53	34%	49	37%
5 or 6	61	(18%)	82	(24%)		12	22%	47	29%	23	18%
>7	9	(3%)	16	(5%)		5	8%	6	3%	5	4%

Note- Odds ratio for mortality who expired as compared to discharge as shown was increased for all comorbid conditions except hypertension and malignancy. To evaluate risk factors influencing the time of mortality, discharged patients were compared in the three groups according to time of mortality. Our results showed that chronic kidney disease was significantly associated (P=0.005) with mortality in groups I and II and obesity was significantly (P=0.003) associated with late mortality (group III). * P<0.05
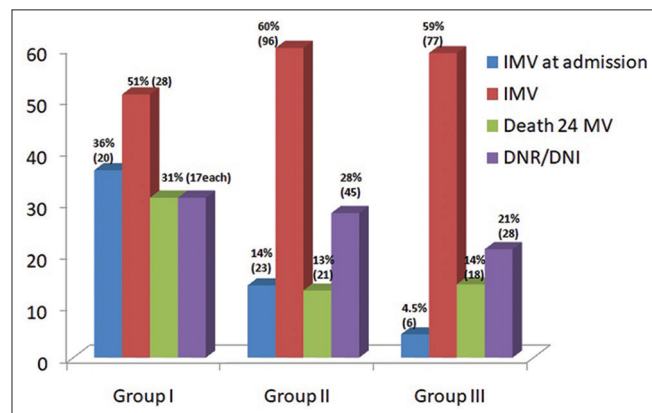
Figure 2: Graphical representation of patients in each group according to time mortality that were on ventilation at admission, needed ventilation later on, died within 24h of ventilation, or had DNR/DNI orders in place (limitation:~16% of missing data regarding details of ventilation)

to nonacceptance of mechanical ventilation as the mode of treatment or financial issues of the families. DNR/DNI was followed as per the attendant's consent in 21%(73) during hospital admission.

Figure 3 shows the patient distribution by peak WHO ordinal scale. We divided the patients on high oxygen support (category 5) into two groups based on the presence of organ failure into 5a and 5b.

In the comparison of vital parameters (systolic blood pressure -SBP, respiratory rate, GCS, and oxygen saturation) at the time of admission with the outcome (discharge and time of demise) hypotension defined as SBP <90mmHg was significantly associated with early death ($P < 0.001$), and low oxygen saturation was associated with poor outcome upto 10 days ($P < 0.001$). However, tachypnea was an ominous sign to be associated highly significantly ($P < 0.001$) with death at all times. GCS of the patient on admission was not associated with poor outcome ($P > 0.05$) [Table 2].

At ICU admission, 49 patients (14%) were on invasive mechanical ventilation. Severe COVID-ARDS causing refractory hypoxia was the major cause of death in all groups, accounting for 85% of deaths in groupI, 69%(108) ingroup II, and 51%(67) in grup III [Figure 4]. In group I, the next major cause of mortality was acute kidney injury, noted in 30%(17) of patients.

