Research Article

ISSN: 3065-5641

Global Journal of Critical Care and Emergency Medicine

Effect of Early Vs Late Intubation on Outcomes in Critically ill Patients with COVID-19 A Protocolised Approach

Akhilesh VU[1]*, Vivek P[1], Naveen J[1], Swathy K[1], Rathenmurugan Mithun[1], Sreenath Sreelekshmi[1], Sudhakaran PR[2] and Oommen OV[2]

[1]*Department of Critical Care Medicine, PRS Hospital, Trivandrum-695002, Kerala, India.*

[2]*Department of Computational Biology & Bioinformatics, University of Kerala, Kariavattom, Trivandrum, Kerala, India.*

***Correspondence:**
Akhilesh VU, Department of Critical Care Medicine, PRS Hospital, Trivandrum-695002, Kerala, India, Phone: +918089313161.

Received: 01 Oct 2024; **Accepted:** 04 Nov 2024; **Published:** 15 Nov 2024

Citation: Akhilesh VU, Vivek P, Naveen J, et al. Effect of Early Vs Late Intubation on Outcomes in Critically ill Patients with COVID-19 A Protocolised Approach. Glob J Emerg Crit Care Med. 2024; 1(2); 1-7.

ABSTRACT

Introduction: *COVID-19 related ARDS (CARDS) is associated with high mortality. Optimal timing of intubation in these patients is still under research. Early intubation could avoid alternate means of oxygenation like High Frequency Nasal Canula (HFNC) or Non Invasive Ventilation(NIV), which prevents Self Inflicting Lung Injury (SILI) in patients breathing spontaneously. At the same time intubation itself may generate aerosols and delaying of intubation may mean patient could be managed with other means of oxygenation thus preventing Ventilator Induced Lung Injury (VILI). Moreover, the concept of SILI is not supported by scientific data. This study investigated the effect of timing of intubation on 28-day mortality in CARDS patients.*

Methodology: *A retrospective observational study was performed in patients admitted in COVID ICU, between January 1st and August 31st 2021, requiring ventilation. Following data collection patients were categorised into two groups. 'Delayed 'intubation group consisted of patients receiving Non Re-Breathing Mask (NRBM) /HFNC /NIV initially and got intubated after 24 hrs of ICU admission. The remaining patients who were intubated within 24 hrs comprised the 'early' intubation group. The decision for early intubation was made by following the institution protocol for ventilatory management.*

Results: *Among 114 ventilated patients 56 were intubated within 24 hours and 58 were intubated after 24 hours. The 28-day mortality in early and delayed intubation group were 39.7% and 60.3% respectively (p = 0.01). In early intubation group duration of mechanical ventilation (5±1.4), length of ICU stay (7.3±2.1) and hospital stay (9.4±4) were significantly less compared to delayed intubation group (p value <0.05).*

Conclusion: *Decision for intubation is complex and multifactorial which is usually individualized depending on the clinical condition. Early intubation is associated with improved survival rates and reduced duration of mechanical ventilation, length of ICU stay & length of hospital stay in severe CARDS patients.*

Keywords
ARDS, COVID-19, Intubation, Mechanical ventilation, Mortality.

Introduction
Coronavirus disease-2019 (COVID-19) pneumonia, first identified in China as an epidemic in early December 2019 was declared as a pandemic by WHO on March 11th 2020 [1]. COVID-19 mainly affects the respiratory system and presentation of this disease varies widely in severity from asymptomatic to COVID 19 associated severe ARDS and challenges the physicians with its unique features of respiratory failure [2]. The case fatality rate in these patients with COVID-19 is <5% as observed in a single-arm meta-analysis but a subset of the patients (15–18%) requires critical care support [3].

