WITHDRAWN: Epidemiological Study of Patients Admitted in Intensive Care Unit with Severe Acute Respiratory Illness with a Possible Diagnosis of COVID19 (EPIC19), a Multicentre Study.

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EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Background

Global pandemic of COVID 19 has affected many countries. The initial epicenter was in China with gradual spread to various countries including India.

For a developing country like India with limited resources and high population, it is worthwhile to know how these patients requiring intensive care admission were managed and the outcome of these patients. To address these issues, a prospective observational study was planned.

Methods

A multicenter study was conducted from June 2020 to December 2020 including 4 centers across India. Patients > 18 years of age admitted in the intensive care unit (ICU), with the diagnosis of COVID 19 pneumonia confirmed by reverse transcriptase –polymerase chain reaction (RT-PCR) or rapid antigen test (RAT) as applicable were included. Factors associated with ICU mortality were examined using multivariable logistic regression analysis and Cox proportional hazard model.

Results

Of 667 patients were included in the study. ICU mortality was 60 %. In multivariable analysis, history of cerebral vascular accident (CVA), day 1 acute physiology and chronic health evaluation (APACHE II) score, need for invasive ventilator support, minimum PO_2, fluid balance and complications such as pneumothorax and arrhythmia during ICU admission were associated with mortality. Among these parameters, day 1 need for invasive ventilator support (odds ratio OR: 3.01(1.81, 5.00) and development of arrhythmia (OR 3.85 [1.56, 8.06]) had higher odds of mortality. Cox proportional hazard analysis showed, history of ischemic heart disease (IHD) (Hazard Ratio, HR 1.64, 95% CI:1.13, 2.38), day1 APACHE II (HR 1.03, 95% CI:1.00, 1.07), arterial blood gas (ABG) pH (HR 0.14, 95% CI:0.03, 0.56) and use of therapeutic anticoagulation (HR 0.42,95% CI:0.29, 0.61) as a predictor of 7 days ICU mortality. Daywise trend of ventilator parameters showed dynamic compliance was higher on day3 and 4 in survivors.

Conclusion

In this cohort of ICU patients, ICU mortality was 60%. The reason for higher mortality could be the severity of illness as suggested by the day 1 PF ratio (109.31 [77.79-187.26]).

Trial Registration-(IEC131/2020, CTRI/2020/06/025858).

Key Message

EPIC19, study showed predictors of 7 days mortality were history of IHD, APACHE II score, ABG pH and use of therapeutic anticoagulation. ICU mortality was 60% and it was associated with history of CVA, day

1 parameters such as APACHE II score, need for invasive ventilator support, minimum PO2, fluid balance and complications observed such as pneumothorax and arrhythmia during ICU admission.

Background

The global pandemic of COVID 19 has affected more than 200 countries. The initial outbreak was in China, December 2019, where Wuhan was the epicenter for this outbreak [1]. In India first case of this novel illness was seen in January 2020. The disease which was initially limited to international travelers, within few months spread to the community. The illness caused by the novel Coronavirus was similar to viral pneumonia, characterized by Type I respiratory failure with acute respiratory distress syndrome (ARDS), which was of mild, moderate, or severe category [2, 3].

Evidence was constantly evolving amidst the pandemic with emerging new strategies and management protocols. Response to disease, population demographics and case fatalities were variable in different countries [4, 5]. The successful response to any pandemic depends upon how we use available health resources, infrastructure and implement therapeutic strategies [6]. Effective management and treatment of these patients was a major challenge for countries such as India, with high population and limited resources.

The preliminary study published from India with 235 patients showed 24hrs mortality as 8.5% [7]. The study on the timing of intubation including 147 patients showed higher mortality of around 60% [8]. These two studies were single center studies. However, there is limited data that has been published from India that describes the profile of severe COVID cases requiring admission in Intensive Care Units (ICU) and the management of these cases. Therefore this study evaluates the epidemiology and clinical characteristics of the patients with the diagnosis of COVID pneumonia, requiring ICU admission in large tertiary care hospitals across India.

Methods

The study was approved by the Institutional Ethics Committee (IEC) of St. John's Medical College (131/2020) (CTRI/2020/06/025858). Critical care units across the country were invited by email to participate in the study. Nine centers responded and were interested in participating in the study. However, only 4 centers were recruited as others had logistic issues due to a rapid surge in the caseload and delay in getting the IEC approval. Each recruited center obtained approval from the local IEC's of the respective hospitals. As it was an observational study, a waiver of consent was given for three centers, except for one center.

The data were collected prospectively from June 2020 to December 2020, from four tertiary care hospitals. Online training was provided to each center's investigators about data collection and data entry. Data were entered in a standardized excel spreadsheet which was shared with all the centers. Regular checking for data validation and correctness was done throughout the data collection process.

Demographic details, epidemiological details, ventilator parameters and treatment details were collected. As data for 7 days of ICU stay was required, there was an initial hurdle in prospective data collection, this was overcome by retrieving the prospectively collected data from the health records. Data related to the type of oxygen therapy, invasive or noninvasive ventilation therapy, (PO_2/FiO_2) PF ratio, use of rescue therapy such as prone ventilation, or Extracorporeal Membrane Oxygenation (ECMO) were collected. Acute physiology and chronic health evaluation (APACHE II) and Sequential organ failure assessment (SOFA) scores were calculated in the first 24 hours of ICU admission. The sample size for estimating mortality of 50% with the margin of error as 5% and 95% confidence interval was 385. Considering the possibility of missing data in 10% of subjects, the required sample size was decided to be 400. The primary outcome of interest was ICU mortality and the secondary outcomes included length of ICU stay, duration of mechanical ventilation and hospital mortality.

A total of 1273 patients were screened, based on the inclusion criteria, reverse transcriptase- polymerase chain reaction (RT-PCR) or rapid antigen test (RAT) confirmed cases were included in the study. Five hundred and sixty-three patients were RT- PCR negative. Among 710 RT- PCR positive patients, 40 patients were excluded due to incomplete records. Total of 667 patients were included in the study across the 4 centers with maximum enrolment from one center as shown in Figure 1.

