

# Changing Critical Care Patterns and Associated Outcomes in Mechanically Ventilated Severe COVID-19 Patients in Different Time Periods: An Explanatory Study from Central India

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Received on: 27 April 2022; Accepted on: 07 July 2022; Published on: 31 August 2022

## ABSTRACT

**Background:** The outcomes in critical illness depend on disease severity, practice protocols, workload, and access to care. This study investigates the factors affecting outcomes in mechanically ventilated coronavirus disease-2019 acute respiratory distress syndrome (COVID-19 ARDS) patients admitted in a tertiary teaching hospital intensive care unit (ICU) in Central India with reference to different time periods in pandemic. This is one of the largest series of mechanically ventilated COVID-19 ARDS patients, globally.

**Methods:** This retrospective cohort study classified the entire data into four time periods (Period 1: April 2020 to June 2020; Period 2: July 2020 to September 2020; Period 3: October 2020 to December 2020; and Period 4: January 2021 to April 2021). We performed a multivariable-adjusted analysis to evaluate predictors of mortality, adjusted for baseline-severity, sequential organ failure assessment (SOFA score) and time period. We applied mixed-effect binomial logistic regression to model fixed-effect variables with incremental complexity.

**Results:** Among the 56 survivors (19.4%) out of 288 mechanically ventilated patients, there was an up-gradient of survival proportion (0, 18.2, 17.4, and 28.6%) in four time periods. Symptom-intubation interval (OR 1.16; 95% CI 1.03–1.31) and driving pressures (DPs) (OR 1.17; 95% CI 1.07–1.28) were significant predictors of mortality in the model having minimal AIC and BIC values. Patients aged above 60 years also had a larger effect, but statistically insignificant effect favoring mortality (OR 1.99; 95% CI 0.92–4.27). The most complex but less parsimonious model (with higher AIC/BIC) indicated the protective odds of high steroid on mortality (OR 0.59; 95% CI 0.59–0.82).

**Conclusion:** The outcomes in mechanically ventilated COVID-19 ARDS patients are heterogeneous across time windows and may be affected by the complex interaction of baseline risk and critical care parameters.

**Keywords:** Acute respiratory distress syndrome, Coronavirus disease-2019, Intensive care unit, Mechanical ventilation.

*Indian Journal of Critical Care Medicine* (2022): 10.5005/jp-journals-10071-24279

## HIGHLIGHTS

- One of the largest series of mechanically ventilated COVID-19 ARDS patients.
- Outcome model adjusted for different time period and severity at presentation.
- Mixed-effect model created on a theoretical grounds rather than data driven.
- Driving pressure and symptom onset to ICU admission were independent predictors of mortality.

## INTRODUCTION

Severe COVID-19 infection leads to ARDS, which has been managed by intubation and protective lung ventilation.<sup>1</sup> With advent of COVID-19 pandemic, early case-series from Wuhan, China reported that 31 out of 32 patients on mechanical ventilation (MV) died.<sup>2</sup> These early reports of poor outcomes, and worries about aerosol generation during intubation process led to apprehensions regarding use of MV.<sup>3–6</sup> Intensivists initially placed a greater reliance on non-invasive modes of MV (NIV) and high flow nasal oxygen (HFNO) in COVID-19 ARDS, contrary to the traditional practices.

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**How to cite this article:** Saigal S, Joshi A, Panda R, Goyal A, Kodamanchili S, Anand A, *et al.* Changing Critical Care Patterns and Associated Outcomes in Mechanically Ventilated Severe COVID-19 Patients in Different Time Periods: An Explanatory Study from Central India. *Indian J Crit Care Med* 2022;26(9):1022–1030.

As COVID-19 pandemic progressed, more pathophysiologic evidences became apparent. The clinical trials had started reporting utility of anti-inflammatory and anti-viral agents, and various other case-series had started reporting modest survival rates of patients on MV.<sup>7-9</sup> This was the phase of aggressive intensive care management, and the use of a variety of therapeutics including steroids, anti-coagulants, anti-viral drugs, convalescent plasma, interleukin-6 inhibitors, and JAK-2 inhibitors.

While outcomes in critical illness do depend on disease severity, practice patterns, and protocols. It also depends on patient selection, overall workload and turnover in the ICU. Going by the premise that the cumulative impact of successful practices is greater than their individual sum, we have evaluated the outcomes in mechanically ventilated severe COVID-19 ARDS patients at our center over last 1 year period. This is one of the largest series of mechanically ventilated COVID-19 ARDS patients, globally. We used mixed-effect binomial logistic regression to evaluate models of fixed-effect variables with incremental complexity.