COVID-19 pneumonia causing severe ARDS (CARDS) is different from other causes of severe Acute Respiratory Distress Syndrome (ARDS) in that during the initial days of disease progression it is associated with near normal lung compliance with no clinical evidence of derangement in airway resistance or dead space ventilation. Various factors like impaired lung diffusion especially due to the formation of intravascular microthrombi lead to an array of changes in gas exchange leading to a decrease in the partial pressure of oxygen in the blood [4]. Hence an unusual and unique feature of COVID-19 pneumonitis is severe hypoxemia with near normal lung mechanics. This unique pathophysiology of COVID-19 pneumonitis results in failure to sense hypoxia-related dyspnoea, usually resulting in gross mismatch between the extent of arterial hypoxemia and signs of respiratory distress in these patients, known by term "happy hypoxia / silent hypoxia" (severe hypoxia without dyspnoea) [5,6]. In contrast to Berlin criteria of ARDS, the onset of CARDS is reported as 8–12 days. Management of patients presenting with severe acute hypoxemic respiratory syndrome associated with COVID-19 pneumonia (CARDS) often includes High flow nasal oxygen (HFNC), non-invasive ventilation (NIV), intubation, mechanical ventilation and prone ventilation [7]. The L (low elastance) and H (high elastance) phenotypes described by Gattinoni et al. are the basis of instituting various modes of oxygenation and ventilation [8]. Use of high-flow nasal cannula (HFNC), continuous positive airway pressure and non-invasive ventilation (NIV) in L-type dyspnoeic patients, even if they have deteriorated to H type, has delayed invasive mechanical ventilation in SARS-COVID-19 patients. In an editorial, Navas-Branco and Dudaryk suggested that efforts should be focused to avoid intubation and mechanical ventilation in severe COVID-19 patients [8]. However, the fact that COVID-19 patients with high respiratory drive on NIV are at risk of patient -self-inflicted lung injury (P-SILI) during spontaneous breathing leads to consideration of early invasive mechanical ventilation [9].

Although many clinical and laboratory parameters serve as guide in making decision regarding the appropriate timing of intubation, the optimal timing of intubation and invasive mechanical ventilation is still under research. Early endotracheal intubation could avoid alternate means of oxygenation like high flow nasal cannula and NIV which carries the risk of aerosolization of the virus and also prevents self-inflicting lung injury in patients breathing spontaneously due to large transpulmonary pressure swings. At the same time intubation itself may generate aerosols and delaying of intubation may mean patient could be managed with other means of oxygenation thus preventing Ventilator Induced Lung Injury (VILI). Moreover, the concept of SILI is not supported by scientific data and the effect of timing of intubation on the outcome of CARDS is not well understood [10,11]. There is paucity of data and no clear consensus or guidelines regarding timing of intubation and when to switch from NIV to invasive mechanical ventilation. When to intubate - early or late, in severe respiratory distress of COVID-19 patients continues to be debated as far as in-hospital mortality is concerned and hence remains a topic of research in COVID-19. Few retrospective single or multicentred studies have been published with different results.