Statistical analysis- All statistical analyses were performed using STATA v19 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). The clinical and epidemiological characteristics are reported as mean (standard deviation SD) or median (Interquartile range IQR) as applicable for continuous variables and number (%) for categorical variables. Factors associated with ICU mortality were identified by multivariable logistic regression. Several variables which were initially considered as predictors of mortality were collinear and hence a careful selection of variables was made based on perceived importance in the clinical and statistical association. Adjusted odds ratio (95% confidence interval) was reported from the multivariable logistic regression. For ventilated patients, the change in ventilator settings over 7 days of ventilator usage were analysed using the mixed logistic model and are represented as trend lines with error bars. The Kaplan Meir survival curve was used to estimate the seven-day survival probabilities in ICU. Seven-day mortality was considered because mortality within this period can be attributed to COVID infection and not affected by known confounders such as hospital-acquired infections. The factors associated with 7day mortality in the ICU were identified using the Cox-proportional Hazards model and hazard ratios (HR) with 95% confidence interval (CI) are reported. All p values less than 5% were considered statistically significant.

Results

The patients were predominantly male (70.46%), and the average age was 57 years (SD=15). The majority of the patients were admitted directly to the respective hospitals (65%) and the remaining (35%) were transferred from either local clinics or tertiary care hospitals (Table 1). The predominant comorbidities were hypertension followed by Diabetes Mellitus (DM). Among the comorbidities, the presence of DM, hypertension, Ischemic heart disease (IHD) and cerebral vascular accident (CVA) were

significantly associated with mortality when not adjusted for any confounders. There was no effect of recent travel or attending a mass gathering or any contact with COVID suspects or COVID positive patients on mortality as shown in Table 1.

The predominant symptom was shortness of breath (67%) followed by fever (64%) and cough (55%) (**Table 2**). The median duration from onset of symptoms to admission to hospital was 3 days (IQR: 1-4), 5 days (IQR: 3-7) and 4 days (IQR: 3-7) for shortness of breath, fever and cough respectively. In atypical symptoms generalized weakness (10%) was the most common symptom followed by altered sensorium (5.9%), loose stools (4.9%), chest pain (3.9%) and reduced appetite (2.1%). The mean APACHE II score was 29.8(SD=6.1) and the median SOFA score was 7(IQR 4-11). Patients who were directly admitted to the ICU were 348 (52.17%).

Day1 biomarkers such as Neutrophil**:** Lymphocyte ratio (NLratio), ferritin, procalcitonin and lactate dehydrogenase (LDH) were all significantly elevated among non-survivors as shown in unadjusted analysis (Table 2). The requirement of renal replacement therapy (RRT) was higher (15.3 % vs 8.6% p=0.011) among non-survivors than survivors. In patients (319, 47.82%) who were transferred to ICU from the ward or intensive therapy unit (ITU), use of noninvasive ventilation (NIV) before ICU admissions (36.14% vs 21.37 % p=0.006) was higher among non-survivors than survivors (Table2).

The mortality in ICU was 60% and mortality in the hospital was 63%. There was no difference in mortality between males and females (59% vs 61% respectively, p=0.504). Length of ICU stay and number of days on ventilator support were similar in survivors and non-survivors (Table2).

Echocardiography and ultrasonography on admission were routinely done in one of the centers. Among echocardiographic parameters, the presence of systolic dysfunction as evaluated by the visual gestalt method and the presence of regional wall motion abnormality were associated with worse outcomes. E/A ratio for evaluating diastolic dysfunction was lower in non-survivors than survivors (0.91 vs 1.13 p= <0.001) (Supplementary Table S1)

The E/e` ratio indicative of LV (left ventricle) filling pressure was lower 8.06(2.63) and was not significant among survivors 8.03(2.59) and non-survivors 8.09(2.66), p=0.87 (Supplementary Table S1). There was no difference in outcome based on lung score by USG (ultrasonography) and the number of quadrants involved based on CXR.

Among the medications, the steroid was used in 84.6% survivors vs 92.5% non-survivors (p=0.001) and plasma was used in 10.8% survivors vs 5.3% non-survivors (p=0.007). (Supplementary Table S1)

Various complications were observed in these patients. Predominant complication being the development of pneumothorax 66(10%) followed by subcutaneous emphysema 28(4%), both were associated with the higher mortality. Incidence of Pneumothorax was seen in 32 (10.70%) patients requiring invasive ventilator support on day 1(Supplementary Table S1).

In these patients on Day1, the median P/F ratio was 109.31 (77.79-187.26). Mortality in mild, moderate and severe ARDS was 48.64%, 62.56 % and 67.86% respectively.

The most common mode of ventilation used was pressure regulated volume control (PRVC) (43%). Among the total of 667 patients, invasive ventilation was used in 445 (66.7%) patients during their hospitalization and the mortality was 59.8% among the intubated patients. The average time taken for intubation was 2days (1-5) from the date of ICU admission. Prone positioning was used in 67 (22.41%) mechanically ventilated patients and awake proning was used in 44(11.96%) spontaneously breathing patients on the day1 of ICU admission. Severe ARDS was seen in 132 (43.4%) intubated (299) patients on day1. Awake proning was used in 134(23.1%) patients at least once during their ICU stay.

Among the ventilator parameters, tidal volume was around 6.24(1.36) ml/kg of predicted body weight. Other ventilator parameters like minimum PO_2, PCO_2, Peak inspiratory pressure (P Peak) and positive end-expiratory pressure (PEEP) were found to be significant as shown in Table 3.

Factors associated with mortality

In multivariable analysis, comorbidities such as CVA, day 1 parameters such as APACHE II score, need for invasive ventilator support, minimum PO_2, fluid balance and development of complications such as pneumothorax and arrhythmia during ICU stay were associated with mortality (Table 4). Among these parameters, the requirement of invasive ventilator support on day 1 and the development of arrhythmia during ICU admission were statistically significant with OR= 3.01 (1.81-5.00) and 3.85 (1.56-8.06) respectively.