## METHODS

### Design and Ethics Statement

We performed a retrospective cohort study of mechanically ventilated COVID-19 patients admitted to an ICU of a tertiary care teaching hospital located in Central India. At the beginning of the pandemic in the last week of March 2020, a dedicated 16-bedded ICU was established which was later expanded to a 40-bedded unit over next 2 months. This study was conducted on the patients admitted to ICU for a little over 1 year from 1 April 2020 to 15 April 2021. Subsequently, from April 2021 to July 2021, our health facility was overwhelmed with the onset of the second wave. At this time, the ICU beds were even extended to areas outside ideal ICU settings, and intensive care had to be provided by non-intensivists; hence, we truncated our study period. During the study period, COVID-19-ICU was operated under trained intensivists, who recorded all patient details on ICU charts. All investigation details were available from the hospital information system. The study design with a request for waiver of consent was approved by Institutional Ethical Committee, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India (IHEC-LOP/2020/ IM0281).

### Standard ICU Practices

All patients presenting to the emergency area of the hospital are triaged and those with severe illness ( $SpO_2 < 90\%$  on room air) are considered for ICU admission. The patients admitted to ICU are regularly monitored and depending on the severity of the infection, they are managed with NIV/HFNO/ $O_2$  therapy. The patients who have either tachypnea [Respiratory rate (RR)  $> 30$ /minute] or a high oxygen demand ( $FiO_2$  more than 0.60) are considered for invasive MV. Subsequent to MV, we follow a protective lung ventilation as per ARDS-net criteria.<sup>10</sup> Prone ventilation is initiated in mechanically ventilated patients and continued as per tolerance and hemodynamic stability.

### Participants

We included all COVID-19 reverse transcription-polymerase chain reaction (RT-PCR) positive patients who were admitted between 1 April 2020 and 15 April 2021 to the ICU and required invasive MV. We excluded pregnant women, all patients who died within 24 hours

Source of support: Nil

Conflict of interest: None

of initiation of MV, and patients whose caregivers decided to leave against medical advice.

### Study Procedures

A list of all eligible patients was drawn from the ICU admission register, and their case records and ICU charts for all the days of their ICU stay were retrieved. We retrieved and abstracted information pertaining to demography (age and gender), pre-admission morbidity [diabetes mellitus (DM), hypertension (HTN), ischemic heart disease, chronic kidney disease (CKD), malignancies, etc.], COVID-19 related disease history (onset and nature of symptoms, date of admission to hospital, and admission to ICU), vitals, oxygenation and SOFA score at the time of ICU admission, pre-intubation treatment in the ICU, date of intubation, onset of MV, parameters related to MV related mechanics, best  $PaO_2-FiO_2$  ratio in each 24 hours, investigations, administration of key therapeutic agents, and outcome during hospital stay. The operational definitions used in the study are further described in Supplementary Appendix S1.<sup>11,12</sup>

