CPAP Treatment In COVID-19 Patients: A Retrospective Observational Study In The Emergency Department

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Original Research

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Abstract

Background

During COVID-19 outbreak, with the increasing number of patients presenting with acute respiratory failure (ARF), a large use of non-invasive positive pressure ventilation (NIPPV) was done in the Emergency Departments (EDs) and medical wards despite the lack of recommendations. We aimed to assess the use of continuous positive airway pressure (CPAP) in the ED. The primary endpoint was the rate of CPAP failure and the need of endotracheal intubation (ETI). Secondary endpoints were in-hospital mortality and intensive care unit (ICU) and in-hospital length of stay.

Methods

A retrospective observational study enrolling adult patients admitted to the ED of Niguarda Hospital, Milan, Italy, with ARF due to COVID-19 pneumonia from March 18th to April 18th 2020, was conducted. Only patients who strictly followed a local CPAP protocol were enrolled.

Results

A total of 52 patients were included in this study. 38 patients (73%) were judged eligible for ETI. 18 (34.6%) were intubated. 16 (30.8%) patients died: 7 (38.9%) and 9 (26.5%) in the ETI and non-ETI group respectively. The median hospital length of stay was different in ETI and non-ETI patients: 26 days [IQR 16–37] vs 15 days [IQR 9–17] (p = 0.005). The median invasive mechanical ventilation time was 11 days [IQR 7–21] with an ICU length of stay of 14.5 days [IQR 10–28]. During the CPAP trial, variations between ETI and non-ETI patients over time were found for positive end-expiratory pressure (PEEP) (p = 0.003) and respiratory rate (RR) (p = 0.059).

Conclusionss

A short closed monitored CPAP trial could be considered for ARF due to COVID-19 pneumonia before considering ETI. A progressive PEEP titration should target patient's RR reduction. More studies are needed to evaluate the efficacy and predictors of failure of CPAP and NIPPV in patients with ARF due to COVID-19 pneumonia.

Introduction

With the exponential rising of patients with *Coronavirus Disease 2019* (COVID-19), hospitals of affected countries had to face an increasing number of patients presenting with hypoxemic respiratory failure, with a demand of mechanical support and endotracheal intubation (ETI) higher than normal, often exceeding available resources.

15% of patients with COVID-19 develops severe respiratory failure, with a rate highly dependent on patient's age and comorbidities such as obesity, diabetes mellitus, hypertension, and chronic pulmonary disease.[1] Estimated overall case fatality varies from 1.4% in patients younger than 60 years to 4.5% in those 60 years and older.[2]

Patients with COVID-19 pneumonia present an atypical form of acute respiratory distress syndrome (ARDS). The first phases of the disease are characterized by a severe hypoxemia associated with a fairly preserved lung compliance ("silent" hypoxemia).[3,4] The severe hypoxemia is likely due to the loss of hypoxic pulmonary vasoconstriction, with a remarkable hyperperfusion of gasless tissue, and impaired regulation of pulmonary blood flow, with ventilation/perfusion (VA/Q) mismatch. Positive end-expiratory pressure (PEEP) and prone positioning can improve oxygenation through recruitment of collapsed areas and redistribution of pulmonary perfusion, improving the VA/Q ratio. In many patients the disease stabilizes at this first stage while in others, about 20–30%, it may worse to a clinical picture similar to ARDS, with bilateral CT consolidations and low compliance.[5]

Evidence on non-invasive positive pressure ventilation (NIPPV) in acute respiratory failure (ARF) due to viral pneumonia is lacking and its use is still of uncertain benefit.[6,7] Data from observational studies on the use of NIPPV in Influenza A (H1N1) viral pneumonia showed a variable successful rate between 40,7% and 48%.[8–10] Some studies reported an increased ICU mortality in patients who failed NIPPV trial compared with early invasive mechanical ventilation (IMV), whereas NIPPV success resulted in shorter hospital stay. NIPPV failure was associated with higher SOFA scores and lower P/F levels. A high rate of NIPPV failure (92,4%) was reported in critically ill patients with the Middle East Respiratory Syndrome.[1,8,9]

Due to the lack of Randomized Controlled Trials no recommendations are offered on NIPPV use in these patients, but according to data from observational studies, a cautious NIPPV trial in selected patients and in a protected environment and experienced centers can be tried. The application of a PEEP during ARF secondary to pneumonia has been demonstrated to improve arterial oxygenation by increasing functional residual capacity, to shift the tidal volume to a more compliant part of the pressure-volume curve and to reduce the work of breathing.[1,8,9] Furthermore, it recruits non-aerated alveoli in dependent pulmonary regions, stabilizes the airways, and reduces the inhomogeneity of lung volume distribution.[11]

During COVID-19 spreading, NIPPV with helmet CPAP was largely used to support patients with ARF in emergency departments (ED) and medicine wards, in order to face the large number of affected patients.

