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Combined non-invasive respiratory support therapies to treat SARS-CoV-2 patients: A prospective Observational Study.

Running head: HFNC and Combined therapy in COVID-19 respiratory failure

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Abstract

Background: The role of high-flow nasal cannula (HFNC) and CPAP in COVID-19 are controversial. The objective of the study was to evaluate the impact of the application of a non-invasive respiratory support (NIRS) algorithm on clinical outcomes in COVID-19 subjects with acute respiratory failure (ARF).

Methods: We performed a single center prospective observational study of subjects with respiratory failure from COVID-19 managed with high-flow nasal cannula (HFNC) and CPAP+HFNC (combined therapy). The main outcome was the intubation rate, which defined failure of therapy. We also analyzed the role of the ROX index ([SpO_2/FiO_2]/respiratory rate) to predict the need for intubation.

Results: From June to December 2020, 113 subjects with COVID-19 respiratory failure were admitted to our respiratory intermediate care unit (RICU). HFNC was applied in 65 subjects (57.52%) and combined therapy in 48 (42.47%). A total of 83 subjects (73.45%) were successfully treated with NIRS. The intubation rate was 26.54 %, and overall mortality was 14.15%. Mortality rate in intubated subjects was 55.2%. ROX index of 6.28 at 12 hours predicted NIRS failure, with 97.6% of sensitivity and 51.8% of specificity.

Conclusions: Data from our cohort managed on RICU showed that combined NIRS are feasible with favorable outcomes. Further prospective studies are required.

Key words: COVID-19; SARS-CoV-2; high-flow nasal cannula; continuous positive airway pressure; combined therapy; hypoxemic respiratory failure

Introduction

On March 11st, 2020, the World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a pandemic due to the constantly increasing number of cases outside China.[1]Subjects with SARS-CoV-2 infection can develop coronavirus disease 2019 (COVID-19), which has resulted in high rates of hospitalization and intensive care unit (ICU) admission.[2] The clinical spectrum of SARS-CoV-2 infection appears to be wide, including asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and even death, with many subjects being hospitalized with pneumonia.[3] In the COVID-19 population, 14% of the subjects were categorized as severe cases and 5% as critical cases.[4] A systematic review and meta-analysis has pooled 31 articles involving 46,959 cases with COVID-19 and reported that the incidence of ICU admission was 29.3%.[5] Some experts have argued that invasive mechanical ventilation (IMV) should be employed early in order to prevent COVID-19 subjects progressing from mild disease to more severe lung injury. [6] Subjects with COVID-19 that require IMV are at high risk for poor outcomes and have a likelihood of mortality estimated at approximately 50%-97%.[7-9] Mortality may be related to the progressive course of the viral infection but could perhaps be perpetuated by the inherent complications of mechanical ventilation itself.

Other recommendations at the beginning of the pandemic were to avoid NIRS.[10] Two main concerns dealing with the use of NIRS are the risk of delaying intubation in case of failure and the fear of virus spreading among health care workers (HCW) during non-invasive respiratory treatment.[11] At the early stage, the high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV) was used in 20%-62% of hospitalized subjects.[12,13] Comparing different countries, the use of NIRS has been highly variable. Thus, in Lombardy Region, Italy, NIV was used in 11% of ICU subjects, but in the Seattle

Region, USA, HFNC was used in 42% of critically ill subjects.[14,15] Current recommendations state that subjects with COVID-19 related acute respiratory failure (ARF) should be monitored and supported with HFNC or NIV when standard oxygen therapy (SOT) fails.[16] In this regard, during the months of June to December of 2020, the COVID-19 pandemic conditioned a significant increase in healthcare burden across Argentina, as 45–59% of admitted subjects required critical care management.[17] The ICU beds and invasive mechanical ventilators were assumed to have limits of availability during the pandemic, so the conviction and availability of NIRS was a valuable option to maintain respiratory conditions. Therefore, a proper healthcare resource management is necessary to warrant adequate patient care. Respiratory intermediate care units (RICU) can be a useful resource for the management of complex subjects that do not require ICU admission, invasive mechanical ventilation (IMV) or invasive monitoring. RICU can function as a place for management of treatment escalation and de-escalation between the general ward and the ICU, especially when closer patient monitoring is needed and/or when NIRS are required. Benefits of RICU include reducing ICU admission time and increasing ICU bed capacity, as well as lowering mortality and health care costs.[10-12] The objective of the study was to evaluate the impact of the application of a NIRS algorithm on clinical outcomes in COVID-19 subjects with ARF.