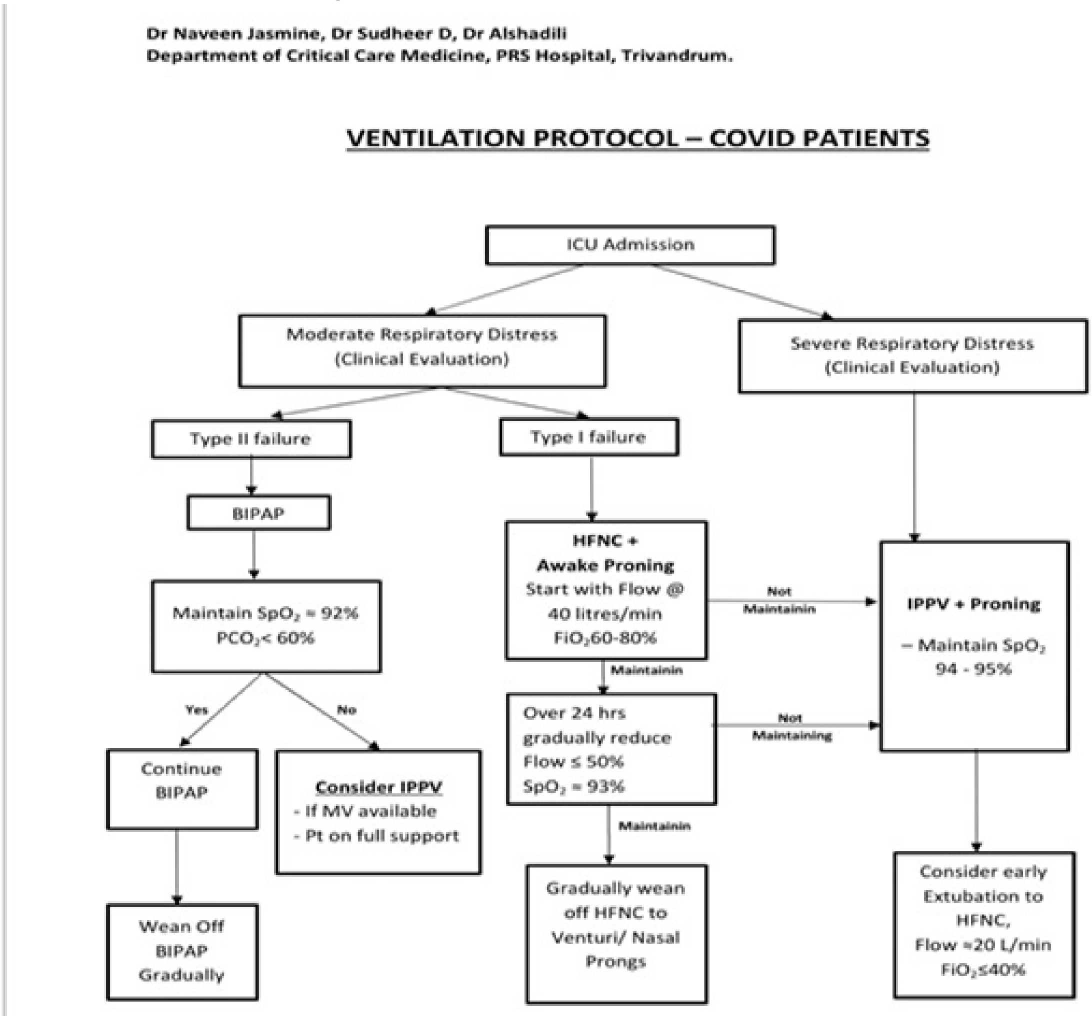
This retrospective observational study in CARDS patients was conducted to observe the appropriate timing of intubation from intensive care unit (ICU) admission. Our primary hypothesis was that delay in intubation in patients with COVID -19 associated severe ARDS for more than 24 hours since ICU admission may be associated with worse outcomes of mortality and morbidity. Additionally, we also observed the effect of timing of intubation on secondary clinical outcomes such as length of ICU stay, length of hospital stay, duration of mechanical ventilation and complications.

Methods

This Retrospective single centre observational study was done in COVID – ICU, Department of Critical Care Medicine, PRS Hospital, Trivandrum from January 2021 to august 2021. All intubated patients with Laboratory confirmed COVID-19 (CBNAAT OR TRUENAT positive) and associated severe ARDS admitted in COVID ICU, PRS Hospital were included. Patients who were intubated outside hospital before shifting to ICU, those with Written/informed consent for DNR/ palliative care and patients who were referred to other hospitals after intubation were excluded from this study. After Hospital Research and Ethical Committee approval for the study, data of all patients eligible for study as per inclusion and exclusion criteria till the sample size was achieved were collected. Patient data were obtained retrospectively from IP files, nursing charts, and treatment sheets which were accessible as hard copy records or digital archives. Data that were collected included patients' age, gender, comorbid conditions, SOFA score at admission to ICU, CT Severity score (CTSS), timing of intubation, duration of mechanical ventilation, length of ICU stay, length of hospital stay and data of complications related to the illness and mechanical ventilation. Laboratory parameters WBC count, lymphocyte count, D-dimer level, serum ferritin level, LDH and PaO2/FiO2 ratio before intubation were also obtained. Following data collection, patients with acute hypoxemic respiratory failure due to COVID-19 related severe ARDS, who were intubated were categorised into the "early intubation" and the "delayed intubation" groups. Acute hypoxemic respiratory failure is defined as the need for more than 5L per minute of nasal oxygen or venturi mask more than 40% to keep a SpO2 of equal to or more than 92%. Delayed intubation group consisted of patients receiving non re-breather mask or HFNC or NIV for equal to or more than 24 hours and got intubated after 24 hours of ICU admission. The remaining intubated patients who were intubated within 24 hours of ICU admission comprised the early intubation group. The decision for early intubation was made by following the institution protocol for ventilatory management of COVID -19 ARDS (Figure 1).