In group II, the median time to death was 5 days (range: 1–8; IQR: 3–7) days, where sepsis in 20% (32), AKI in 18%(28), and MODS in 10%(16) of patients were the cause for succumbing to illness. However, groupIII patients had relatively different causes of mortality, apart from refractory hypoxia. These untoward events in decreasing
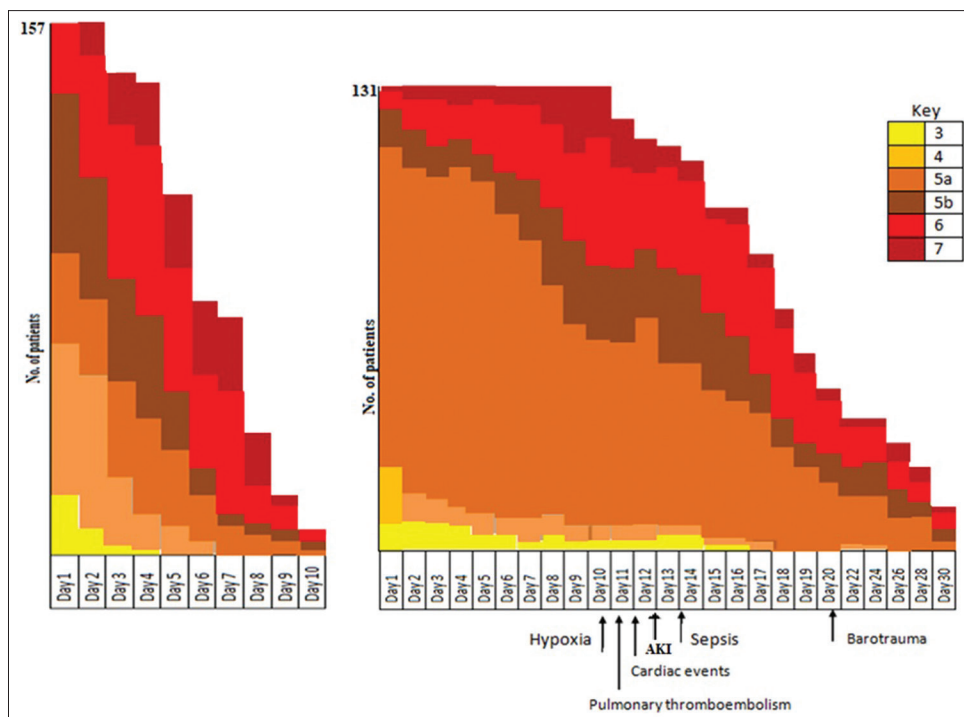
Figure 3: Distribution of patients according to the WHO ordinal scale. Note- WHO ordinal scale: 0-Uninfected; 1,2-Ambulatory; 3-Hospitalized, no oxygen therapy; 4-Hospitalized, oxygen therapy by mask or nasal prongs; 5-Hospitalized, severe disease, noninvasive ventilation, or high-flow oxygen; 6-Intubation and mechanical ventilation; 7-Ventilation and additional organ support (vasopressors, renal replacement therapy, or ECMO). We divided category 5 into 5a-only oxygen requirement with no organ support, 5b-oxygen requirement and additional organ support. Y-axis represents the total number of patients who died in hospital (A) group II, n = 157 (B) group III, n = 131. The arrows represent the median time of adverse events leading to death in this group of patients
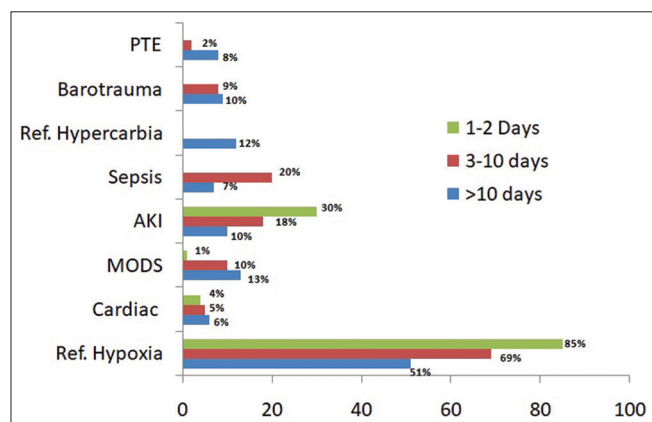
Figure 4: Comparison of causes of death in three groups according to time since hospital admission

order of frequency were barotrauma in 10%(18), pulmonary thromboembolism in 8%(10), and refractory hypercarbia in 12%(15), followed by MODS, AKI, sepsis, and cardiac events in 13%(21), 10%(16), 7%(11), and 6%(10), respectively. On further analysis, refractory hypoxia developed at a median of 10 days (range: 4–28) after admission, followed by thromboembolic events at 11 days (range: 5–17), cardiac failure at 11.5 days (range: 5–22), acute kidney injury at 12 days (range: 5–18), sepsis at 13.5 days (range: 4–19), and barotrauma at a median of 20 days (range: 8–35).