A better tolerability of the helmet and a reduced room contamination compared with oronasal masks may also improve patients' clinical management, increasing the safety of healthcare workers.[12] Despite the relative simplicity of setting up a helmet CPAP, the need for attentive and careful monitoring of the respiratory and hemodynamic response to the application of PEEP should be part of the standard operating procedures of the unit.

The aim of the study is to describe the treatment with helmet CPAP in patients with ARF due to COVID-19 related pneumonia. The primary endpoint is the proportion of CPAP failure evaluated as need of ETI. The secondary endpoints are intra-hospital mortality and ICU and in hospital length of stay.

Methods

Study design and setting

This was a retrospective descriptive study enrolling adult patients admitted to the Emergency Department of the Niguarda Ca' Granda Hospital of Milan, Italy, from March 18th to April 18th 2020 with acute respiratory failure due COVID-19 pneumonia.

A local protocol was drawn up to standardize a first trial of CPAP, and only patients who strictly respect the protocol were considered.[13] STROBE guidelines for reporting observational studies were followed.[14]

Ethical consideration

The study was approved by the ethical committee of the Niguarda Ca' Granda Hospital of Milan, whereas informed consent was waived due to the retrospective and descriptive nature of the study according to the Italian law on observational studies.

Participants

Patients admitted to the ED from March 18th to April 18th 2020 with ARF due to COVID-19 pneumonia treated with helmet CPAP according our operational flowchart were included in the study.

Diagnosis of COVID-19 pneumonia was made if typical CT scan patterns were present (ground-glass opacities, crazy-paving pattern, consolidations) and a SARS-CoV2 infection was confirmed by positive real-time reverse transcriptase–polymerase chain reaction assay of nasopharyngeal swab.[15]

According to the local protocol, the inclusion criteria were age 18 years or older, diagnosis of COVID-19 related pneumonia, a preserved state of consciousness (Kelly Score 1 or 2) and stable hemodynamics, SpO_2 level < 94% and a respiratory rate (RR) ≥ 28 despite 5 L/min oxygen administration through nasal googles or face mask.[16] All these patients started a trial of helmet CPAP. Exclusion criteria were: the achievement and maintenance of a SpO2 ≥ 94% and FR < 28 with standard O2 support (5 L/min of O2 administered with goggles or facemask); the need for immediate ETI for cardiovascular arrest, impaired and ineffective respiratory mechanics (e.g. agonic breathing and thoracic-abdominal dyskinesia); hemodynamic instability or severe arrhythmias; altered state of consciousness (Kelly score ≥ 3); contraindications to CPAP (severe bleeding of the upper digestive tract, vomiting, inability to protect the airways; recent surgery on the skull or esophagus; trauma and cranio-facial burns; undrained pneumothorax). Patients with symptoms and radiological imaging suggestive for COVID-19 pneumonia but no microbiological confirmation were also excluded.

All the patients enrolled started a trial of helmet CPAP and were followed up to from the day of hospital admission to the day of death or hospital discharge.

CPAP was delivered through helmet and high-flow generating devices as first choice. The CPAP trial lasted 120 minutes. Initial settings were a PEEP of 7,5 cm/H20, a Flow $\geq$ 60 L/Min and a FiO_2 titrated to reach a $SpO_2 \geq$ 94% and a RR $\leq$ 25 bpm. PEEP was increase by 2.5 cmH_2O up to a maximum of 12.5 cmH_2O in case of failure to reach the RR established target. Alternatively, in patients with risk of muscular exhaustion (e.g. history of Chronic Obstructive Pulmonary Disease, neuromuscular disease) a trial of Bi-PAP was started with a face mask.

Data collection.

Demographics, comorbidities, time from symptoms onset, Arterial Blood Gases (ABG), clinical and laboratory findings on admission were recorded.