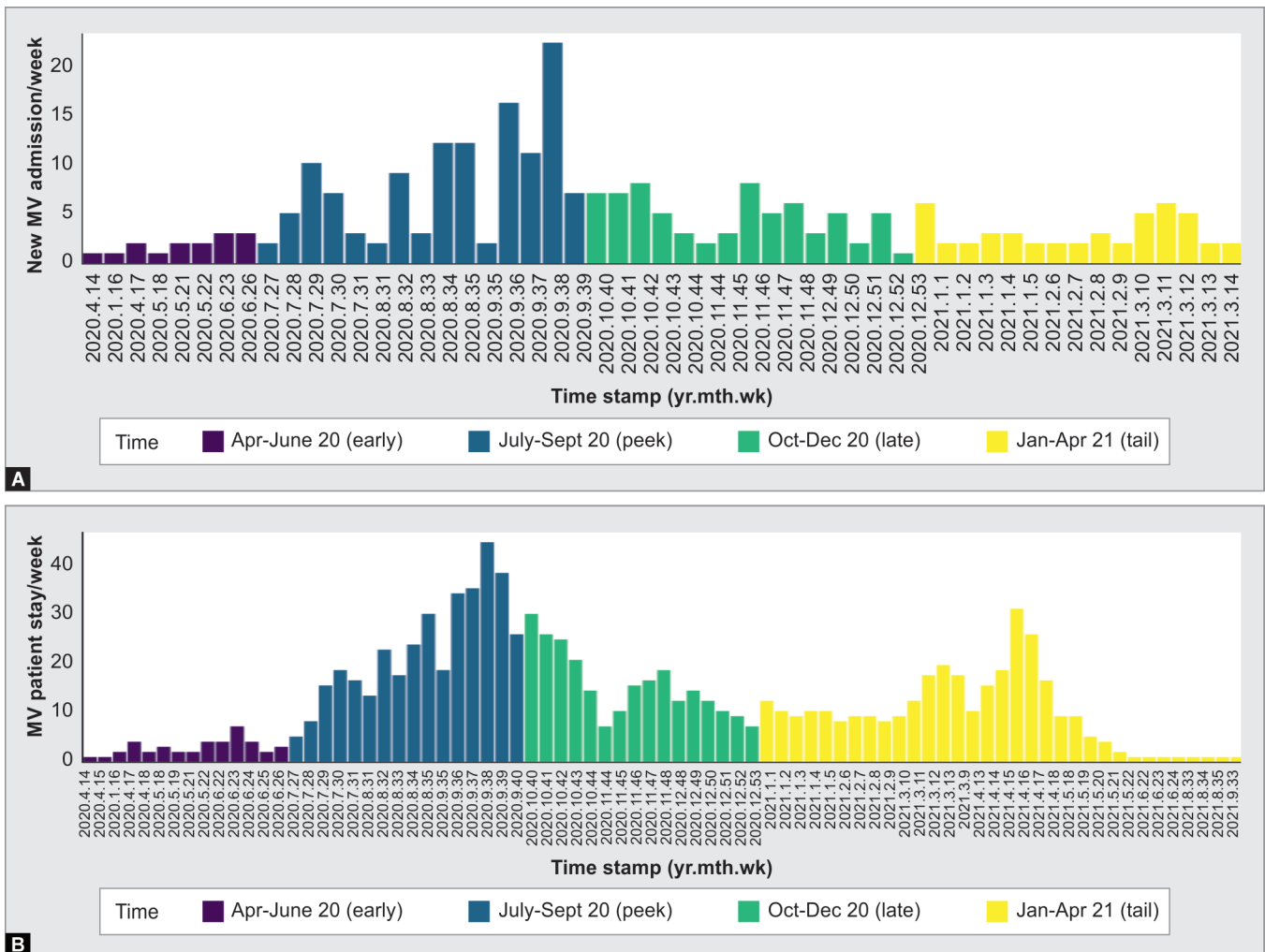
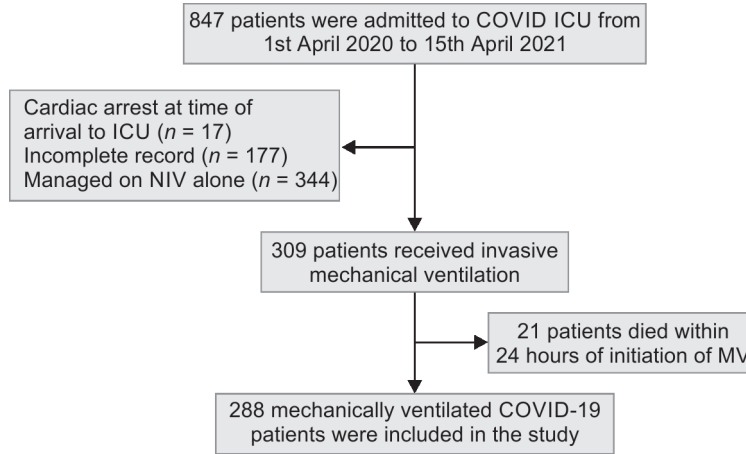
### Statistical Analysis

Abstracted data was entered in Microsoft Excel, cleaned and analyzed using R software [version 4.1.2 (Bird Hippie)]. The entire data was stamped week-wise and classified in time periods (Period 1: April 2020 to June 2020; Period 2: July 2020 to September 2020; Period 3: October 2020 to December 2020; Period 4: January 2021 to April 2021). Distribution of new and cumulative patients on MV, in weeks of these time periods was demonstrated using bar charts. We compared distribution of demographic, pre-admission morbidity, and in-hospital treatment characteristics across these time periods. The distributions and dispersions of continuous variables collected at multiple time points [C-reactive protein (CRP), absolute lymphocyte count (ALC), fraction of oxygen in inspired air ( $FiO_2$ ),  $PaO_2-FiO_2$  ratio (PFR)] collected on multiple days were understood through visualizations like rain cloud, kernel density, composite box plots, and bubble diagrams. We also compared the characteristics of survivors with non-survivors through an exploratory unadjusted bivariate analysis. We performed a multivariable-adjusted analysis to evaluate predictors of mortality, adjusted for baseline severity SOFA score and time period. We used mixed-effect binomial logistic regression models to calculate the odds ratios (ORs) of fixed-effect variables in models with incremental complexity. The process of model construct is further described in details in Supplementary Appendix S1.

## RESULTS

A total of 288 patients were mechanically ventilated during the study period (Flowchart 1) overall, a total of 56 (19.4%) patients survived after MV. The distribution of patients in four study periods was 17 (5.9%), 132 (45.8%), 69 (24%), and 70 (24.3%), respectively. Incident and cumulative distribution is shown in Figure 1. The proportion of survivors in each of the four periods was 0, 18.2, 17.4, and 28.6%, respectively. Trend toward higher survival was statistically significant ( $p = 0.043$ ).