Among the 667 patients, 208 (31.18%) died within the first seven days of ICU admission (**Figure 2**). The estimated mean survival time in the first seven days of ICU admission was 5.9 days (95% CI: 5.8-6.1). Cox proportional hazard regression analysis was done to identify the predictors of 7day ICU mortality. Patients with IHD as comorbidity and higher APACHE II score at ICU admission had significantly higher mortality as shown by hazard ratios, HR=1.64(95% CI:1.13,2.38) and HR=1.03(95% CI:1.00,1.07) respectively (Table 5). Patients who received therapeutic anticoagulation were 58% less likely to be non-survivors at Day 7 of ICU stay compared to the patients who did not receive this treatment. Day 7 mortality was negatively associated with higher ABG (Arterial blood gas) pH done on Day 1 of ICU admission, HR=0.14(95% CI: 0.03, 0.56) (Table 5).

Figure 3 shows the trend of ventilator parameters over 7 days. Mean PCO_2 was significantly higher in the non-survivors throughout the 7 days. The mean driving pressure was higher in the survivors on days 5 and 6. Although static compliance was comparable between the time groups at all time points, mean dynamic compliance was higher in the survivor group on days 3 and 4. However, there was no difference in the change in any of these ventilator parameters over time (day 1 to day 7) between the survivor and non-survivor groups (Figure 3).

Discussion

This is one of the largest multicenter studies from India which showed 7 days trend of patients with COVID pneumonia. The parameters which were statistically significant among survivors and non-survivors were CVA, APACHE II score, day1 requirement of invasive ventilator support, minimum PO_2, fluid balance and complications such as pneumothorax and arrhythmia as shown by multivariable analysis (Table 4). The ICU mortality observed was higher (60%) as compared to other studies.

The largest study from Italy by Grasselli, et al, which included 1591 patients, with a larger proportion of patients received invasive mechanical ventilation (1150/1591;88%). The population was elderly and required higher PEEP 14 (12-16) and ICU mortality was 26% [4].

The (Pro vent COVID) study which included 553 patients who were mechanically ventilated showed median tidal volume was 6·3 ml/kg of predicted body weight (IQR 5·7–7·1), PEEP was 14 cm H_2O (IQR 11·0–15·0), and driving pressure was 14 cm H_2O (11·2–16·0) with the ICU mortality of 35% [5].

In our study, tidal volume was 6.24(1.36) ml/kg to 7.45(2.28) ml/kg and maximum PEEP of 10.29(3.5) cm of H_2O, dynamic compliance was 17.55(5.18) ml/cm of H_2O and static compliance was 24.20(8.57) ml/cm of H_2O. The driving pressure was 18.22(6.16) cm of H_2O which was higher in our study, correlating with the higher mortality as shown by previous studies of ARDS [9].

The study by Ferrando, et al, of 742 patients requiring invasive ventilation showed all- cause ICU mortality was 32% and mortality seen in severe ARDS patients was 39% [10]. The multicenter study from the US with 2215 patients showed a mortality of 39.5% [11].

As compared to above-mentioned studies, in our study one of the reasons for high mortality was the severity of illness as shown by the mean APACHE II score 29.8(6.11), (27.89 survivors vs 31.05 in non-survivors). Also, the P/F ratio on day 1 of ICU admission was lower with a median PF ratio of 109.31(77.79-187.26) as compared to Italian study 160 (114-220), Pro vent COVID 158·8 (128·6–200·5), Spanish study 120 (83–177) and US study 124 (86-188) as mentioned [4–5, 10–11].

One of the largest multicenter studies of COVID patients, from 138 hospitals, including > 4000 patients showed that 90 days mortality was around 31%. Mortality was higher among older, obese, diabetics and severe ARDS patients. In this study, the PF ratio on day1 was 154 (106–223) which was higher than that observed in our study 109.31(77.79-187.26) [12].

In our study among the ventilator parameters, routine parameters such as tidal volume and plateau pressure (P Plat) were not found significant. Probably due to the practice of low tidal volume and monitoring of P Plat was the established standard in the majority of the ICUs. P Peak and PCO_2 were found to be significant parameters, along with minimum PO_2. This suggests the possibility of impaired oxygenation as well as ventilation, indicating higher PCO_2 levels in non-survivors as compared to survivors (46.15mm of Hg (18.30) vs 39.64mm of Hg (11.36). This also suggests the possibility of intrapulmonary shunt due to micro-thrombi or dead space.

Another peculiar finding in our study was the 7days trend of ventilator parameters. Among the ventilator parameters, change in any of the ventilator parameters over 7 days was not statistically significant, but dynamic compliance was higher on day3 and 4 in survivors (Figure 3). This highlights that pathophysiology of COVID is not only due to impaired static compliance alone but dynamic compliance also plays a role which is a measure of compliance and airway resistance [13]. It also indicates possibility of different phenotypes of ARDS in COVID patients [14].

A retrospective study by Xie, et al, of 733 patients showed a median age of 65 years, and mortality was around 53.8 %. The higher mortality was due to associated organ failure like respiratory failure, shock and acute kidney injury. These findings were similar to our study as indicated by higher APACHE II score and SOFA score in non-survivors [15].

There were two small studies by Bhataraju, et al and Arentz, et al, that showed higher mortality of 50% and 67% respectively [16, 17].

The study by Yang, et al, of 52 critically ill patients showed 28- day mortality of 61.5%, with a lower PF ratio, similar to our study. Surprisingly these patients had a lower incidence of barotrauma of 2 % as against 9.9% in our study, possibly due to timely use of rescue therapy such as ECMO in 17% of patients. In our study, only 1 patient received ECMO [18].

A study looking at the timing of intubation from India showed baseline mortality of 60 % which was similar to our study [8].

