High flow nasal oxygen therapy to avoid intubation in SARS-CoV-2 pneumonia: A multicenter retrospective study

Nicolas Bonnet (nicolas.bonnet@aphp.fr)
Hôpital Avicenne: Hopital Avicenne https://orcid.org/0000-0003-0598-1242
Olivier Martin
Hôpital Avicenne: Hopital Avicenne
Marouane Boubaya
Hôpital Avicenne: Hopital Avicenne
Vincent Levy
Hôpital Avicenne: Hopital Avicenne
Nathan Ebstein
Hôpital Avicenne: Hopital Avicenne
Philippe Karoubi
Hôpital Avicenne: Hopital Avicenne
Yacine Tandjaoui Lambiotte
Hôpital Avicenne: Hopital Avicenne
Guillaume Van Der Meersch
Hôpital Avicenne: Hopital Avicenne
johanna Oziel
Hôpital Avicenne: Hopital Avicenne
Marie Soulie
Hôpital Avicenne: Hopital Avicenne
Mohamed Ghalayini
Hôpital Avicenne: Hopital Avicenne
Anais Winchenne
Hôpital Avicenne: Hopital Avicenne
Jean Ralph Zahar
Hôpital Avicenne: Hopital Avicenne
Passem Ahmed
Hôpital Avicenne: Hopital Avicenne
Stéphane Gaudry
Hôpital Avicenne: Hopital Avicenne
Yves Cohen

Hôpital Avicenne: Hopital Avicenne

Research

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Abstract

Background:. The efficacy of high flow nasal canula oxygen therapy (HFNO) to prevent invasive mechanical ventilation (IMV) is not well established in severe coronavirus disease 2019 (COVID-19). The aim of this study was to compare the risk of intubation between two strategies of oxygenation (conventional oxygenation and HFNO) in critically ill COVID 19 patients

Methods: This was a multicenter retrospective case series witch took place in two intensive care units (ICU) of tertiary hospitals in the Paris region from March 11, to May 3, 2020. We enrolled consecutive patients hospitalized for COVID-19 and acute respiratory failure (ARF) who did not receive IMV at ICU admission. The primary outcome was the rate of IMV after ICU admission. Secondary outcomes were death at day 28 and day 60, length of ICU stay, ventilator-free days and number of patients with ventilator-free days >14 days. Data from the HFNO group were compared with those from the standard oxygen therapy (SOT) group.

Results

Among 138 patients who met the inclusion criteria, 62 (45%) were treated with SOT alone, and 76 (55%) with HFNO. In HFNO group, 39/76 (51%) patients were intubated and 46/62 (74%) in SOT group. After using a standard logistic regression on the original sample, HFNO was associated with significantly lower rate IMV (OR [IC-95%] 0.37 [0.18 – 0.76] p = 0.007). After propensity score application, HFNO was still associated with a lower rate of intubation (OR [IC-95%] 0.31 [0.14-0.66] p = 0.002). Length of ICU stay and mortality at day 28 and day 60 did not significantly differ between HFNO and SOT groups after propensity score application. In a univariate analysis, ventilator-free days at days 28 was higher in HNFO group (21 days vs 10 days, p=0.005). The number of patients with ventilator free-days >14 days was higher in HFNO group after propensity score application (66% vs 39%; OR 3.91[1.91-7.99], p=0.0002).

Conclusions

High flow nasal canula oxygen for ARF due to COVID-19 reduces the need for intubation.

Background

On March 11, 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]. Acute respiratory failure (ARF) due to acute hypoxemia is the main manifestation in severe coronavirus disease 2019 (COVID-19). In most severe cases, COVID-19 patients are hospitalized in intensive care unit (ICU) and may require invasive mechanical ventilation (IMV). The need for IMV is associated with high mortality[2, 3]. Up to April 9, 2020, a total of 112 950 patients had tested positive for the new SARS-CoV-2 coronavirus in France, and 7148 (9%) had been admitted to the ICU[4].