Flowchart 1: Study flow



**Table 1:** Distribution of baseline variables in mechanically ventilated COVID-19 patients across time periods

Parameter	Total (n = 288)	April–June 17 (5.9%)	July–September 132 (45.8%)	October–December 69 (24%)	January–April 70 (24.3%)	p-value
Age (years) (Median + IQR)	60 (19–90)	62 (58–90)	60 (52–76)	62 (52–76)	56 (45–82)	0.455
SOFA (Median + IQR)	6 (3–16)	8 (7–12)	6 (4–12)	7 (4–12)	6 (4–12)	0.036
Gender (M:F)	197:90	13:04	97:35:00	49:20:00	38:31:00	0.046
Number of comorbid illnesses (Median + IQR)	1.0 (0–4)	1 (0–3)	1 (1–3)	1 (1–3)	1 (1–3)	0.704
DM [n (%)]	151/288 = 52.4%	8 (47.1%)	71 (53.8%)	36 (52.2%)	36 (51.4%)	0.955
HTN [n (%)]	183/288 = 63.5%	10 (58.8%)	82 (62.1%)	46 (66.7%)	45 (64.3%)	0.09
CKD [n (%)]	25/288 = 8.7%	1 (5.9%)	12 (9.1%)	10 (14.5%)	2 (2.9%)	0.105
Symptom-admission interval days (Median + IQR)	5 (1–30)	8 (3–17)	5 (4–11)	5 (3–15)	5 (4–11)	0.444
Mild ARDS [n (%)]	18 (6.3%)	0	6 (4.5%)	9 (13%)	3 (4.3%)	0.004
Moderate ARDS [n (%)]	135 (46.9%)	11 (64.7%)	53 (40.2%)	40 (58%)	31 (44.3%)	
Severe ARDS [n (%)]	135 (46.9%)	6 (35.3%)	73 (55.3%)	20 (29%)	36 (51.4%)	
Admission PFR (Median + IQR)	107 (45–280)	105 (90–219)	100 (82.5–178)	130 (96–232)	97 (80–185)	<0.001

DM, diabetes mellitus; IQR, interquartile range

This increased survival was despite more severe ARDS patients in second, third, and fourth time periods (Tables 1 and 2). The patients, in later time periods were longer on MV, had higher length of ICU and hospital stay. As compared to the patients in earlier time periods, those in later time periods received more proning sessions, anti-viral medication, Remdesivir, and higher dose of steroids. Age and proportion of patients with comorbidities were of no-different in each of the quarters. There was a trend for early intubation in fourth time period, that is, 2 days but was statistically not significant (Table 2).

Overall, the survivors were significantly different from non-survivors in terms of lower age, lower median SOFA scores, and lower proportion of comorbidity (Table 3). While the initial disease severity was similar in survivors and non-survivors, survivors were admitted to ICU 1 day earlier, and their median duration of intubation was 1 day earlier from the onset of tachypnea and  $FiO_2 > 0.6$  (HACOR >5). Survivors also had better MV compliance and lower DPs as compared to non-survivors. A significant fall in CRP-levels and a significant rise in absolute lymphocyte count by day-10 of ICU-stay was seen in the survivors. Survivors stayed in hospital and ICU longer than the non-survivors (Table 3; Supplementary Appendix S2).

In multivariable mixed-effect model, symptom–intubation interval (OR 1.16; 95% CI 1.03–1.31) and DPs (OR 1.17; 95% CI 1.07–1.28) were significant predictors of mortality in models 3 and 4 (Table 4). These models had the minimal AIC and BIC values (model 3: AIC = 250.98/BIC = 291.2; model 4: AIC = 251.178/BIC = 295) with the  $R^2_{con} = 0.42$ . Group having age >60 years also had a larger but statistically insignificant odds favoring mortality [model 3: OR 1.99 (0.92–4.27); model 4: OR 1.96 (0.91–4.24)]. The more complex models (models 5 and 6) had the higher AIC/BIC than other parsimonious models. High adequate steroid category had a significant protective effect on mortality (OR 0.59; 95% CI 0.59–0.82) in most complex model (model 6: AIC = 254.39; BIC = 305.5,  $R^2_{con} = 0.43$ ) (Table 4). Interested readers may further refer to Supplementary Appendix S2, where some additional exploratory analysis along with r-codes used to create them are given.

## DISCUSSION

In this current study, we found that one in five patients with ARDS, who required invasive MV, survived. Ours is one of the largest series of mechanically ventilated COVID-19 ARDS patients, globally. We found that survival among patients requiring MV improved in the later quarters of the study period. This change was despite patients with lower  $PaO_2/FiO_2$  (P/F) ratios getting admitted to the ICU. This indicates better ICU care over the period of time, which is also reflected in longer duration of MV, more proning sessions, higher steroid, and Remdesivir use in the later quarters.