Discussion

This study, conducted in a tertiary care referral center in India, provides insight into the temporal patterns of mortality of COVID-19 patients during their hospital course. Providing quality care to a high volume of patients is a challenge for all health care systems; thus, many authors have studied the risk factors for the prediction of mortality, but few have highlighted the patient trajectory. Our attempt to analyze the day-wise mortality is important to understand the disease course and improve care for critically-ill hospitalized patients. As mortality from trauma is classically described with a trimodal distribution, with immediate deaths at the scene, early deaths due to hemorrhage, and late deaths from organ failure, we divided the patients who succumbed to COVID-19 into three groups according to the time to demise.[15]

Reports of mortality among critically ill ICU patients of COVID-19 vary significantly from 20% to 62%.[16,17] We report an overall mortality rate of 20% among patients with severe disease. The majority of patients in our series required ICU care, and a higher proportion were on ventilator at the time of admission. This is because our institute is a referral center catering to a large population of north India. A study from Wuhan reports a mortality of 97% in patients on ventilator.[18] This high rate can be attributed to the

Table 2: Analysis of vital parameters (systolic blood pressure, respiratory rate, GCS, oxygen saturation) at the time of admission with the outcome (discharge and time of demise) of the patient

Characteristics	Discharge	Mortality			P		
		0-2 days	3-10 days	>10 days			
Systolic Blood Pressure (mmHg)							
<90	0	5	1	0	HS	0.015	0.452
90-150	292	42	132	113			
>150	25	3	24	13			
Respiratory Rate (/min)							
<30	292	38	132	100	HS	HS	HS
>30	7	10	20	20			
GCS							
<8	0	1	2	0	0.051	0.079	1.000
>8	140	6	53	54			
SPO$_2$ (%)							
<70	10	11	20	4	HS	HS	0.013
70-80	8	5	9	13			
80-90	63	10	43	22			
90-100	250	19	83	89			

lack of appropriate knowledge about the pathophysiology and characteristics of the new disease at the time of the study (March2020) at the beginning of the pandemic. ICU outcome study from central Florida reports that 80% of patients remained alive at the end of their study, similar to our results.[19]

Desaturation and tachypnoea are hallmarks of hypoxic respiratory failure with severe COVID-19.[20] Our results are in coherence with this as these indicators were significantly associated with early death (groupsI and II). Most patients who died in group I had severe physiological disarrangements in the form of oxygen desaturation and hemodynamic instability; the rapid progression of disease after admission provided a narrow window to intervene to avert these outcomes. *As cardiac and respiratory derangements often interplay, focusing on aggressive resuscitation by using dynamic tools of fluid assessment and vasopressor may have been helpful in patient management and improving the outcome.*

The major cause of mortality in group II was refractory hypoxia followed by renal failure. According to our data, about 60% patients were ventilated in each group.As the ideal time to initiate ventilation in these patients is debatable, our results support that decreasing time to mechanical ventilation may not translate into improved survival. Another challenge encountered while managing refractory hypoxia in patients on invasive mechanical ventilation was increased minute ventilation and respiratory drives despite heavy sedation and neuromuscular blockade. There is evidence in the literature regarding a significant mismatch between the degree of hypoxemia and respiratory system compliance in COVID patients.[21] This needs the understanding that there are

different phenotypes of lung involvement in COVID-19 and the usual strategy of ARDS management may not benefit all. *Thus, timely focus on lung-protective ventilation and optimizing personalized ventilator strategy might benefit patients.*