The strengths of our study include, the patients who were admitted to the ICU were having severe disease, which is a true representation of the critically ill population. Also as shown in Table S1, echocardiographic parameters suggest, these were the patients, with low LV filling pressure as shown by E/e' ratio, as a true representation of the ARDS population. This study also describes characteristics of the patients requiring invasive as well as non-invasive ventilator support. The trend of parameters for 7 days for each patient helped in understanding the progress of the disease. Collection of data was a big challenge when healthcare workers were already overburdened by the caseload which was overcome by a volunteered team of research enthusiasts.

There were certain limitations to our study. Although the study was designed as a multicenter project, the actual number of ICUs which could participate was only 4, hence the data cannot represent the practices across various ICUs. The second limitation was depending on the type of hospital and case surge, criteria for admission for each ICU may be variable hence mortality among various ICUs may differ. The third limitation was the enrolment of different centers that happened at variable times during the study, which might have affected the number of patients recruited from each center. In addition to this, there was a difference in the timing of the surge of cases in various states. So during the study period, it was difficult to figure out the approximate number of patients who could be enrolled in the study, which resulted in a total enrolment of 667patients that was higher than the calculated sample size.

This study helped in evaluating the management of patients with COVID across the centers and also helped to check the practice patterns of managing ARDS, especially the use of low tidal volume strategy and prone positioning for which evidence is already established [19]. It also highlights the challenges for healthcare workers while taking care of these sick patients, such as the use of awake proning, prone positioning and managing the complications as mentioned in one of the largest meta-analyses [20].

Conclusion

In this cohort of ICU population of 667 patients, the primary outcome of ICU mortality was 60% and risk factors associated with poor prognosis as shown in multivariable analysis were history of CVA, day 1 parameters such as APACHE II score, need for invasive ventilator support, minimum PO_2, fluid balance and development of complications such as pneumothorax and arrhythmia during ICU stay. Predictors of 7 days mortality were IHD, APACHE II score, ABG pH and use of therapeutic anticoagulation. Our study also showed improving trend of dynamic compliance in survivors. Future studies with classifying ARDS based on the phenotypes such as compliance, resistance and elastance, will be helpful to guide in the management.

List Of Abbreviations

ABG: Arterial blood gas; ARDS: Acute respiratory distress syndrome; APACHE II: acute physiology and chronic health evaluation; CVA: cerebral vascular accident; ECMO: Extracorporeal membrane oxygenation; HR: Hazard ratio; ICU: Intensive care unit; IEC: Institutional ethics committee; IHD: Ischemic heart disease; IQR: Interquartile range; OR: Odds ratio; PF Ratio: PO_2/FiO_2; RT-PCR: Reverse transcriptase –polymerase chain reaction; RAT: Rapid antigen test; SD: Standarad deviation; SOFA: Sequential organ failure assessment

Declarations

Ethics approval and consent for participation- Obtained from each centre's IEC. (IEC131/2020. CTRI/2020/06/025858). Waiver of consent was given for all the centres except one.

Consent for publication- Not applicable

Availability of data and material- Upon request deidentified data will be available after approval from the ethics committee.

Competing/ Conflicts of Interest- On behalf of all the authors as a PI,I declare that there are no conflicts of interest or competing interest.

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Authors contribution- AH – concept, design, conduct, writing and finalizing manuscript. VK, BV, RT,VL, CS,NC helped in data collection. JR,TT helped in statistical analysis and writing the manuscript. MK,SY,KM, AS,SK,JP,MS and RK helped in data collection and participation from the respective centers. All the authors had approved the final manuscript.

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Tables

Table 1. Sociodemographic characteristics and epidemiological details

Values are n (%), p value from Chi-Square test of association.

¥Mean (SD), Independent sample t-test was used for comparison.

Parameter	All (n=667)	Survivors (n=267)	Non-survivors (n=400)	P value
Age¥	57(15.28)	54.10(15.10)	58.495(15.10)	<0.001
Gender	M/F 470/197 (70.46/29.54)	M/F (192/75) (70.77/29.23)	M/F (278/122) (69.90/30.10)	0.504
DM	375(56.22)	134(50.19)	241(60.25)	0.010
Hypertension	377(57.21)	138 (52.27)	245 (60.90)	0.028
ACE inhibitors	49(17.25)	22 (18.97)	27 (16.07)	0.526
ARB	73(25.70)	30 (26.55)	43 (25.15)	0.791
CLD	15(2.25)	4 (1.50)	11 (2.75)	0.285
CKD	90 (13.49)	29 (10.86)	61(15.25)	0.104
CVA	46(6.9)	10 (3.75)	36 (9)	0.009
IHD	98(14.69)	25 (9.36)	73 (18.25)	0.001
COPD	27 (4.05)	9 (3.37)	18 (4.5)	0.468
Bronchial Asthma	25 (3.75)	8 (3)	17 (4.25)	0.404
ILD	5 (0.75)	1 (0.37)	4 (1)	0.359
Retroviral disease	2 (0.30)	0 (0)	2 (0.50)	0.247
TB	15(2.25)	5 (1.87)	10 (2.50)	0.592
Immunosuppressants	26(3.9)	6(2.25)	20 (5)	0.072
Malignancy	12(1.8)	2(0.75)	10 (2.5)	0.096
Occupation				
Frontline workers	1 (0.15)	1 (0.37)	0 (0)	0.466
Healthcare workers	7 (1.05)	3 (1.12)	4 (1)	
Others	659(98.8)	263 (98.5)	396(99)	
Transfer from Other hospital	232(34.78)	93(34.83)	139(34.75)	0.983
History of Travel 30 days	19(2.85)	9 (3.37)	10(2.5)	0.508
History of Travel 14 days	16 (2.4)	9(3.37)	7 (1.75)	0.180
History of attending mass gathering	31(4.65)	15 (5.62)	16(4)	0.331

Taken HCQ Prophylaxis	13(1.95)	5(1.87)	8(2)	0.907
Patients Home Quarantined	36(5.40)	19(7.12)	17(4.25)	0.108
Similar complaints in close contacts	24(3.6)	9(3.37)	15 (3.75)	0.797
History of contact with COVID positive patient	28(4.20)	9(3.37)	19 (4.75)	0.384
History of contact with COVID suspect patient	21(3.15)	13 (4.87)	8 (2)	0.038