### Comparison of Demographic, Ventilatory, Inflammatory Variables, Therapeutic, Complications across Time Periods

In the first quarter from April 2020 to June 2020, we did not use any anti-viral medication, and we only sparingly used hydroxychloroquine or ritonavir. Further, the confidence in utility of steroids was also low in this period, especially because of reported harms of steroids in the previous H1N1 epidemic.<sup>13</sup> In pre-COVID era, the use of steroids in ARDS has been controversial, and there were only a handful of advocates of steroid use in severe community acquired pneumonias.<sup>14</sup> Further, NIV/HFNC was the preferred mode of ventilation at this time, with invasive ventilation being practiced as a last-resort measure.

In the subsequent quarter, more evidence in favor of invasive MV, steroids, and anti-viral drugs had emerged.<sup>7,15,16</sup> Gattinoni et al. suggested that there are basically two phenotypes L and H where L type is associated with low elastance; in these types of patients low PEEP and proning helps. The other phenotype is H type where patients have low compliance, this is typical ARDS lung where high PEEP and proning works.<sup>17,18</sup> The same is reflected in this study where patients had compliance in range of 9–42 mL/cm H<sub>2</sub>O. This led to conclusion that individualized patient care is needed. The self-inflicted lung injury (SILI) concept, that is, if the patient is allowed to breath spontaneously, the generation of high tidal

**Table 2:** Distribution of inflammatory variables, therapeutic interventions, complications in mechanically ventilated COVID-19 patients across time periods

Parameter	Total (n = 288)	April–June 17 (5.9%)	July–September 132 (45.8%)	October–December 69 (24%)	January–April 70 (24.3%)	p-value
CRPO (Median + IQR) mg/dL	115.48 (7.24–550)	106 (50–373)	120.45 (57.6–355)	115 (44–343)	104.5 (62–316)	0.713
CRP10 (Median + IQR) mg/dL	75 (1.79–550)	91 (80–297)	67 (30.3–245)	95.34 (59–234)	53 (26–174)	0.131
ALCO (Median + IQR) Thousand/ $\mu$ L	745 (120–5,730)	850 (49–2,246)	670 (410–1,830)	740 (510–1,620)	780 (570–1,470)	0.216
ALC10 (Median + IQR) Thousand/ $\mu$ L	570 (10–4,860)	750 (535–3,553)	560 (360–1,840)	480 (300–2,470)	695 (440–1,720)	0.145
Timing of intubation days* (Median + IQR)	3 (1–30)	4 (1–14)	3 (2–14)	3 (1–12)	2 (1–15)	0.085
DP cm H <sub>2</sub> O (Median + IQR)	19 (9–31)	16 (15–26)	19 (16–26)	18 (16–30)	19 (16–27)	0.562
Compliance mL/cm H <sub>2</sub> O (Median + IQR)	21 (9–42)	24 (19.95–42)	20 (16–30)	22 (16–36)	21.5 (15–30)	0.373
Duration of MV days (Median + IQR)	6 (0–43)	6 (4–21)	5 (4–19)	6 (4–24)	10 (5–27)	<0.001
Number of proning sessions (Median + IQR)	2 (1–10)	1 (0–6)	1 (0–5)	2 (1–5)	3 (1–7)	<0.001
First dose of steroids mg (Median + IQR)	250 (0–1,000)	120 (60–1,000)	500 (125–1,000)	250 (80–500)	250 (80–500)	<0.001
No steroid use [n (%)]	43 (15%)	10 (58.9%)	21 (15.9%)	10 (14.5%)	2 (2.9%)	<0.001
High steroid use [n (%)]	182 (63.2%)	6 (35.3%)	98 (74.2%)	34 (49.3%)	44 (62.9%)	
Low steroid use [n (%)]	63 (21.9%)	1 (5.9%)	13 (9.8%)	25 (36.2%)	24 (34.3%)	
Remdesivir usage [n (%)]	187 (64.9%)	0	76 (57.6%)	55 (79.7%)	56 (80%)	<0.001
TCZ usage [n (%)]	12 (4.2%)	0	11 (8.4%)	0	1 (1.4%)	0.012
BSI [n (%)]	82 (28.5%)	8 (47.1%)	37 (28%)	24 (34.8%)	13 (18.6%)	0.055
VAP [n (%)]	105 (35.8 per 1,000)	7 (41.2%)	43 (32.6%)	22 (31.9%)	31 (44.3%)	0.325
Vasopressor [n (%)]	204 (70.8%)	16 (94.1%)	90 (68.2%)	61 (88.4%)	37 (52.9%)	<0.001
AKI [n (%)]	163 (56.8%)	14 (82.4%)	70 (53%)	43 (62.3%)	36 (51.4%)	0.073
AF [n (%)]	41 (14.2%)	1 (5.9%)	25 (18.9%)	7 (10.1%)	8 (11.4%)	0.19
Hospital LOS days (Median + IQR)	13 (1–90)	10 (6–25)	12 (8–36)	12 (7–46)	16 (9–54)	0.086
ICU LOS days (Median + IQR)	11 (1–57)	9 (6–21)	10 (6–31)	9 (6–33)	14 (9–47)	0.011
Survival [n (%)]	56 (19.4%)	0	24 (18.2%)	12 (17.4%)	20 (28.6%)	0.043