A total of 325 patients admitted in COVID ICU between January 1st, 2021 and August 31st, 2021. A total of 124 patients out of 325 were intubated and mechanically ventilated. Out of these 114 patients, who were intubated and ventilated during ICU stay after admission to hospital were included in the study cohort after applying inclusion and exclusion criteria. Patients who consented for DNR/Palliative care (n=6) and those intubated prior to transfer from other hospitals (n=4) were excluded from study population

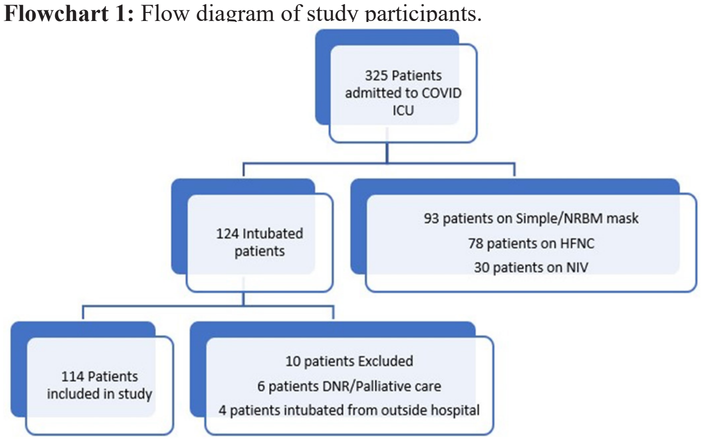
Figure 1: Institution Ventilation Protocol in COVID Patients.



BIPAP: Bilevel Positive Airway Pressure, IPPV: Invasive Positive Pressure Airway, MV: Mechanical ventilation, HFNC: High Flow Nasal Cannula, FiO_2: Fraction of Inspired Oxygen, SpO_2: Peripheral Arterial Oxygen Saturation.

(n=10). Of the 114 patients, 56 patients (49%) were intubated within 24hours (early intubation group) and 58 patients (51%) were intubated after 24hours (delayed intubation group) (Flowchart 1).

Flowchart 1: Flow diagram of study participants.



NRBM: Non Re-Breathing Mask, HFNC: High Flow Nasal Cannula, NIV: Non Invasive Ventilation, DNR: Do Not Resuscitate.

All the data were entered into a Microsoft Excel spread sheet and analysed using SPSS software. Continuous variables were presented as mean and standard deviation. Independent Sample T test was used to compare continuous variables. Categorical variables were presented as number of patients (percentage). Chi square test was used to compare categorical variables. All statistical tests were 2-tailed and statistical significance would be defined as $p < 0.05$.

Results

The demographics and comorbidities of 114 patients by time from ICU admission to intubation are shown in Table 1. The mean age was 56.5 ± 7.5. Mean age of the early intubation group was 55±7 and late intubation groups was 58±8. Majority of the study population were males comprising 66% of the total sample size. Of the total 114 patients studied, 57.9% had T2DM, 48.2% had systemic hypertension, 13.2% had CAD, 11.4% had COPD, 11.4% had CLD and 17.5% had some other comorbidities including CVA, CKD, malignancy, hypothyroidism, obesity etc.

Table 1: Demographics and comorbidities of mechanically ventilated patients by time from ICU admission to intubation.