SpO2, RR and body temperature were recorded before CPAP trial was started and then every 30 minutes together with PEEP and FiO2 used until the end of the trial (t0 - t30 – t60 – t90 – t120).

ETI was performed according to clinical judgment of ICU specialist. Patients not considered eligible for ETI due to their age and comorbidity and the severity of the disease, received a Do Not Intubate (DNI) order after the evaluation of a ICU specialist in agreement with the emergency physician. Data on time from the beginning of CPAP trial to ETI together with data on duration of NIPPV (intended as cycles of CPAP or Bi-PAP longer than 6 hours for day) or of IMV were collected. Pharmacological treatment was recorded too.

Statistical analysis

No statistical sample size calculation was performed a priori, and sample size was equal to the number of patients treated with helmet CPAP during the study period.

Socio-demographic variables and clinical data were reported as absolute and relative frequencies for categorical variables, while for numerical ones the mean and the corresponding standard deviation (SD) or median and InterQuartile Range (IQR) were reported, as appropriate.

Percentage of subjects who needed invasive mechanical ventilation and died were calculated with their 95% confidence interval (95% CI).

To explore the risk factors associated with ETI, the χ^2 test or Fisher's exact test and the student or Mann-Whitney U test were used to compare the socio demographic and clinical variables with the use of IMV.

To better understand the time trend of parameters related to the use of CPAP (Fio2, PEEP, RR, SP02), graphical representations were done using mixed models, which take into account for repeated measures within subjects. The same models, adding as covariate the use of ETI, were also performed to evaluate if significant changes between groups were observed.

Survival curves were plotted using the Kaplan-Meier method and compared between patients with vs without ETI using the log-rank test.

A two-sided α of less than 0.05 was considered statistically significant. Statistical analyses were done using the SAS software (version 9.4).

Results

In the period from 18 March 2020 to 18 April 2020, a total of 456 COVID-19 patients were admitted to the ED. A total of 52 (11.4%) patients we included in this study. The median age was 62.5 years (IQR, 50-72.50 years) and 40 (76.9%) were male. The most commonly self-reported symptoms at illness onset were fever followed by dyspnea and cough. Thirty-eight (73%) patients had at least one comorbidity, with hypertension, obesity, and cardiomyopathy being the most prevalent. No differences in demographics, clinical features and laboratory findings were found between subjects undergoing ETI compared to the others, except for P/F ratio (103 vs 214, p=0,03) (Table 1).

The median waiting time from the first ED evaluation to the beginning of CPAP treatment was 118 minutes [IQR 79-216] with minimum of 9 minutes to maximum of 911 minutes. 11 subjects (21.15%) received morphine in the first two hours of CPAP trial.

38 patients (73%) were judged eligible for ETI, whereas 18 were intubated with a rate of 34.62% [95% CI 21.68-47.55]. For these 18 patients the median time lapse between hospital admission and ETI was 2 days [IQR 1-6] with a range from a minimum of 1 to a maximum of 30 days. The median length of stay in hospital was different in subjects with and without ETI: 26 days [IQR 16-37] vs 15 days [IQR 9-17] respectively (p=0.005). The median CPAP time was 4.50 days [1-7], ranging from 1 to 14 days. The median IMV time was 11 days [IQR 7-21] with an ICU length of stay of 14.5 days [IQR 10-28].

The CPAP-related parameters (PEEP, FiO2, RR and SpO2) and their variation over time analyzed for patients eligible to ETI, are shown in figure 1. Considering the models with ETI as covariate, changes between the two groups were found for PEEP (p=0.003) and RR (p=0.059). No significant changes were found for FiO2 (p=0.245) and SpO2 (p=0.076).

A total of 16 (30.8% IC95% 18.22-43.31%) subjects died: 7 (38.9%) and 9 (26.5%) in the ETI and non-ETI group, respectively. Figure 2 shows the survival curve, separated for the two groups, considering the time from the beginning of CPAP use until death. The survival curves of ETI (solid line) and non-ETI patients (dash line) did not differ significantly (p=0.944). However, it seems that patients without ETI had lower survival in the first days. Considering only patients eligible to ETI, ETI patients had significant higher mortality rate compared to the others (N=7, 38.9% vs N=0; p=0.002)

Discussion

During COVID-19 outbreaks a large use of NIPPV was done in Northern Italy especially outside the ICUs, in the EDs and medical wards, despite the lack of evidence and clear indications for its use in these patients. We produced a flowchart for the use of non-invasive ventilation to standardize the first patient approach, reducing the heterogeneity of treatment between health professionals.[14] Starting from low PEEP values, we titrated it to reach a SpO2 increase and a RR reduction.