\*Timing: Day from which intubation was attempted once RR >30/minute and FiO<sub>2</sub> requirement of more than 0.6; IQR, interquartile range

volumes due to hypoxic drive would eventually lead to wide pressure swings which will subsequently lead to lung injury.<sup>8,19</sup> In the first quarter, we were intubating patients too late which might have exacerbated SILI, resulting in low compliance and in turn high DP. Hence, we started intubating the patients early in the second quarter (median 3 days) and the survival rate improved to 18.2%. Recovery trial results were published, and confidence in use of steroids for cytokine storm increased.<sup>19</sup> In this quarter, benefits of Remdesivir emerged as part of ACTT trial, and the drug also became available outside of clinical trials to us.<sup>16</sup> About 57% of

our mechanically ventilated patients had received this drug during this time. This time period also coincided with peak of first wave of COVID-19 hospitalizations.

By the third quarter (October 2020 to December 2020), COVID-19 care protocols were well established. Usual intensive care practices of early intubation, prone ventilation, and infection prevention were mainstays of management. The last quarter of the study (January 2021 to April 2021) coincided with reduced incidence of hospital admissions and this was also a period associated with early intubations, longer periods of MV, and inflammatory marker





**Table 3:** Comparison of demographic, ventilatory, inflammatory variables, therapeutic, complications among non-survivors and survivors

Parameter	Non-survivors (n = 232)	Survivors (n = 56)	p-value
Age (years) (Median + IQR)	61 (53–80)	50 (45–69)	<0.01
SOFA (Median + IQR)	7 (4–12)	4 (4–8)	<0.01
Gender (M:F)	162:89	35:21	0.27
Number of comorbid illness (Median + IQR)	2 (1–3)	1 (1–2)	<0.001
DM [n (%)] 151/288	128 (55.2%)	23 (41.1%)	0.058
HTN [n (%)] 183/288	156 (67.2%)	27 (48.2%)	0.008
CKD [n (%)]	24 (10.3%)	1 (1.8%)	0.041
Symptom-admission interval days (Median + IQR)	6 (4–13)	5 (3–11)	0.006
Category of ARDS [n (%)] mild	14 (6%)	4 (7.1%)	0.623
Category of ARDS [n (%)] moderate	112 (48.3%)	23 (41.1%)	
Category of ARDS [n (%)] severe	106 (45.7%)	29 (51.8%)	
P/F ratio on admission (Median + IQR)	95 (80–180)	94.5 (80–212)	0.996
DP cm H <sub>2</sub> O (Median + IQR)	19 (16–27)	17 (14–24)	<0.001
Compliance mL/cm H <sub>2</sub> O (Median + IQR)	20 (15.6–33)	24 (19–35)	<0.001
Timing of intubation* days (Median + IQR)	3 (2–14)	2 (1–14)	<0.001
NIV failure [n (%)]	171 (73.7%)	26 (46.4%)	<0.001
Duration of MV (Median + IQR)	6 (4–20)	12 (5–31)	<0.001
Number of proning sessions (Median + IQR)	1 (1–6)	2 (1–7)	0.001
First dose of steroids mg (Median + IQR)	250 (80–500)	250 (250–500)	0.153
Category of steroids [n (%)] high	138 (59.5%)	44 (78.6%)	0.029
Category of steroids [n (%)] low	56 (24.1%)	7 (12.5%)	
Category of steroids [n (%)] inadequate	38 (16.4%)	5 (8.9%)	
Remdesivir usage [n (%)]	137 (59.1%)	50 (89.3%)	<0.001
TCZ usage [n (%)]	8 (3.5%)	4 (7.1%)	0.217
CRP0 (Median + IQR) mg/dL	113 (52.3–342)	136 (63.33–357)	0.479
CRP10 (Median + IQR) mg/dL	90 (46–274)	49 (19.56–170)	<0.001
ALC0 (Median + IQR) Thousand/ $\mu$ L	730 (470–1,780)	770 (470–1,820)	0.274
ALC10 (Median + IQR) Thousand/ $\mu$ L	520 (330–1,650)	1,000 (640–2,270)	<0.001
BSI [n (%)]	65 (28%)	17 (30.4%)	0.728
VAP [n (%)]	74 (31.9%)	29 (51.8%)	0.005
Vasopressor [n (%)]	186 (80.8%)	18 (32.1%)	<0.001
AKI [n (%)]	154 (66.4%)	9 (16.1%)	<0.001
ICU LOS days (Median + IQR)	10 (6–26)	17 (10–53)	<0.001
Hospital LOS days (Median + IQR)	11 (7–27)	27 (19–55)	<0.001