Patient characteristics	Total no n=114 Mean ± SD/ (%)	Time from ICU admission to Intubation		p-value
		<24 hrs (n = 56)	>24 hrs (n = 58)	
Age (year)	56.5 ± 7.5	55 ± 7	58 ± 8	0.1
Male	75 (66%)	36 (48%)	39 (52%)	0.1
Female	39 (34%)	39 (34%)	19 (49%)	0.1
Comorbidities				
CAD	15 (13.2%)	7 (46.7)	8 (53.3)	0.8
S.HTN	59 (48.2%)	30 (54.5)	25 (45.5)	0.3
DM	66 (57.9%)	34 (51.5)	32 (48.5)	0.5
COPD	13 (11.4%)	6 (46.2)	7 (53.8)	0.8
CLD	13 (11.4%)	8 (61.5)	5 (38.5)	0.3
OTHERS	20 (17.5%)	9 (45)	11 (55)	0.8

CAD: Coronary Artery Disease, S.HTN: Systemic Hypertension, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, CLD: Chronic Liver Disease, SD: Standard Deviation.

The descriptive statistics for inflammatory markers, P/F ratio prior to intubation, SOFA Score and CTSS among early and late intubation group are given in Table 2. 28-day mortality, duration of mechanical ventilation, ICU length of stay and Hospital length of stay by time from ICU admission to intubation are given in Table 3.

Table 2: Laboratory characteristics and clinical scoring of mechanically ventilated patients by time from ICU admission to intubation.

Laboratory Values	Time from ICU admission to Intubation		P value
	<24 hrs (n = 56)	>24 hrs (n = 58)	
Serum Ferritin (ng/ml)	926.7 ± 350.0	959.1 ± 248.5	0.6
D-Dimer (ng/ml)	743.9 ± 578.2	674.3 ± 265.5	0.4
WBC Count (no. of cells/mm^3)	9093 ± 2699	9916 ± 4919	0.3
Absolute Lymphocyte Count %	7.6 ± 2.7	7.9 ± 4.2	0.6
Serum. LDH (U/L)	565.4 ± 196.5	453.6 ± 172.2	0.002
CRP (mg/dl)	79 ± 49	60 ± 42	0.03
P/F Ratio Prior To Intubation	66 ± 9	67 ± 11	0.5
Clinical scoring			
SOFA	6 ± 2	5 ± 1	0.000
CTSS	18 ± 3	18 ± 3	0.3

WBC: Whole Blood Count, LDH: Lactate Dehydrogenase, CRP: C-Reactive Protein, SOFA: Sequential Organ Failure Assessment, CTSS: CT Severity Score.

28-day mortality among total 114 patients were 68 (59.6%). Mortality among early and late intubation group were 27(39.7%) & 41 (60.3%) respectively. Mean duration of mechanical ventilation in early and late intubation group were 5 & 7 days respectively. Mean duration of ICU stay among early and late intubation group were 7.3 & 13.8 days respectively. Mean duration of hospital stay among early and late intubation group were 9.4 and 15.9 days respectively. The percentage distribution of complications developed in mechanically ventilated patients with regard to timing of ventilation were also analysed and given in Table 4. Incidence of Subcutaneous emphysema, acute kidney injury, need for renal replacement therapy, acute coronary events, ventilator associated pneumonia, bacteremia, septic shock, tracheostomy and ICU acquired weakness in both early and delayed group were almost similar and were not statistically significant.

Table 3: 28-day mortality, duration of mechanical ventialation, ICU length of stay and Hospital length of stay by time from ICU admission to intubation.

OUTCOME	Time from ICU admission to Intubation		p-value
	<24 hrs (n = 56)	>24 hrs (n = 58)	
28 Day Mortality – n=68 (59.6%)	27 (39.7%)	41 (60.3%)	0.01
Duration of Mechanical Ventilation	5 ± 1.35	7 ± 1.87	0.002
ICU Length of Stay	7.3 ± 2.1	13.8 ± 3.8	.000
Hospital Length of Stay	9.4 ± 4	15.9 ± 5.4	.01

Table 4: Percentage Distribution of Complications of MV by time from ICU admission to intubation.