Causes of mortality in groupIII were more related to complications related to hyper-coagulable state or lung injury (SILI/VILI/barotrauma) as patients in our cohort developed pneumothorax even on NIV or spontaneous breathing during vigorous cough episodes. There were 10 (8%) cases of pulmonary thromboembolism in our cohort. Among 18 (10%) patients who developed barotrauma (pneumothorax/pneumomediastinum), 10 were on non-invasive ventilation. High respiratory drive and large pleural pressure swings could have led to this. In addition, patient–ventilator dys-synchrony as reverse triggering are also associated with increments of tidal volume that may induce VILI.[22]

Incidence of organ failure secondary to sepsis leading to multi-organ failure in our cohort was much less than previously reported. Sepsis and cardiac events have been reported in 100% and 52% of patients, respectively, as complications of COVID-19 during the first wave.[23] Although some of these respiratory-related and infectious complications are preventable, at times, they are inevitable. This decline in incidence during the second wave could be from the lessons learned during the earlier wave.

Age has been shown to be a predictor of mortality by most studies; similarly, mortality in our cohort was highest in patients in the sixth decade.[24] In addition, patients in this group succumbed to the disease early, with 62% of early

deaths occurring in patients >60 years. This potential poor outcome can be related to immunosenescence and dysregulated host response in the elderly that leads to excessive viral multiplication and prolonged inflammatory response.[25,26]

Various comorbid conditions significantly add to the risk of mortality of COVID-19, with obesity having the highest odds ratio followed by chronic respiratory disorders in our cohort.[27] Literature supports that increased BMI is strongly associated with severe disease or death.[28] Obesity can also impair respiratory mechanics. A Brazilian study that reports diabetes and cardiac disease as risk factors for lethal outcomes had a limited number of patients with high BMI to perform an over-weight categorized analysis.[29] We also calculated the CCI for all patients, and our patients were equally distributed with regard to CCI among different groups. Hence, it suggests that though the presence of comorbid conditions increases the susceptibility to COVID-19, once affected, early or late mortality was not affected by underlying comorbid conditions; the infection itself plays the dominant role.

Limitations

Our study has limitations too. First, data were derived from a single health system, thus limiting generalizability. Second, due to retrospective data collection, there was about 16% missing data about comorbid conditions. Third, days of illness from the first symptom onset was not analyzed, and delayed presentation to the hospital can cause higher mortality in the early period. Lastly, post-discharge outcomes were not considered if they occurred later after discharge. Moreover, we did not compare patients this data of the second wave with that of the first wave.

Another missing dimension in published literature, including ours, which has complexity and dynamism very similar to ICU, is the SHELL model of aviation safety. The peculiar organizational aspects of the interaction of software (S), hardware (H), environment (E), and liveware (L) are known as the SHELL model.[28] Each component has inherent falsies that can be substantial attributing to mortality and have not been discussed ever. The guidelines and algorithms that form the software were framed based on substantial evidence through fast-track literature and were changed very frequently. Hardware included the loads of equipment (ventilators) that were purchased on an emergency basis. Moreover, many health care workers may not have been exposed to work in such critical settings before. Lastly, the interaction of liveware among themselves through effective communication is paramount for successful outcomes and reducing medical errors. Looking into each of the component of SHELL model, as a posthoc air crash investigation, may make us wiser and capable of handling crisis situations.

Lessons learned

Suggestions to make the system less prone to errors and achieve improved outcomes

- Preparedness of facility infrastructure to cohort critically ill patients at one location
- Retain and recruit adequate staff
- Regular training and motivation of staff
- Adjustments in duty schedule to minimize the variation of staff and at the same time prevent burn-out
- Secure enough personal protective equipment
- Develop institutional protocols according to best practice recommendations.

Conclusion

Despite limitations, the strength of the study is that we tried to analyze the disease course of patients who died in the hospital to find out events associated with severe outcomes. To conclude, our study is the first of its kind from the region to find out potential areas of improvement to fight against the COVID-19 pandemic. This will help to contribute to better outcomes and mortality reduction.

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Conflicts of interest
There are no conflicts of interest.

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