\*Timing: Day from which intubation was attempted once RR >30/minute and FIO<sub>2</sub> requirement of more than 0.6; DM, diabetes mellitus; P/F, PaO<sub>2</sub>/FIO<sub>2</sub>

targeted immunosuppressive therapies. Our practices were also supported by available literature that suggested benefits of early intubation.<sup>18,20–22</sup> This period was also associated with best survival outcomes of 28% in our series.

### Comparison of Demographic, Ventilatory, Inflammatory Variables, Therapeutic, Complications among Survivors and Non-survivors

The median age in survivors was 50 as compared to 61 in non-survivors. This is in sync with previous studies where elderly patients on MV had a higher mortality.<sup>7–9</sup> The median SOFA score in survivors was 4 as compared to 7 in non-survivors. The SOFA score in our study basically reflects respiratory SOFA as 93% of our patients had moderate-to-severe ARDS which itself contributed to a score of 3–4. The need of vasopressors along with mild degree of renal dysfunction contributed to higher SOFA scores in

non-survivors. The median number of comorbidities in survivors was 1 as compared to 2 in non-survivors, this is consistent with the previous studies where increased comorbidities led to worse outcomes.<sup>7–9</sup>

We had 95% patients with moderate-to-severe ARDS. Our survival rate was 17% in moderate ARDS vs 21.5% in severe ARDS which was statically insignificant. The previous studies have demonstrated a higher mortality in patients with severe ARDS.<sup>9</sup> Here, we would like to emphasize that it is not the classification of ARDS on admission which decides the outcome, but the disease progression and intervention associated with it finally decides the outcome. The patients had better survival rate in patients' severe ARDS which indicates that the diseased had reached its nadir and things had to improve thereafter.

The median time for intubation in survivors was 2 as compared to 3 in non-survivors. In our study, a delay in intubation by one day

**Table 4:** Multivariable logistic regression models for predictors of mortality

Variables	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age-group (>60 years)	<b>3.08 (1.12–8.49)</b>	<b>2.86 (1.05–7.83)</b>	1.99 (0.92–4.27)	1.96 (0.91–4.24)	1.88 (0.86–4.08)	<b>1.9 (1.89–1.91)</b>
Age-group (40–60 years)	2.02 (0.80–5.14)	1.83 (0.72–4.65)				
Diabetes mellitus	1.08 (0.55–2.12)					
Symptom-admission interval		<b>1.15 (1.03–1.29)</b>	<b>1.16 (1.03–1.31)</b>	<b>1.21 (1.06–1.38)</b>	<b>1.16 (1.03–1.31)</b>	<b>1.17 (1.17–1.18)</b>
DP			<b>1.17 (1.07–1.28)</b>	<b>1.17 (1.07–1.29)</b>	<b>1.15 (1.04–1.26)</b>	<b>1.17 (1.17–1.18)</b>
ALC on admission				0.71 (0.36–1.42)	0.74 (0.37–1.47)	<b>0.73 (0.73–0.73)</b>
Indication to intubation interval					1.09 (0.97–1.22)	
Steroid category (high adequate)						<b>0.59 (0.59–0.59)</b>
Steroid category (low adequate)						<b>1.04 (1.04–1.05)</b>
Model predictiveness (conditional R2)	0.26	0.30	0.41	0.41	0.44	0.43
Model AIC	270.27	262.36	250.97	251.17	252.22	254.39

All models are adjusted for baseline severity (SOFA) and study period. Significant variables in each model are depicted in bold

increased mortality by 4%. The recent meta-analysis by Papousi et al. found no effect of timing of intubation on mortality in CARDS, in their meta-analysis they defined early, as need of intubation within 24 hours of ICU admission.<sup>23</sup> In their meta-analysis, in fact, early intubation was associated with higher mortality, the reason for the same could be more sick patients (likely to die) would have been intubated early. Tobin also raised this issue and suggested that timing of intubation should be calculated from time of onset of dyspnea and not ICU admission.<sup>24,25</sup> We, in this study, defined timing as day from which intubation was attempted once RR >30/minute and FIO<sub>2</sub> requirement of more than 0.6 (whether on NIV/HFNC), that is, HACOR score >5.<sup>26</sup>