Methods

Study design and subjects

This is a prospective observational study conducted in Hospital General de Agudos Juan A. Fernández, Buenos Aires, Argentina. Institutional Review Boards reviewed the protocol and authorized prospective data collection. We collected data from subjects admitted to the RICU from June 1st, 2020 to December 31th 2020. A confirmed case of

COVID-19 was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs.

Criteria for RICU admission were suspected COVID-19 pneumonia with at least of the following: ratio of oxygen blood pressure/oxygen inspired fraction (PaO_2/FiO_2) ≤200, supplemental oxygen requirement greater than 10 L/min, and respiratory rate (RR) ≥ 30 breaths/min, with or without use of accessory muscles.

Subjects were transferred to the ICU in case of rapid deterioration or need for intubation to start IMV. Decisions on ceiling limits of care and escalation to the ICU were made within an agreed ethical framework and based on clinical need and appropriateness for escalation. There were no limitations on resources.

Non-invasive respiratory support protocol

Respiratory support was provided throughout a decision-making algorithm (figure 1). All subjects received respiratory support in awake prone-position (awake-PP) or decubitus position changes at least 18 hours per day, avoiding supine position as much as possible. Prone position was not considered in case of patient intolerance, morbid obesity, or patient refusal. In these cases, alternating lateral decubitus position was performed. To check the initial response to treatment, all subjects underwent a two-hour trial of HFNC at 60 L/min and 0.6 FiO_2 and, as adjuvant therapy, awake-PP or decubitus position changes were performed. Subjects were considered as responders when respiratory rate decreased below 30 breaths/min and SpO_2 increased above 94% with FiO_2 less than 0.6. Subjects who did not meet those criteria after the trial, were considered as non-responders and were assigned an alert code (ventilatory alert), escalating ventilatory support with CPAP, and initiating closer monitoring for 6 hours. CPAP and HFNC were

used alternatively and complementarity in accordance to patient's ventilatory needs and clinical endpoints, within a strategy of therapy rotation to increase comfort and tolerance to treatment. Subjects who did not improve throughout the treatment were transferred to ICU for close monitoring and invasive ventilation if necessary. Weaning from NIRS to STO was performed following a strict protocol (figure 1). Monitoring and clinical evaluation were performed every 3 hours for responders and every hour for the first 6 hours to non-responders.

The CPAP interface was chosen according to the patient's tolerance. CPAP was delivered by dedicated ventilator (Astral 150, Resmed, San Diego (CA), USA) provided with a low-pressure oxygen source via a non-vented oronasal mask with blue elbow (FreeMotion RT041, Fisher & Paykel, Auckland, New Zealand) or a helmet (NIV Helmet, Ecleris, Buenos Aires, Argentina). In the case of oronasal mask a double limb circuit with an expiratory valve was used, whereas in the case of a helmet, we used a single limb circuit with an exhalation hole in one of the helmet ports. In order to limit the production of virus-laden aerosols, filters were placed between the interfaces and the circuit, and in the inlet and outlet ventilator ports. HFNC was delivered using standard devices (Airvo 2, Fisher and Paykel, Auckland, New Zealand). HFNC was set at 60 L/min. CPAP was initially set at 10 cm H_2O with an increase up to 14 cm H_2O if needed. CPAP levels were modified at the discretion of the attending physician according to the clinical situation of the subjects. In both treatments, FiO_2 was titrated to maintain SpO2 between 94-96%.

Data collection

On admission to the unit the following data were recorded: demographics (age, gender, body mass index [BMI]), comorbidities [obesity, hypertension, diabetes, COPD, asthma,

cardiovascular disease, no history for comorbidities], disease chronology (time from onset of symptoms, time from hospital admission to initiation of respiratory support and time from COVID-19 diagnosis to NIRS onset), symptoms at RICU admission, vital signs [respiratory rate, temperature, mean arterial pressure (MAP), heart rate], blood gas analysis and laboratory test. We calculated the following scores: National Early Warning Score (NEWS), Acute Physiology and Chronic Health Evaluation II (APACHE II), SOFA Sequential sepsis related Organ Failure Assessment (SOFA) and LUS Lung Ultrasound Score (LUS). PaO_2/FiO_2 ratio (P/F), and SaO_2/FiO_2 (S/F) were calculated before starting ventilatory support. We also recorded RICU length of stay (LOS) and hospital LOS. Endotracheal intubation (ETI) rates, mortality of intubated subjects and overall hospital mortality were also recorded. The ROX index ([SpO2/FIO2]/respiratory rate) was calculated at different times (T). After 30 minutes, 2, 6 and 12 hours, after initiation of NIRS (ROX index-T30, ROX index-T2, ROX index-T6, ROX index-T12 respectively).