52 patients were included in the study. The population enrolled was mainly male with a median age of 62,5 years. It was similar in terms of comorbidities and clinical features to other studies populations of COVID-19 patients described in literature.[1,17] Median time from symptoms onset and hospital admission was 7 day [IQR 5–10] whereas only 1 [0–3] from dyspnea onset. Delayed hospital presentation was in part due to the attempt to manage patients at home. The late appearance of dyspnea might be due to the typical fairly normal pulmonary compliance in the first phases of the disease and the initial "silent hypoxia".[3–4]

All patients had severe or moderate ARF and most of them started CPAP treatment within 3 hours from hospital admission; few of them started it later due to progressive worsening of respiratory failure during ED observation. 73% were eligible to ETI. The ETI rate was 34,6%. This rate is concordant to other case series even if still few data on NIPPV failure in these patients are available.[18]

Patients who were intubated had a significant lower P/F ratio compared to those treated only with NIPPV. ETI was performed with a median time lapse of 2 days. When it was not performed immediately after the CPAP trial, the delay was never due to the prolongation CPAP treatment but to a subsequent worsening of respiratory failure or to a lack of resources available.

General mortality was 30,7% with not significant differences between ETI and non-ETI patients. All patients eligible to ETI but treated only with CPAP survived. The mortality rate was similar to other studies populations even if a comparison is not easy due to differences in disease severity among different studies groups.[1–18] A significant difference in the median length of hospital stay hospital resulted between ETI and non-ETI patients, 26 days [IQR 16–37] vs 15 days [IQR 9–17] respectively (p = 0.005), certainly due, in addition to initial patients' severity, to complications related to IMV and ICUs stay.

We decided to evaluate CPAP-related parameters and their variation on time only in patients eligible to ETI to assess whether an early RR improvement with a step-up PEEP titration could be useful in identifying patients treatable without IMV. Patients with an early RR improvement likely have a prevalent hypoxic stimulus on respiratory drive, which is reduced by correcting hypoxia through alveolar recruitment and oxygenation. We found that non-ETI patients, while using lower mean PEEPs, had a sharper and faster decline in RR after starting the CPAP trial. We think that a close monitoring of respiratory parameters and in particular of RR should be done when a CPAP trial is started, to identify patients likely to respond to CPAP treatment

Our study has some limitations. It was a retrospective, descriptive and single-center study. The results must be considered cautiously due to the small sample of patients evaluated. On the other hand, its strength and novelty lie on the application of a local flow chart for the use of helmet CPAP to treat COVID 19 patients. We standardized the initial approach to COVID-19 patients presenting with ARF to the ED, proposing a progressive up titration of PEEP to increase SpO2 and lower RR.

Conclusions

A first short closed monitored CPAP trial could be considered for ARF due to COVID-19 pneumonia before considering ETI. A progressive PEEP titration should target patient's SpO2 improvement and RR reduction. A rapidly RR decrease could help to identify patients likely to respond to to CPAP treatment.

More studies are needed to evaluate the efficacy and predictors of failure of CPAP and NIPPV in patients with ARF due to COVID-19 pneumonia.

Abbreviations

ABG: Arterial Blood Gases

ARDS: acute distress respiratory syndrome

ARF: acute respiratory failure

Bi-PAP: bilevel positive airway pressure

COPD: chronic obstructive pulmonary disease

COVID-19: *Coronavirus Disease 2019*

CPAP: continuous positive airway pressure

CT: computerized tomography

DNI: do-not-intubate

ED: emergency department

ETI: endotracheal intubation

FiO2: inspiratory oxygen fraction

ICU: intensive care unit

IMV: invasive mechanical ventilation

NIPPV: non-invasive positive pressure ventilation

PEEP: Positive end-expiratory pressure

RR: respiratory rate

SpO2: peripheral oxygen saturation

Declarations

References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet [Internet]. 2020;395(10229):1054–62. Available from: http://dx.doi.org/10.1016/S0140-6736(20)30566-3

2. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020;20(6):669–77.

3. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med [Internet]. 2020;46(6):1099–102. Available from: https://doi.org/10.1007/s00134-020-06033-2

4. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. JAMA [Internet]. 2020 Jun 9;323(22):2329–30. Available from: https://doi.org/10.1001/jama.2020.6825

5. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care. 2020;24(1):1–3.

6. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: Noninvasive ventilation for acute respiratory failure. Eur Respir J [Internet]. 2017;50(4). Available from: http://dx.doi.org/10.1183/13993003.02426-2016

7. Arabi YM, Fowler R, Hayden FG. Critical care management of adults with community-acquired severe respiratory viral infection. Intensive Care Med [Internet]. 2020;46(2):315–28. Available from: https://doi.org/10.1007/s00134-020-05943-5

8. Masclans JR, Pérez M, Almirall J, Lorente L, Marqués A, Socias L, et al. Early non-invasive ventilation treatment for severe influenza pneumonia. Clin Microbiol Infect. 2013;19(3):249–56.

9. Rodríguez A, Ferri C, Loeches IM, Díaz E, Masclans JR, Gordo F, et al. Risk factors for noninvasive ventilation failure in critically ill subjects with confirmed influenza infection. Respir Care. 2017;62(10):1307–15.

10. Nicolini A, Tonveronachi E, Navalesi P, Antonelli M, Valentini I, Melotti RM, et al. Effectiveness and predictors of success of noninvasive ventilation during H1N1 pandemics: A multicenter study. Minerva Anestesiol. 2012;78(12):1333–40.

11. Navalesi, P.; Maggiore, S.M. Positive end-expiratory pressure. In Principles and Practice of Mechanical Ventilation, 3rd ed.; Tobin, M.J., Ed.; McGraw Hill Medical: New York, NY, USA 2013; pp. 253–302. Navalesi, P.

12. Radovanovic D, Rizzi M, Pini S, Saad M, Chiumello DA, Santus P. Helmet CPAP to Treat Acute Hypoxemic Respiratory Failure in Patients with COVID-19: A Management Strategy Proposal. J Clin Med. 2020;9(4):1191.

13. Privitera D, Angaroni L, Capsoni N, Forni E, Pierotti F, Vincenti F, et al. Flowchart for non-invasive ventilation support in COVID-19 patients from a northern Italy Emergency Department. Intern Emerg Med 15, 767–771 (2020). https://doi.org/10.1007/s11739-020-02370-8

14. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbrouckef JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. Bull World Health Organ. 2007;85(11):867–72.

15. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-NCoV). Radiology. 2020;295(1):202–7.

16. Kelly BJ, Matthay MA. Prevalence and severity of neurologic dysfunction in critically ill patients: Influence on need for continued mechanical ventilation. Chest [Internet]. 1993;104(6):1818–24. Available from: http://dx.doi.org/10.1378/chest.104.6.1818

17. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA - J Am Med Assoc. 2020;323(16):1574–81.

18. Nightingale R, Nwosu N, Kutubudin F, Fletcher T, Lewis J, Frost F, et al. Is continuous positive airway pressure (CPAP) a new standard of care for type 1 respiratory failure in COVID-19 patients? A retrospective observational study of a dedicated COVID-19 CPAP service. BMJ open Respir Res. 2020;7(1):8–10.

Tables

Table 1. Demographics, clinical features, laboratory findings and treatments.