Table 2
Presenting symptoms, Day1 characteristics and Outcomes

Parameters	N	All	Survivors (n=267)	Non-survivors (n=400)	P Value
History of Fever	667	424(63.57)	174 (65.17)	250(62.50)	0.483
Cough	667	364(54.57)	154(57.68)	210 (52.5)	0.188
Shortness of Breath	667	447(67.02)	179(67.04)	268 (67)	0.991
Sore throat	667	23(3.45)	13 (4.87)	10 (2.5)	0.100
Running Nose	667	10(1.50)	5(1.87)	5 (1.25)	0.517
SOFA score	522	7(4-11)	5(3-7)	8(5-12)	<0.001
APACHE II score	599	29.80(6.11)	27.89(6.10)	31.05(5.79)	<0.001
Day1 use of invasive ventilation	667	299(44.83)	73(27.34)	226 (56.50)	<0.001
ABG PH Day1	630	7.33(0.13)	7.37(0.10)	7.29(0.14)	<0.001
Pt requiring vasopressors on Day1	667	174(26.09)	54 (20.22)	120 (30)	0.006
NL ratio§	628	14.22(8.3-25.32)	11.25(6.67-21.14)	15.33(9.37-30.32)	<0.001
Ferritin§	440	630.20(259.10-1399)	445.45(222-1195.50)	729.10(339.9-1650)	<0.001
Procalcitonin§	374	0.59(0.18-3.09)	0.30(0.12-1.50)	0.83(0.21-4.82)	<0.001
DDimer§	281	972(566-1424)	1059.50(690-2323)	933(552-1398)	0.0809
LDH§	349	580(383-740)	496.5(344-679)	612(425-822)	<0.001
CRP§	504	18.22(7.36-32)	18.23(7.10-32)	18.15(7.96-32)	0.9301
Troponin I§	306	0.05(0.01-0.39)	0.04(0.01-0.22)	0.06(0.01-0.50)	0.0453
Use of NIV Prior to ICU	319	98(30.72)	25(21.37)	73(36.14)	0.006

Values are n (%), p value from Chi-Square test of association.

§Median (IQR), p value from Mann Whitney U test.

Units of measurement -D Dimer, Ferritin, Procalcitonin and Troponin I (ng/ml), CRP (mg/dl), LDH (U/L)

Parameters	N	All	Survivors (n=267)	Non-survivors (n=400)	P Value
Use of HFNC Prior to ICU	319	30(9.40)	9(7.69)	21(10.40)	0.425
From Hospital admission to ICU admission§	667	1(1-4)	1(1-3)	2(1-5)	0.004
ICU admission to Intubation timing§	667	2(1-5)	2(1-5)	2(1-5)	0.54
Need for RRT	667	84(12.59)	23(8.61)	61(15.25)	0.011
Need for Blood Transfusion	667	45(6.75)	14(5.24)	31(7.75)	0.206
Outcomes					
Primary Outcome	667				
ICU Mortality	667		267(40.03%)	400(59.97%)	
Secondary Outcomes					
Hospital Mortality	667		248(37.18%)	419(62.82%)	
ICU length of Stay	667	7(4-13)	6(4-11)	7(4-14)	0.303
Days on Mechanical ventilation	667	6(3-11)	7(5-10)	6(3-12)	0.120
Values are n (%), p value from Chi-Square test of association.					
§Median (IQR), p value from Mann Whitney U test.					
Units of measurement -D Dimer, Ferritin, Procalcitonin and Troponin I (ng/ml), CRP (mg/dl), LDH (U/L)					

Table 3
Oxygen therapy and ventilator parameters

Day1 Parameters	N	All	Survived (n=267)	Non-survived (n=400)	P-value
Type of Oxygen Therapy	667				
Invasive ventilation	299	299(44.83)	73(27.34)	226(56.50)	<0.001
HFNC	15	15(2.25)	7(2.62)	8 (2)	
Face Mask	65	65(9.75)	51(19.10)	14(3.5)	
NIV	166	166(24.89)	64(23.97)	102(25.5)	
NRBM	74	74(11.09)	46(17.23)	28(7)	
Other devices	27	27(4.05)	15(5.62)	12(3)	
Room Air	21	21(3.15)	11(4.12)	10(2.5)	
PF Ratio	572	109.31 (77.79-187.26)	117.50 (82.33-208)	104 (75.78-168.75)	0.006
Worst Fio2 on Day1 of ICU	649	78.36(23.63)	71.99 (24.12)	82.38(22.44)	<0.001
Mode of Ventilation	667				
PRVC	286	286(42.88)	71(26.59)	215 (53.75)	<0.001
PCV	2	2(0.30)	1 (0.37)	1(0.25)	
VCV	9	9 (1.36)	0(0)	9(2.26)	
PS-PEEP	1	1 (0.15)	0 (0)	1(0.25)	
SIMV	1	1 (0.15)	1 (0.37)	0 (0)	
Spontaneous	368	368 (55.17)	194(72.66)	174(43.50)	

Values are n (%), p value from Chi-Square test of association.

¥Mean (SD), Independent sample t-test was used for comparison; §Median (IQR).

Mann Whitney U test was for comparison.