Protective personal equipment

The RICU consisted of 5 negative pressure beds located in two shared rooms and one single room with 2 beds containing a High Efficiency Particulate Air (HEPA) filter. For staff safety, personal protective equipment (PPE) protocols were readjusted in conjunction with the hospital's infectious disease service, since most procedures related to the care of these subjects are considered "super spread". Thus, the PPE level 3 model recommended by the WHO was modified, designing a water-repellent and disposable hood that covers the whole head, neck and leaves vision free. PPE included a respirator mask (N95 respirators, FFP2, FFP3, or equivalent), a disposable long-sleeved gown or protective suit, double gloves, goggles or, in alter-native, a face shield, shoe covers.

Statistical analysis

We used data of all available subjects without formal sample size calculation as the purpose of the analysis was exploring the effect of NIRS, we did not specify any *a priori* effect size. Continuous variables are reported as median and interquartile ranges and categorical variables as n (%). Normality of distributions was assessed by inspecting quantile–quantile plots. If variables were normally distributed, the two–sample t–test was used; if not, the Wilcoxon rank sum test was used. We used the Chi–square test or Fisher's exact test for categorical variables. Statistical uncertainty was expressed by showing the 95%–confidence intervals (CI). We assessed the ability of the ROX index to classify the success of NIRS treatment by fitting receiver operating characteristics curves (ROCs) at all timepoints and calculating the C index (Area Under Curve, AUC). The ROCS for each timepoint were compared by DeLong U-test. Statistical significance was considered for two–tailed $P<0.05$. No imputation routine of missing values and no correction for multiple comparisons was prespecified; thus, all the findings should be viewed as exploratory. All analyses were performed with R 4.0.3 (The R Foundation for Statistical Computing, www.r-project.org)

Results

A total of 121 subjects were admitted to the RICU from June 1st to December 31st, 2020 due to COVID-19 pneumonia. The flowchart of enrolled subjects is shown in Figure 2. Eight subjects were excluded because CPAP or NIV was used as first line treatment. A

total of 113 subjects were included in the final analysis. Among them, HFNC was used as the only therapy in 65 subjects and combined therapy (HFNC+CPAP) in 48 subjects (Figure 1). Among subjects who were treated with HFNC alone, 10 could not be treated with CPAP due to interface intolerance, requiring further intubation.

The primary outcome was to assess the rate of ETI. Eighty-three subjects (73,45%) were discharged from the RICU (success group) and thirty subjects (26,54%) required ETI and ICU admission (failure group). The causes of treatment failure were septic refractory hypoxemia (57%), alterations of consciousness (10%), interface intolerance (33%).

The clinical characteristics of subjects according to success or failure are summarized in Table 1. Median age was significantly higher in the failure group (53.00 [40.50, 60.50] vs 63.50 [57.00, 69.50], *P<.01*). Disease severity scores, APACHE II and SOFA, were higher in the failure group (8 vs 10, *P<.01* and 2 vs 2.5, respectively). There were no differences in the proportion of comorbidity, symptoms, and laboratory tests between the groups. Oxygenation rates on admission were similar between those subjects who failed and succeeded. We found a significant difference in ROX index values at 2, 6 and 12 hours (Table 2), with the maximum difference between groups at 12 hours (9.13 [7.92, 11.88] success group vs 6.28 [5.45, 8.71] failure group, *P<.01*).

Secondary outcomes such as RICU length of stay (LOS), hospital LOS, mortality in the failure group, hospital mortality and ROX index at different times were evaluated in both groups. The RICU LOS of success group was 7 days vs. 2 days in the failure group (*P<.01*). Hospital LOS was significantly longer in the failure group (26 days vs. 12 days, *P<.01*). In subjects in whom NIRS failed, 16 (55.2%) died (Table 3). Overall mortality was 14.15%. The ROX index at 2, 6 and 12 hours shown to have good diagnostic performance in predicting the need for intubation. Area under the ROC curve (AUC) for ROX index at 30 minutes, 2, 6 and 12 hours were 0.535 (0.478–0.593), 0.588 (0.533–

0.643), 0.627 (0.567–0.687) and AUC: 0.772 (0.719–0.824), respectively (Figure 3). Using the ROX index of 6.28 at 12 hours as cutoff value to predict failure, the sensitivity was 97.6% and specificity was 51.8%.