COMPLICATIONS	Total N= 114	Time from ICU admission to Intubation		P value
		<24 hrs (n = 56)	>24 hrs (n = 58)	
S/C Emphysema & Pneumomediastinum	21(18.4%)	9(42.9%)	12(57.1%)	0.5
AKI	46(40.4%)	19(41.3%)	27(58.7%)	0.2
RRT	16(14%)	6(37.5%)	10(62.5%)	0.3
ACS	15(13.2%)	6(40%)	9(60%)	0.4
VAP	9(7.9%)	3(33.3%)	6(66.7%)	0.3
Bacteremia	10(8.8%)	4(40%)	6(60%)	0.5
Septic Shock	26(22.8%)	11(42.3%)	15(57.7%)	0.4
Tracheostomy	2(1.8%)	0	2(100%)	0.2
ICU AW	2(1.8%)	0	2(100%)	0.2

AKI: Acute Kidney Injury, RRT: Renal Replacement Therapy, ACS: Acute Coronary Syndrome, VAP: Ventilator Associated Pneumonia, ICU AW: Intensive Care Unit Acquired Weakness.

Discussion

COVID-19 clinical presentation varies from asymptomatic infection to severe respiratory distress requiring intubation and mechanical ventilation and presents a clinical challenge to physicians and intensivist. Different rates of mechanical ventilation in COVID 19 associated severe ARDS have been reported across the world [12].

Demographic parameters that attributes to adverse outcomes in COVID-19 patients are increasing age and male sex [13]. This trend was also observed in our study in which out of 114 mechanically intubated patients 66% were male patients and mean age of the study population was 56.5 with a trend of adverse outcome with increasing age.

In our study population, Type 2 diabetes mellitus (57.9%) and systemic hypertension (48.2%) were the most commonly reported comorbidities followed by CAD, COPD, CLD and others. Various previous studies also reported diabetes and hypertension as most common comorbidities and its association with patients requiring intubation in CARDS. In our study population, comorbid characteristics were no different from the ones reported worldwide [14,15].

The mean values of laboratory parameters viz. Serum ferritin, D-dimer, WBC count, Absolute lymphocyte count, P/F ratio prior to intubation except Serum LDH value were comparable in the two study groups as mentioned in the previous published similar studies [16].

Clinical and radiological scoring systems i.e., SOFA score and CT Severity score have been evaluated in our study for the severity of illness in COVID-19. Our present study population had a relatively high mean SOFA score of 6 ± 2 in early intubation group compared to a lower SOFA score of 5 ± 1 in late intubation group. This was contrary to the findings in a retrospective study done by Siempos et al. [17] were the mean SOFA score was relatively higher in the late intubation group. An interesting observation in our study was that patients intubated early within 24 hours of critical care admission were consistent with higher Serum LDH values along with higher SOFA score. These findings highlight that high severity scores and elevated inflammatory markers are linked with a greater risk of severe COVID-19 as well as risk factors for intubation and mechanical ventilation and related morbidity and mortality.

In the study by Alfonso et al., only 20.5% of COVID-19 study patients had PaO2/FiO2 ratio less than 100, whereas all patients in our study cohort had PaO2/FiO2 ratio less than 100 at the time of intubation [18]. Mortality rates in critically ill COVID 19 patients ranging from 17 to 62% were reported globally in small studies [19]. Richardson et al. reported that the mortality rate was 76.4% in the age-group 18–65 years and 97.2% of more than 65 years amongst those required mechanical ventilation [20]. In our study, the overall mortality was found to be 59.6% in patients who received invasive mechanical ventilation.

In this study those patients intubated and mechanically ventilated within 24 hours of critical care unit admission showed statistically significant reduced 28 day mortality (39.7%) as compared to those intubated after 24 hrs of critical care admission (60.3%) (p = 0.014). These observations were in agreement with studies done by Hyman et al. [21], Zirpe et al. [22], Siempos et al. [17] and Kangelaris et al. [23].