Units of measurements- PO_2, PCO_2 (mmHg)

Driving Pressure, PEEP, P Peak, Pplat (cm H_2O). Static and Dynamic Compliance (ml/cmH_2O)

Tidal volume (ml), Fluid balance (ml)

Day1 Parameters	N	All	Survived (n=267)	Non-survived (n=400)	P-value
PO2 min§	587	76 (61.70-99.20)	78.5 (62.95-105.7)	74.6 (60-97.80)	0.013
PO2 Max§	589	106(78.6-148.30)	106(77-146)	106(80.15-149)	0.784
PCO2 min¥	600	35.73(10.93)	34.39(8.91)	36.59(11.98)	0.016
PCO2 max¥	598	43.63(16.27)	39.64(11.36)	46.15(18.30)	<0.001
PEEP max¥	451	10.29(3.5)	9.35(3.26)	10.68(3.52)	<0.001
PEEP (mean) ¥	451	9.55(3.1)	8.80(2.99)	9.86(3.10)	<0.001
Ppeak max¥	421	29.06(10.94)	25.30(9.82)	30.67(11.02)	<0.001
Ppeak mean¥	421	25.99(9.46)	22.78(8.64)	27.36(9.49)	<0.001
Pplat max¥	193	30.60(6.78)	29(5.63)	31.04(7.02)	0.084
Pplat mean¥	193	29.26(6.30)	27.73(5.32)	29.69(6.49)	0.075
Dynamic compliance¥	194	17.55(5.18)	19.74(5.52)	16.94(4.93)	0.002
Static compliance¥	193	24.20(8.57)	26.16(9.52)	23.66(8.23)	0.093
Driving pressure¥	193	18.22(6.16)	16.66(4.50)	18.65(6.49)	0.064
Tidal volume min¥	112	383.83(59.87)	384.38(64.15)	383.39(56.83)	0.931
Tidal volume max¥	433	472.08(147.32)	491.25(144.01)	464.12(148.18)	0.081
Tidal volume based on PBW (minimum) ml/kg¥	240	6.24(1.36)	6.45(1.72)	6.14(1.14)	0.097

Values are n (%), p value from Chi-Square test of association.

¥Mean (SD), Independent sample t-test was used for comparison; §Median (IQR).

Mann Whitney U test was for comparison.

Units of measurements- PO_2, PCO_2 (mmHg)

Driving Pressure, PEEP, P Peak, Pplat (cm H_2O). Static and Dynamic Compliance (ml/cmH_2O)

Tidal volume (ml), Fluid balance (ml)

Day1 Parameters	N	All	Survived (n=267)	Non-survived (n=400)	P-value
Tidal volume based on PBW (maximum) ml/kg¥	240	7.45(2.28)	8.01(2.48)	7.20(2.15)	0.011
Use of paralytics	667	186(28.48)	41 (15.95)	145 (36.62)	<0.001
Infusion					
Fluid Balance§	667	286(-77.80 -854.5)	80(-192 - 550)	480(-0.30-1060)	<0.001
Prone positioning¥	667	111(17.18)	33 (12.79)	78 (20.10)	0.016
Values are n (%), p value from Chi-Square test of association.					
¥Mean (SD), Independent sample t-test was used for comparison; §Median (IQR).					
Mann Whitney U test was for comparison.					
Units of measurements- PO_2, PCO_2 (mmHg)					
Driving Pressure, PEEP, P Peak, Pplat (cm H_2O). Static and Dynamic Compliance (ml/cmH_2O)					
Tidal volume (ml), Fluid balance (ml)					

Table 3 **Oxygen therapy and ventilator parameters**

Table 4
Multivariable Logistic Regression

Parameters	Crude Odd's ratio (95% C.I)	P value	Adjusted Odd's ratio (95% C.I)	P-Value
History of CVA	2.54(1.24,5.21)	0.011	2.49(1.04,5.96)	0.040
History of IHD	2.16(1.33,3.51)	0.002	1.40 (0.76,2.57)	0.282
Arrhythmia	4.27(2.14,8.52)	<0.001	3.85 (1.56,8.06)	0.002
Pneumothorax	2.05(1.16,3.65)	0.014	2.45(1.22,4.92)	0.012
Day1 invasive ventilation	3.45(2.47,4.82)	<0.001	3.01(1.81,5.00)	<0.001
NL Ratio	1.01(1.00,1.02)	0.007	1.00 (0.99,1.01)	0.459
Age	1.02(1.01,1.03)	<0.001	1.01(0.99,1.02)	0.149
APACHE II score	1.10(1.06,1.13)	<0.001	1.06(1.02,1.10)	<0.001
PO2 min	1.00(0.99,1.00)	0.038	0.99 (0.99,1.00)	0.025
Fluid Balance	1.00(1.00,1.00)	<0.001	1.00(1.00,1.00)	0.002
PCO2 max	1.03(1.02,1.04)	<0.001	1.00(0.98,1.01)	0.998

C.I – Confidence interval

Table 5
Survival analysis on Day7 of ICU admission

Parameter	Univariate		Multivariate	
	Hazard Ratio (95% C.I)	P value	Hazard Ratio (95% C.I)	P value
History of fever	0.75(0.57,0.99)	0.044	1.04(0.74,1.44)	0.829
History of cough	0.60(0.45,0.78)	<0.001	0.72(0.52,1.00)	0.051
DM	1.25(0.95,1.65)	0.115	1.08(0.79,1.49)	0.603
CLD	2.48(1.27,4.83)	0.008	1.88(0.81,4.34)	0.137
CKD	1.59(1.12,2.26)	0.01	0.82(0.52,1.30)	0.411
IHD	1.91(1.38,2.63)	<0.001	1.64(1.13,2.38)	0.009
Invasive mechanical ventilation	1.42(1.08,1.87)	0.012	0.80(0.54,1.18)	0.268
APACHE II score	1.07(1.05,1.10)	<0.001	1.03(1.00,1.07)	0.019
ABG Ph day1	0.06(0.02,0.14)	<0.001	0.14(0.03,0.56)	0.006
Fluid balance	1.00(1.00,1.00)	<0.001	1.00(0.99,1.00)	0.055
Worst Fio2 value	1.01(1.00,1.01)	0.026	1.00(0.99,1.01)	0.114
Therapeutic anticoagulation	0.45(0.34,0.61)	<0.001	0.42(0.29,0.61)	<0.001
Arrhythmia	1.52(1.03,2.23)	0.035	1.14(0.74,1.75)	0.549
Need for RRT	2.00(1.42,2.82)	<0.001	1.24(0.80,1.94)	0.323
Need for blood transfusion	2.17(1.42,3.33)	<0.001	0.93(0.55,1.58)	0.925
C.I – Confidence Interval				