All subjects received dexamethasone (100%), convalescent plasma (3%), interferon beta (4%), remdesivir (2%), prophylactic/intermediate dose heparins (12%) and anticoagulation (4%).

Discussion

This is the first study to evaluate the application of combined NIRS in subjects with ARF secondary to COVID-19 through a stepwise treatment algorithm. Our main findings were a low ETI rate and mortality. Only 26.54% of our subjects were intubated, similar to previous studies reporting the use of NIRS outside the ICU.[18-20] Regarding overall mortality, in previous studies using HFNC and CPAP as first-line respiratory support in subjects with ARF secondary to COVID-19 the rates ranged from 24% to 50%.[18-20] One explanation for our results is that the use of combined NIRS, specially in subjects with severe hypoxemic ARF, allowed a longer therapy time and better comfort, increasing adherence to treatment. A relevant aspect of our protocol was the implementation of a strategy of interface rotation and use of different types of NIRS for avoiding periods without ventilatory support. Moreover, our algorithm was based on close monitoring and treatment escalation, trying not to delay intubation in case of failure. NIV/CPAP failure has been considered a risk factor for increased mortality in subjects with hypoxemic ARF.[14] In this regard Bhatraju et al. showed an extremely high mortality rate both with NIV and HFNC failure (80% and 52%, respectively) in COVID-19 subjects admitted to the ICU with SARS-CoV-2. In our study, mortality in intubated subjects was 55.2%,

like those in whom IMV was used as first-line treatment, suggesting the usefulness of the algorithm.[15]

Another point to highlight is that during admission in our unit we encourage subjects to be in a prone position for at least 18 hours per day. Prone positioning has strong evidence in subjects undergoing IMV. Recent work published by Yoshida et al. shows that the prone position may reduce the risk of stress-dependent lung injury in ARDS. Compared to the supine position, the prone position during spontaneous breathing improves gas exchange, reduces the intensity of spontaneous inspiratory effort and dynamic lung stress, and attenuates systemic inflammation.[21] Despite this, the benefits of awake-PP in subjects with NIRS remains controversial. In a recent study in subjects with COVID-19 ARF treated with HFNC, the use of awake-PP did not reduce the need for intubation or affected mortality.[22] On the other hand, other studies have observed that the use of awake-PP in subjects with ARF treated with HFNC and CPAP was safe and feasible in most of them, improving physiological measures of oxygenation and contributing to avoid intubation.[23-26] There is no current evidence supporting the use awake-PP in COVID-19, however some observational studies have tested this coadjuvant strategy with promising results.[27]

The ROX index was first described and validated in subjects with hypoxemic respiratory failure treated with HFNC prior to the COVID-19 outbreak.[28] It may help to select subjects that could benefit from HFNC identifying those with low and those with high risk for intubation. In a recent retrospective review, the ROX index was sensitive for the identification of COVID-19 subjects successfully weaned from HFNC. The authors found that the ROXi > 3.0 at 2, 6, and 12 hours after initiation of HFNC was 85.3% sensitive for identifying subsequent HFNC success.[29] Although ROX index was validated in subjects treated with HFNC, a recent study showed that the use of awake-PP

alongside CPAP significantly increased the ROX index, demonstrating that the ROX index can be a good indicator to predict the success of CPAP or NIV in hypoxemic subjects.[23] In our study, we found that a 12-hour ROX index lower than 6.28 showed a high sensitivity (97.6%) for predicting the need for intubation. Interestingly, the ROX index was significantly higher in responder subjects at 2 hours after the onset of NIRS, with a maximum difference at 12 hours. These data suggest that the optimal time for application of NIRS would be at 12 hours and that by monitoring the ROX index at different time intervals after NIRS clinicians can quickly detect treatment failure and not delay intubation. Given the similarity in clinical outcomes between early and late failure subjects in our cohort, prediction of HFNC success may be of clinical utility. Further studies to validate the role of the ROX index in subjects with SARS-CoV-2 receiving NIRS are required.