Our present study clearly defines only two groups in association with time i.e., intubation in less than 24 hours and that after 24 hours which is different from the study by Alfonso et al., who defined study groups of less than 8 hours, 8 to 24 hours and greater than 24 hours. Clinical decision and timing regarding switching from NIV or high-flow oxygen therapy to invasive mechanical ventilation is variable and multifactorial, hence its impact on outcome is debatable. Therefore, Alfonso et al. failed to observe association between timing of intubation and mortality [24].

Our study identified that increased mortality in delayed intubation group was not explained by demographics, comorbidities, and severity of illness measured in 24 hours of ICU admission (SOFA score & CTSS). In contrast, patient with early intubation had high SOFA score, and this finding was similar to study by Kangelaris et al., which reported higher average severity score in early intubation group of critically ill non-CARDS patients [23].

Our analysis also showed that secondary outcomes like duration of mechanical ventilation, length of ICU stay and length of Hospital stay were significantly less in early intubation group among the two groups. These findings were contrary to the observations made by other similar studies. Other studies with mortality benefit in early intubation groups failed to find any significant reduction in duration of Mechanical ventilation, length of ICU stay or length of Hospital stay. Younger age group in early intubation group, a protocolized approach in management and early proning may have contributed to the above significant findings in our study.

The complications and morbidity associated with long-time invasive mechanical ventilation like VAP and hospital-acquired infections are not an exclusion for COVID-19 patients [25]. AKI among critical COVID-19 patients serves as a negative prognostic factor for survival [26]. Experience in Europe and the USA with critical COVID-19 patients reported that approximately 20–40% of them had AKI [27]. In this study 40.4% of total patients developed renal failure but only 14% required RRT.

This is a retrospective observational study where we relied on the documentation, involving multifactorial analysis. Confounding factors of each factor analysed can cause a bias. Of the targeted biomarkers, we did not analyse serial concentrations of these biomarkers, which might fluctuate considerably over the course of the illness. Patients were sometimes transferred late in their course of illness to our hospital. Lack of effective antivirals, inadequate adherence to standard supportive therapy, and high-dose corticosteroid use might have also contributed to the poor clinical outcomes in some patients. This is a single-centre study, the observations may reflect regional and environment-related population characteristics. Interpretation of our findings might be limited by the sample size and this can be overcome by including other centres, and extending this study as a multicentre study. Decision for intubation is complex and multifactorial which is usually individualized depending on the clinical condition. Certain unmatched confounders affecting such intubation-related decisions in the study population may not have been accounted for in this study. In the setting of the pandemic, though lung-protective ventilation protocol was followed in all cases, data collection and analysis of the effect of SILI and individual ventilation parameters, tidal volume, compliance, peep, were not done in our study. Therefore it is infered that timing of intubation could play a key role in overall outcomes and a further well-planned multicentric prospective trials are required in severe CARDS patients to eventually test the hypothesis that early intubation in high-risk groups improves outcomes and to address the possibilities of unmeasured confounders.

Conclusion

Decision for intubation is complex and multifactorial which is usually individualized depending on the clinical condition. This study concludes that early intubation is associated with improved survival rates and reduced duration of mechanical ventilation, length of ICU stay and length of hospital stay in severe CARDS patients.

Acknowledgement

We are grateful to Department of Critical Care Medicine, Medical Records Department, IT Department and Hospital management, PRS Hospital, Trivandrum, Kerala, for fulfilling all the requirements for successfully completing this study.