High flow nasal oxygen (HFNO) is increasingly used for adults hospitalized with ARF. This non-invasive technic delivers warmed, humidified oxygen with a fraction of inspired oxygen (FiO2) up to 1.0 and a maximum flow rate of 60 L/min. Several potential physiologic advantages of HFNO have been proposed, including improved oxygenation[5] and a reduced respiratory rate[6].

Due to the hypothetic risk of transmission to healthcare workers at the beginning of the sanitary crisis, expert opinion recommend restricting the use of HFNO and limiting the flow rate to 30 L/min for critically ill patients with coronavirus disease 2019 (COVID-19)[7]. This recommendation led intensivists to adopt an early intubation strategy to limit the use of HFNO[8]. However, the risk of bio-aerosol dispersion associated with HFNO has since been questioned[9]. It should be noted that there is a lack of evidence to support such bio-aerosol dispersion,[10–13] including in the SARS CoV outbreak in Toronto[14].

Information about clinical outcomes of patients treated by HFNO in ICU for COVID-19 are limited. The aim of this study was to compare the risk of intubation between two strategies of oxygenation (conventional oxygenation and HFNO) in critically ill COVID 19 patients.

Materiel And Method

Study design:

This was a multicenter retrospective study which took place in two French hospitals located in Paris area: Hôpital Avicenne, Assistance Publique Hopitaux de Paris and Hôpital de Rambouillet. All adult patients who were diagnosed with COVID-19 according to WHO interim guidance were screened[15], and those with a diagnosis of ARF admitted to the ICUs between March 11, 2020 (ie, when the first patients were admitted), and May 3, 2020, were included. We did not include patients who were admitted with a decision to withdraw life-sustaining therapy, including do-not-intubate orders, patients who received non-invasive ventilation, and patients who were intubated before ICU admission.

The study was approved by the Medical Ethics Committee of the Hôpital Avicenne.

We followed the statement guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for observational cohort studies[16].

Oxygenation strategy

All adult patients hospitalized for COVID-19 in participating ICUs required oxygen therapy. Standard-oxygen therapy was applied through a non-rebreather face mask at a flow rate of 6 l/min or more. The oxygen flow rate was adjusted to maintain an oxygen saturation level of more than 92%.

When HFNO was used, oxygen was passed through a heated humidifier (MR850 and AIRVO 2, Fisher and Paykel Healthcare) and applied continuously through large-bore binasal prongs, with a gas flow rate of 60 liters per minute and a fraction inspired of oxygen (FiO2) of 1.0 at initiation. The FiO2 in the gas

flowing in the system was adjusted to maintain an oxygen saturation level of more than 92%. All patients receiving HFNO wore a surgical mask to prevent SARS-Cov-2 transmission.

Before March 27, due to the hypothetic risk of transmission of SARS-Cov-2 to healthcare workers, the use of HFNO was scarce and the flow rate was limited to 30 liters per minute according to the French intensive care society guidelines. After March 27, 2020, in the light of a low risk of transmission by bio-aerosolization with HFNO in the literature, we decided to not restrict the use of HFNO and to allow a high flow rate (60L/min).

Throughout the study period, the decision to intubate was based on clinical characteristics (respiratory rate, worsening of respiratory status, high respiratory-muscle workload) and biological characteristics (arterial partial pressure of oxygen). Worsening respiratory failure was defined by at least two of the following criteria: a respiratory rate of more than 40 breaths per minute; a lack of improvement in signs of high respiratory-muscle workload; the development of copious tracheal secretions; respiratory acidosis with a pH of less than 7.35; and an Spo2 of less than 90% for more than 5 minutes without technical dysfunction.

Data Collection:

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records using a standardized data collection form. Laboratory confirmation of SARS-CoV-2 infection was performed by the local health authority.

The data recorded were the following:

Epidemiological data: age, sex, body mass index (BMI), chronic medical histories (chronic cardiac disease, chronic pulmonary disease, diabetes, malignancy),

Clinical, biological and radiological characteristics at ICU admission: SAPS II, heart rate, arterial blood pressure, respiratory rate, oxygen flow, time from onset of symptoms to ICU admission, blood count, coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), myocardial enzymes, interleukin-6 (IL-6), C-reactive protein (CRP), serum ferritin, procalcitonin, arterial blood gas analysis, lactate concentration, chest CT scan.