This study has several limitations being an uncontrolled, non-randomized observational study including a single center. Also, our cohort included only severe subjects, as we focused on the role of RICU in patient management. This may limit the generalization of our results to less severe cases. However, the number of participants is higher than most previous studies, and our results agree with observations from different cohorts.

Conclusions

The use of combined NIRS in subjects with severe ARF secondary to COVID-19 can be a promising alternative to IMV in selected patients. Strict treatment protocols and algorithms can help clinicians in selecting the most appropriate ventilatory support. The ROX index can be a good indicator of failure at NIRS. Further randomized controlled trials are needed.

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Figure Legend

Figure 1. Decision-making algorithm of Non-invasive Respiratory Support (NIRS) treatment

Figure 2. Patient allocation to Non-invasive Respiratory Support therapies (NIRS) and related clinical outcomes. Legend: SARS-COV= severe acute respiratory syndrome coronavirus 2; ARF= Acute Respiratory Failure; NIV= Non-Invasive Ventilation; HFNC = High Flow Nasal Cannula; CPAP = Continuous Positive Airway Pressure.

Figure 3. Receiver operator characteristic curves (ROC) for ROX index at 30 minutes (A), 2 hours (B), 6 hours (C) and 12 hours (D), after initiation of Non-invasive Respiratory Support (NIRS) as predictor of NIRS failure. Legend: AUC= area under the curves. Data presented with 95% confidence interval (CI).

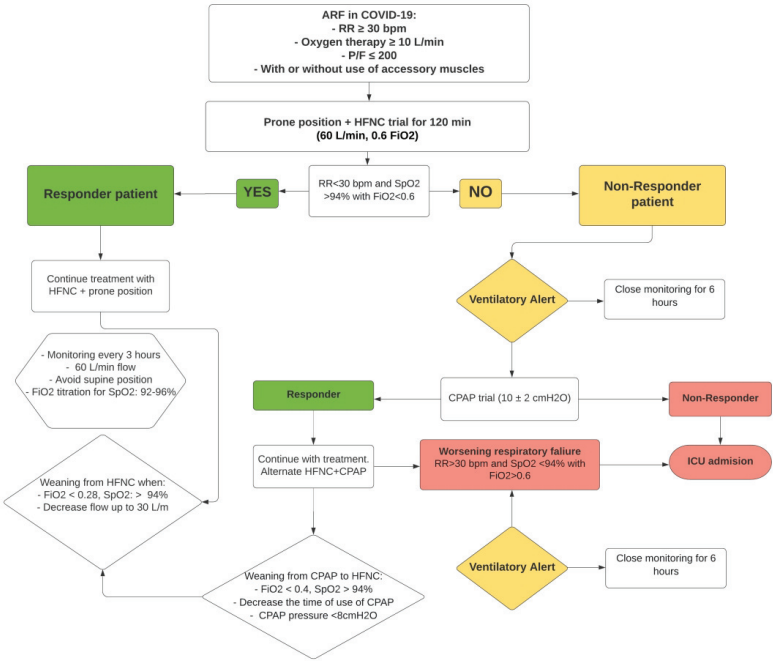
Quick Look

Current Knowledge

High-flow nasal cannula (HFNC) and CPAP are routinely used as part of the care of subjects with COVID-19-related respiratory failure. There is significant debate about the effectiveness of these non-invasive therapies compared to invasive ventilation.

What this article adds to our knowledge

This article adds to our knowledge, the feasibility of being able to perform combined therapies of NIRS and the possibility of using ROXi as a predictor of NIRS failure. Prolonged use of HFNC or Combined therapy may be reasonable in the care of subjects with COVID-19 as a measure to avoid ETI.



Decision-making algorithm of Non-invasive Respiratory Support (NIRS) treatment

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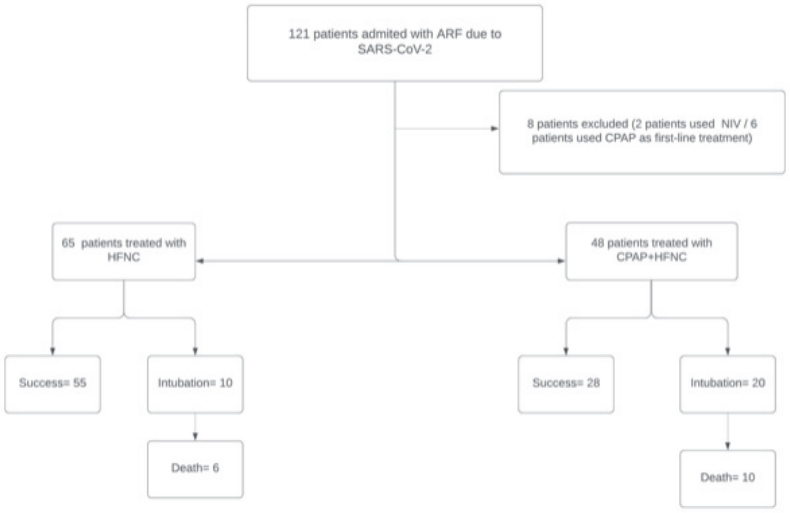