Figures

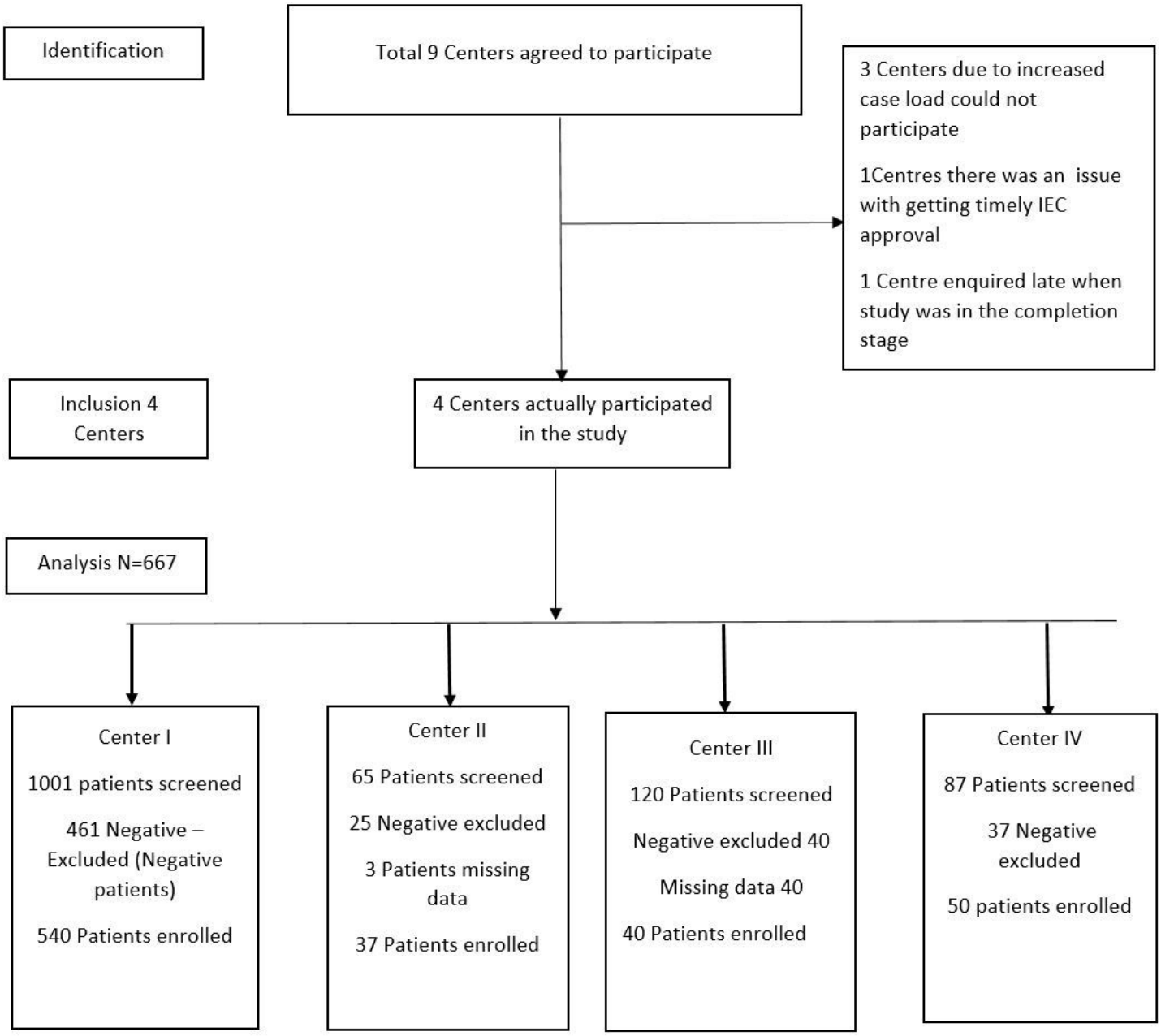

Figure 1

Strobe Diagram showing study participants

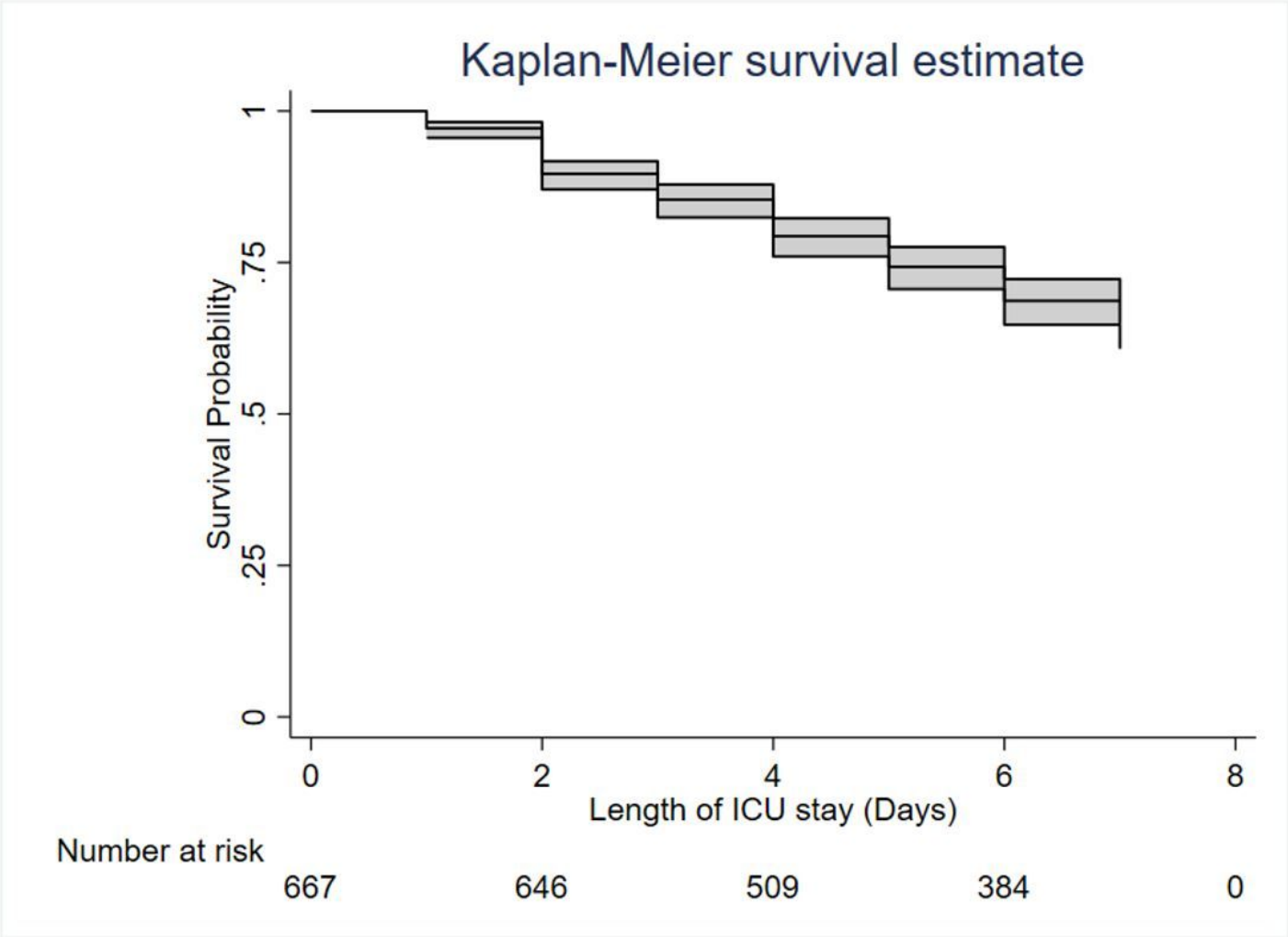

Figure 2

Kaplan Meier curve showing 7days survival trend