The median compliance in survivors was 24 mL/cm H<sub>2</sub>O as compared to 20 mL/cm H<sub>2</sub>O in non-survivors (*p* < 0.001). The average compliance reported in patients with COVID ARDS in western literature is around 35–40 mL/cm H<sub>2</sub>O, whereas in our study, the median compliance was around 21 mL/cm H<sub>2</sub>O.<sup>7–9,22</sup> The DP were low in survivors, that is, 17 cm H<sub>2</sub>O vs 19 cm H<sub>2</sub>O in non-survivors. In a study by Amato et al., DP >15 cm H<sub>2</sub>O were associated with poor outcomes.<sup>27</sup> Both parameters mentioned above just indicates that the majority of our patients had poor compliance and in turn needed high DPs. The tracheostomy rates and extubation failure rates were comparable across both the groups. The ICU length of stay, number of proning sessions and duration of MV were significantly increased in survivors which argues well that survivors take a long time to recover.

We also looked upon inflammatory markers, on admission survivors had a higher CRP than non-survivors but on day 10 non-survivors had a higher CRP as compared to survivors which was statistically significant. The non-survivors had a chaotic pattern of CRP and had secondary rise in CRP which was due to secondary infection (Supplementary Appendix S2). Increased neutrophil lymphocyte ratio (NLR) ratios have been correlated with ICU admission rates but ours is the first study which has looked into serial lymphocyte count.<sup>28</sup> The serial lymphocyte count argues well with cell mediated immunity, on day 10 survivors had a higher lymphocyte count as compared to non-survivors. There is gradual

increase in the ALC in survivors, in contrast to non-survivors where chaotic pattern is observed as some of the non survivors had sepsis with septic shock where ALC is bound to increase (Supplementary Appendix S2).

Using Remdesivir and high-dose steroids in our study was found to be protective odds on mortality in univariate analysis. In composite model 6, high steroids category had sizable survival benefits (OR 0.59–0.67) while the low steroid category actually increased the odds of mortality. However, a composite model 6 could not explain the more model variability by adding complexity (steroid) compared to model 3/4 (where the steroid category was not added as predictors) so a cause–effect relationship may not be established. Still, it may assign a clinical intuition that high steroid might add to the survival benefits for patients lying on the sickest spectrum of the disease. Adding to this context we report the incidence of blood stream infection (BSI) and ventilator associated pneumonia (VAP) was 28.5 and 35.8%, respectively. A total of 49% of our patients on MV received colistin; 14.2% of them received anti-fungal medication. Remdesivir had an overall protective effect on mortality as shown by unadjusted analysis but we did not keep it as predictors for adjusted analysis. As this association seems to be more incidental rather than causal in nature. There was nil use of Remdesivir in the early phase where mortality odds were highest and then there was consistent uptrends in both Remdesivir usage and survival rates. The role of Remdesivir on this skewed sickness spectrum MV patients needs to be explored more in the future.

The overall survival rates in this study were lower than most other reported series. Comparable survival rates following MV in other studies have ranged from 33% to 64%. A study from India by Zirpe et al. had a 33% survival rates, whereas others such as Italian, the USA, and German groups had much better survivals of 70, 64, and 50%, respectively.<sup>7–9,22,29</sup>

We received sickest of the patients which is reflected by poor lung compliance and higher DP compared to studies mentioned above. Moreover, this study attempts to look the phenomenon in longitudinal prospective, in which patients from early phase of pandemic are included. This phase had minimal success rate



because of combination of factors like doubts in benefits of MV, lack of the previous clinical experience and inherent chaos, logistics and resource management.

Last, this is a large single center experience, different intensive care centers could have had a very different patient selection and care practices, and their outcomes in mechanically ventilated COVID-19 ARDS patients could be very different. The study may not establish causality in totality and the control on confounders might be imperfect which is considered as an integral limitation of the retrospective cohort. Yet the methodological meticulousness in adding sequential complexity and choosing random and fixed effects rationally may assign it a methodological superiority over other studies.

## CONCLUSION

In this study, we have demonstrated that both COVID care as well as outcomes in mechanically ventilated COVID ARDS patients were heterogenous across time windows. We believe that that this effect is because of variety of factors such as enhanced knowledge of disease specific management, and implementing basic tenants of intensive care more diligently toward the last quarter of the year.

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## SUPPLEMENTARY MATERIAL

All supplementary materials are available online on the website of [www.ijccm.org](http://www.ijccm.org)

## ACKNOWLEDGMENTS

To my teachers, especially Prof AK Baronia who taught me the basics of critical care. To all the authors for their contribution in writing the manuscript and most importantly contributing in patient management. Special thanks to all staff, residents in managing these patients without whom this would have not been possible.

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