Patient allocation to Non-invasive Respiratory Support therapies (NIRS) and related clinical outcomes. Legend: SARS-COV= severe acute respiratory syndrome coronavirus 2; ARF= Acute Respiratory Failure; NIV= Non-Invasive Ventilation; HFNC = High Flow Nasal Cannula; CPAP = Continuous Positive Airway Pressure.

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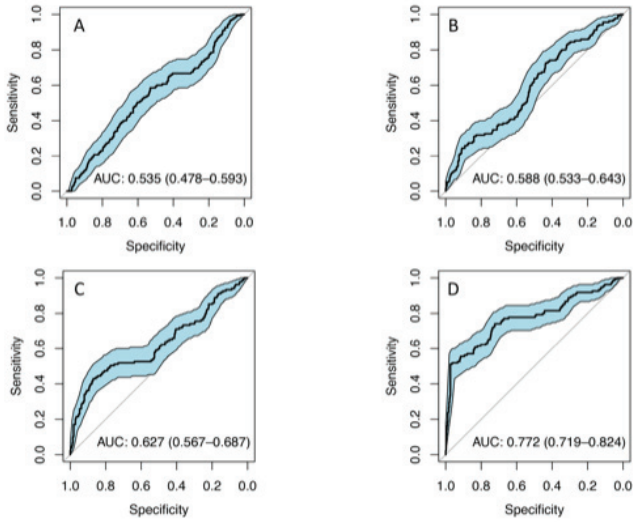

Receiver operator characteristic curves (ROC) for ROX index at 30 minutes (A), 2 hours (B), 6 hours (C) and 12 hours (D), after initiation of Non-invasive Respiratory Support (NIRS) as predictor of NIRS failure.
Legend: AUC= area under the curves. Data presented with 95% confidence interval (CI).

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Table 1. **Baseline characteristics of patients treated with NIRS**

	Total cohort (n= 113)	Success (n= 83)	Failure (n= 30)	p-value
Age, years (median [IQR])	55 [46, 64]	53 [41, 61]	64 [57, 70]	<.01
Female, n (%)	24 (21.2)	18 (21,7%)	6 (20%)	.98
Days from symptom onset to hospital admission, (median [IQR])	9 [6, 10]	9 [6, 10]	8[6, 11]	.76
Days from symptom onset to RICU admission), (median [IQR])	8-[6, 10]	8 [7, 10]	9 [6, 11]	.77
APACHE II (median [IQR])	8 [7, 10]	8 [6, 9]	10 [8, 11]	<.01
SOFA (median [IQR])	2 [2, 3]	2 [2, 2]	3[2, 3]	<.01
NEWS Score (median [IQR])	10 [9, 12]	10 [9, 12]	11[10, 12]	.17
LUS Score (median [IQR])	21[18, 25]	20 [17, 24]	23 [20, 26]	.10
BMI (kg/m2)	28.4 [25.5, 32.8]	28.6 [25.0, 32.8]	27.6 [26.0, 31.8]	.83
Comorbidities				

Obesity	49 (43.4%)	38 (45.8%)	11 (36.7%)	.51
Hypertension	22 (19.5%)	13 (15.7%)	9 (30.0%)	.15
Diabetes, n (%)	10 (8.8%)	8 (9.6%)	2 (6.7%)	.90
COPD, n (%)	1 (0.9%)	1 (1.2)	0 (0.0)	.95
Asthma, n (%)	3 (2.7%)	3 (3.6)	0 (0.0)	.69
Cardiovascular disease, n (%)	1 (0.9%)	0 (0.0)	1 (3.3)	.59
Chronic kidney disease, n (%)	1 (0.9%)	0 (0.0)	1 (3.3)	.59
no history of comorbidities, n (%)	35 (31.0)	29 (34.9)	6 (20.0)	.19
Symptoms				
Dyspnea, n (%)	85 (75.2%)	63 (75.9)	22 (73.3%)	.97
Cough, n (%)	83 (73.5%)	58 (69.9%)	25 (83.3%)	.23
Fever, n (%)	101 (89.4%)	73 (88.0%)	28 (93.3%)	.63
Myalgias, n (%)	22 (19.5%)	18 (21.7%)	4 (13.3%)	.47
Diarrhea, n (%)	18 (15.9%)	14 (16.9%)	4 (13.3%)	.87
Nausea, n (%)	6 (5.3%)	4 (4.8%)	2 (6.7%)	.97