Variable	ALL (N=52)	ETI (N=18)	Non-ETI (N=34)	p-values
Gender				
Female, Mean (DS)	12 (23.08)	4 (22.22)	8 (23.53)	0.9999
Male, Mean (DS)	40 (76.92)	14 (77.78)	26 (76.47)	
Age (years)				
Median [IQR]	62.50 [50-72.50]	57 [51-67]	66 [48-75]	0.2655
Comorbidities				
None, Number (%)	14 (26.92)	5 (27.78)	9 (26.47)	0.9195
At least one, Number (%)	38 (73.08)	13 (72.22)	25 (73.53)	
Hypertension, *Number (%)*	23 (44.23)	8 (44.44)	15 (44.12)	
Obesity, *Number (%)*	14 (26.92)	7 (38.89)	7 (20.59)	
Cardiomyopathy, *Number (%)*	9 (17.31)	1 (5.56)	8 (23.53)	
Diabetes, *Number (%)*	8 (15.38)	4 (22.22)	4 (11.76)	
Lung disease, *Number (%)*	8 (15.38)	1 (5.56)	7 (20.59)	
Vasculopathy, *Number (%)*	5 (9.62)	1 (5.56)	4 (11.76)	
Immunosuppression, *Number (%)*	4 (7.69)	1 (5.56)	3 (8.82)	
Rheumatoid arthritis, *Number (%)*	3 (5.77)	0 (0.00)	3 (8.82)	
Chronic renal failure, *Number (%)*	2 (3.85)	0 (0.00)	2 (5.88)	
Malignancy, *Number (%)*	1 (1.92)	0 (0.00)	1 (2.94)	
Symptoms				
Dyspnea, *Number (%)*	49 (94.23)	18 (100.00)	31 (91.18)	
Fever, *Number (%)*	48 (92.31)	17 (94.44)	31 (91.18)	
Cough, *Number (%)*	22 (42.31)	9 (50.00)	13 (28.24)	
Asthenia and/or myalgia, *Number (%)*	6 (11.54)	3 (16.67)	3 (8.82)	
Gastrointestinal, *Number (%)*	5 (9.62)	2 (11.11)	3 (8.82)	
Time from symptoms onset to hospital admission, days, *Median [IQR]*	7 [5-10]	8 [4-10]	7 [5-10]	0.8551

Time from dyspnea onset to hospital admission, days N=49, *Median [IQR]*	1 [0-3]	0.50 [0-3]	1 [0-4]	0.7586
Treatment in Hospital				
None, Number (%)	7 (13.46)	4 (22.22)	3 (8.82)	0.2180
At least one, Number (%)	45 (86.54)	14 (77.78)	31 (91.18)	
Hydroxychloroquine, *Number (%)*	40 (76.92)	12 (66.67)	28 (82.35)	
Steroid, *Number (%)*	28 (53.85)	10 (55.56)	18 (52.94)	
Kaletra, *Number (%)*	24 (46.15)	11 (61.11)	13 (38.24)	
Azitromicina, *Number (%)*	19 (36.54)	1 (5.56)	18 (52.94)	
Tocilizumab, *Number (%)*	9 (17.31)	5 (27.78)	4 (11.76)	
Morphine, *Number (%)*	11 (21.15)	2 (11.11)	9 (26.47)	
Laboratory findings				
CRP, g/dL, *Mean (DS)*	12.75 (7.7-18.8)	13.85 (9.3-17)	10.15 (7.1-19.3)	0.5446
White Blood Cells, cell/L^{-1}, *Mean (DS)*	8.55 (6.6-10.23)	8.25 (6.66-10.15)	8.55 (6.59-10.78)	0.8701
Lymphocytes, cell/L^{-1}, *Mean (DS)*	4.8 (0.9-12.85)	2.58 (0.71-12.9)	5.3 (0.99-12.5)	0.6374
Platelets, cell/L^{-1}, *Mean (DS)*[1]	220 (188.5-264)	233 (201-316)	215 (172-254)	0.0621
Creatinine, mg/dL, *Mean (DS)*	0.91 (0.77-1.22)	0.87 (0.77-1.17)	1.01 (0.77-1.34)	0.3216
Total bilirubin, mg/dL, *Mean (DS)*	0.59 (0.46-0.78)	0.67 (0.47-0.78)	0.56 (0.42-0.76)	0.6721
INR, *Mean (DS)*	1.21 (1.13-1.28)	1.17 (1.13-1.24)	1.22 (1.13-1.29)	0.4299
aPTT ratio, *Mean (DS)*	1.15 (1.05-1.27)	1.15 (1.05-1.36)	1.15 (1.05-1.26)	0.9233
pH, *Mean (DS)*	7.47 (7.44-7.5)	7.48 (7.44-7.5)	7.47 (7.43-7.5)	0.4036
pCO_2, mmHg, *Mean (DS)*	31 (29-36)	30.8 (29-33)	33 (29-36)	0.3250
pO_2, mmHg, *Mean (DS)*	67.9 (52.5-83.85)	70 (53-79)	65 (52-92)	0.9656

F_iO_2, *Mean (DS)*	0.65 (0.21-0.8)	0.8 (0.21-0.8)	0.45 (0.21-0.8)	0.1408
P/F ratio, *Mean (DS)*	143.5 (86-252.19)	103.38 (85-147)	214 (101-290)	0.0303
SpO_2, %, *Mean (DS)*	94 (89-96)	94.8 (89-96)	92 (89-97)	0.9225