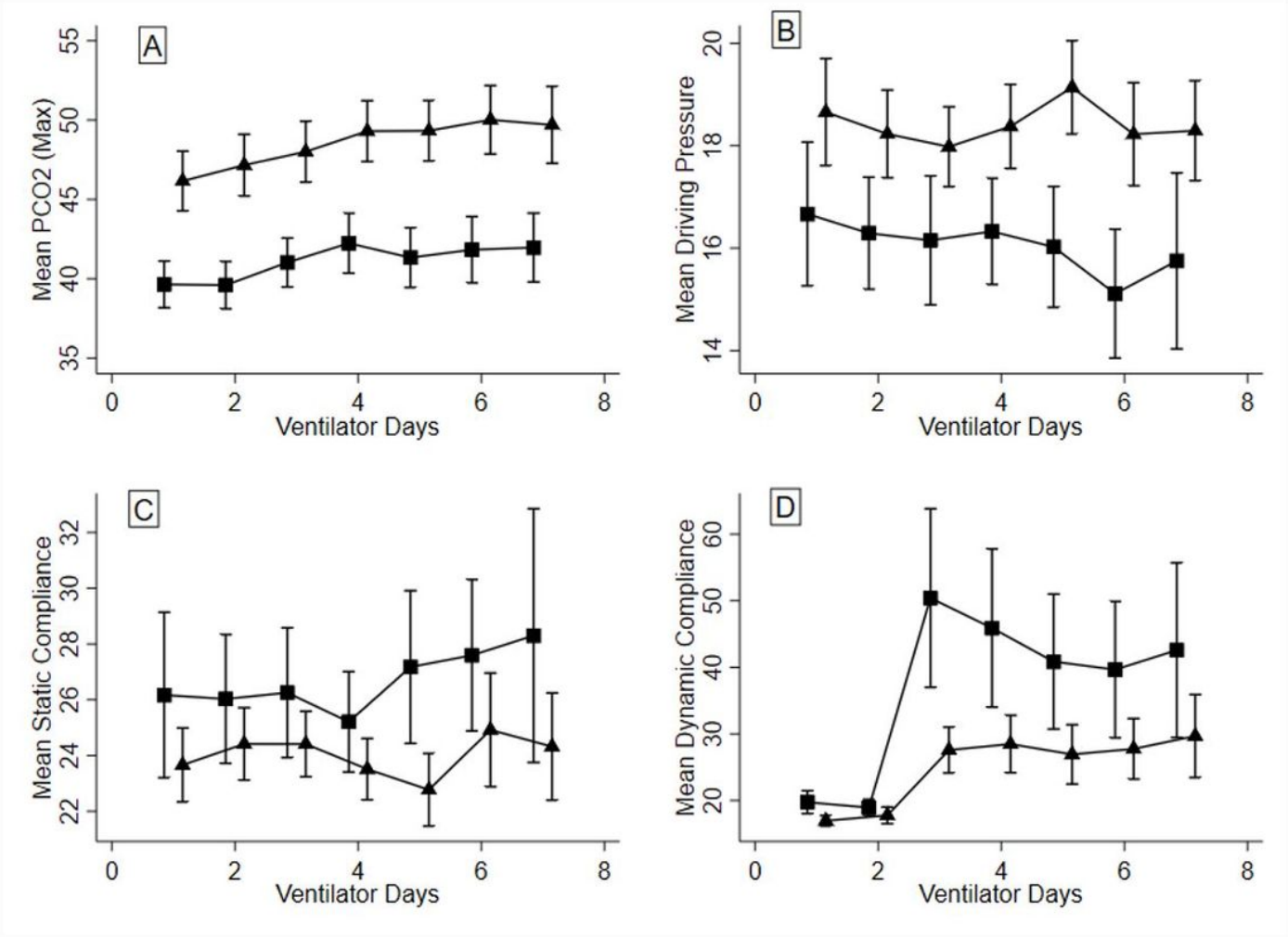

Figure 3

The trend of ventilator parameters

Supplementary Files

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- SupplementaryMaterial.docx