Headache, n (%)	38 (33.6%)	29 (34.9%)	9 (30.0%)	.79
Anosmia and dysgeusia, n (%)	29 (25.7%)	24 (28.9%)	5 (16.7%)	.28
Odynophagia, n (%)	22 (19.5%)	16 (19.3%)	6 (20.0%)	.99
Thoracodinia, n (%)	4 (3.5%)	3 (3.6%)	1 (3.3%)	.98
Laboratory blood tests				
Leukocyte count (x109/L), (median [IQR])	8[6, 10]	8 [6, 10]	8 [6, 11]	.58
Lymphocyte count (x109/L), (median [IQR])	15 [10, 22]	15 [10, 23]	13[6, 19]	.09
D-dimer (µg/L), (median [IQR])	346 [274, 533]	328 [258, 501]	443[313, 619]	.12
Ferritin (µg/L), (median [IQR])	819 [438, 1363]	768 [441, 1108]	1253 [516, 1500]	.14
C-Reactive protein (mg/L), (median [IQR])	11.0 [6.4, 15.5]	10.8 [6.2, 13.7]	12.3 [7.6, 21.7]	.18

Data presented as median (25th percentile, 75th percentile) or n (%) unless otherwise indicated.

NIRS: Non-Invasive Respiratory Support; RICU: Respiratory Intermediate care unit; APACHE II: Acute physiology and chronic health evaluation II; SOFA: Sequential organ failure assessment; NEWS: National Early Warning Score; LUS: Lung Ultrasound Score; BMI: Body mass index; ICU: Intensive care unit; COPD: Chronic obstructive pulmonary disease

Table 2. Oxygenation data

	Success (n= 83)	**Failure (n= 30)**	***P*-value**
pH on admission (median [IQR])	7.41 [7.40, 7.43]	7.41 [7.40, 7.43]	.43
$PaCO_2$, mmHg on admission (median [IQR])	34 [32-, 38]	36 [33, 40]	.15
PaO_2, mmHg on admission (median [IQR])	85 [76, 105]	82.00 [67, 100]	.22
SpO_2/FiO_2 (S/F) on admission (median [IQR])	118 [114, 120]	117 [114, 120]	.46
PaO_2/FiO_2 (P/F) on admission (median [IQR])	106 [95, 131]	103 [84, 125]	.22
ROX index-T1 (median [IQR])	7.52 [6.25, 9.37]	6.88 [5.31, 9.19]	.12
ROX index-T2 (median [IQR])	8.09 [7.04, 10.19]	7.89 [5.64, 8.78]	.04
ROX index-T6 (median [IQR])	8.44 [7.72, 10.66]	7.47 [5.60, 10.10]	.02
ROX index-T12 (median [IQR])	9.13 [7.92, 11.88]	6.28 [5.45, 8.71]	<.01

Data presented as median (25th percentile, 75th percentile) or n (%) unless otherwise indicated.

SpO2: Oxygen saturation; FiO_2: Fraction of inspired oxygen; PaO_2: partial pressure of oxygen; T1: Time 30 minutes; T2: Time 2 hours; T6: Time 6 hours; T12: Time 12 hours

Table 3. Subjects treated with NIRS

	Success (n= 83)	Failure (n= 30)	p-value
LOS RICU in days, (median [IQR])	7 [5, 10]	2 [1, 3]	<.01
LOS hospital in days, (median [IQR])	12 [9, 16]	26 [19, 43]	<.01
Mortality, n (%)	0 (0.0%)	16 (55,2%)	<.01

Data presented as median (25th percentile, 75th percentile) or n (%) unless otherwise indicated.

NIRS: Non-Invasive Respiratory Support; LOS: Length of stay; RICU: Respiratory Intermediate care unit