References

1. Contini C, Di Nuzzo M, Barp N, et al. The novel zoonotic COVID-19 pandemic: an expected global health concern. J Infect Dev Ctries. 2020; 14: 254-264.
2. Matta SK. Dilemmas in COVID-19 respiratory distress: early vs late intubation; high tidal volume and low PEEP vs traditional approach? J Intensive Crit Care. 2020; 6: 7.
3. Sun P, Qie S, Liu Z, et al. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: a single arm meta-analysis. J Med Virol. 2020; 92: 612-617.
4. Dhont S, Derom E, Van Braeckel E, et al. The pathophysiology of 'happy' hypoxemia in COVID-19. Respir Res. 2020; 21: 1-9.
5. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. Am J Respir Crit Care Med. 2020; 202: 356-60.
6. Wilkerson RG, Adler JD, Shah NG, et al. Silent hypoxia: a harbinger of clinical deterioration in patients with COVID-19. Am J Emerg Med. 2020; 38: 2243.e5-2243.e6.
7. Guan L, Zhou L, Le Grange JM, et al. Non-invasive ventilation in the treatment of early hypoxemic respiratory failure caused by COVID-19: considering nasal CPAP as the first choice. Crit Care. 2020; 24: 1-2.
8. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020; 46: 1099-1102.
9. Grieco DL, Menga LS, Eleuteri D, et al. Patient self-inflicted lung injury: implications for acute hypoxemic respiratory failure and ARDS patients on non-invasive support. Minerva Anestesiol. 2019; 85:1014-1023.
10. Lee YH, Choi KJ, Choi SH, et al. Clinical significance of timing of intubation in critically ill patients with COVID- 19: a multi-center retrospective study. J Clin Med. 2020; 9: 2847.
11. Tobin MJ, Laghi F, Jubran A. P-SILI is not justification for intubation of COVID-19 patients. Ann Intensive Care. 2020 10:105.
12. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19 patients. Ann Intensive Care. 2020; 10: 78.
13. Wunsch H. Mechanical ventilation in COVID-19: interpreting the current epidemiology. Am J Respir Crit Care Med. 2020; 202: 1-4.
14. Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism 2020; 108: 154262.
15. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062.
16. Li LQ, Huang T, Wang YQ, et al. COVID- 19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020; 92: 577-583.
17. Zirpe KG, Tiwari AM, Gurav SK, et al. Timing of Invasive Mechanical Ventilation and Mortality among Patients with Severe COVID-19-associated Acute Respiratory Distress Syndrome (CARDS). Indian J Crit Care Med. 2021; 25: 493-498.
18. Siemposs II, Xourgia E, Ntaidou TK, et al. Effect of early vs delayed or no intubation on clinical outcomes of patients with COVID-19: An observational study. Front Med. 2020; 7: 614152.
19. Hernandez-Romieu AC, Adelman MW, Hockstein MA, et al. Timing of intubation and mortality among critically Ill coronavirus disease 2019 patients: a single-center cohort study. Crit Care Med.2020; 48: e1045-e1053.
20. Chaddha U, Kaul V, Agrawal A. What is the true mortality in the critically ill patients with COVID-19? Indian J Crit Care Med. 2020; 24: 383-384.
21. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020; 323: 2052-2059.
22. Hyman JB, Leibner ES, Tandon P, et al. Timing of intubation and in-hospital mortality in patients with coronavirus disease 2019. Crit Care Explorat. 2020; 2: e0254.
23. Zirpe KG, Tiwari AM, Gurav SK, et al. Timing of Invasive Mechanical Ventilation and Mortality among Patients with Severe COVID-19 associated Acute Respiratory Distress Syndrome (CARDS). Indian J Crit Care Med. 2021; 25: 493-498.
24. Kangelaris KN, Ware LB, Wang CY, et al. Timing of intubation and clinical outcomes in adults with ARDS. Crit Care Med. 2016; 44: 120.

25. Alfonso CH, Max WA, Maxwel AH, et al. Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: a single-center cohort study. Crit Care Med. 2020; 48: e1045-e1053.
26. Cox MJ, Loman N, Bogaert D, et al. Co-infections: potentially lethal and unexplored in COVID-19. Lancet Microbe. 2020; 1: e11.
27. Chen YT, Shao SC, Hsu CK, et al. Incidence of acute kidney injury in COVID-19 infection: a systematic review and meta-analysis. Crit Care. 2020; 24: 1-4.
28. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med. 2020; 8: P738-P742.