Therapy in ICU: need for invasive mechanical ventilation, need for catecholamine infusion, antiviral agents, immunomodulator therapy.

Outcomes

The primary outcome was the proportion of patients who required endotracheal intubation after ICU admission.

The secondary outcomes were death 28 days and 60 days after ICU admission, the mean length of stay in ICU, the number of ventilator-free days at day 28, the number of patients with ventilator-free days > 14

days. For ventilator-free days, one point was given for each calendar day during the measurement period (i.e. from the first day of admission in ICU to day 28) that a patient was both alive and free of invasive mechanical ventilation, and zero value was given for patients who died before day 28.

We also assessed the number of health care worker contaminations during 2 periods: before March 27, when the use of HFNO was restricted because of the hypothetical risk of aerosol contamination and after March 27, when the use of HFNO was not restricted.

Statistical analysis

Categorical variables are expressed as number with percentage (%) and continuous variables as mean with standard deviation (SD), or median with interquartile range (IQR). Initial characteristics of the HFNO group and the standard-oxygen therapy group were compared using a Chi-square test or Fisher's exact test for the categorical data, and a t-test or Wilcoxon signed-rank test for continuous data.

The effect of HFNO was assessed using a propensity score analysis to balance the differences in baseline variables between the two groups. The probability for receiving HFNO was calculated by a non-parsimonious logistic regression. Covariates included in this model were selected before analysis: sex, age, BMI, time from onset of symptoms to ICU admission, hypertension, diabetes, and parameters measured at ICU admission: SAPS II, oxygen flow, PaO2, respiratory rate, CRP and chest CT scan severity. Chest CT scan severity was defined by a quantitative evaluation of the abnormal manifestation of chest CT imaging. The abnormal imaging signs included ground glass opacity and consolidation quantified by radiologist. The radiologist estimated the lesion areas on each lung lobe as a percentage of the whole lung lobe[17].

HFNO effect on intubation at 28 days and mortality in ICU at 28 and 60 days were performed with weighted logistic regression using the stabilized inverse probability of treatment weighting (IPTW)[18]. Regarding intubation, there was no competitive risk (no death without intubation at 28 days). Length of ICU stay among patients discharged was compared between oxygenation groups with a weighted log-linear model using the IPTW. The number of ventilation-free days at day 28 was compared using Mann–Whitney U test. Because a non-normal distribution of patients in our sample, we could not perform a weighted logistic regression for this last parameter. To address this shortfall, the number of ventilation-free days was dichotomized at 14 days,and analyzed using weighted logistic regression. Two sensitivity analyses were performed for primary outcome: a truncated IPTW excluding patients with an extreme IPTW (5th-95th percentile) and an analysis excluding patients on HFNO with O2 flow < 50L/min.

To account for missing data, analyses were conducted using multiple imputations by chained equations with 5 imputations obtained after 5 iterations[19]. The propensity scores came from 10 independent complete data sets and were averaged according to an “across approach” [20]. Covariate balances before and after weighting were assessed by standardized mean differences which came from a complete imputed data set[21].

We also sought to determine predictive factors for intubation for patients on HFNO with univariate logistic regressions.

All tests were two-tailed, and the results were considered statistically significant when p< 0.05. Analyses were performed using R statistical software version 3.5.2 (R foundation for Statistical Computing, Vienna, Austria).

Results

A total of 155 COVID-19 patients were admitted in the participating ICUs for COVID-19. Among them, 17 had non-inclusion criteria (invasive mechanical ventilation before ICU-admission n=7, decision to withdraw life-sustaining therapy n=5, non-invasive mechanical ventilation n=5) (figure 1). Among the remaining 138 patients, 62 were treated with standard-oxygen therapy alone, and 76 with HFNO. Characteristics of the patients at ICU admission are presented in the Table 1.

Primary endpoint

In the standard-oxygen therapy group, 46/62 (74%) patients were finally intubated during the ICU stay compared with 39/76 (51%) in the HFNO group (p=0.007). In the univariate model, patients in the HFNO group were more likely to have hypertension (49% vs 31%, p = 0.0049), and had a higher time from the onset of symptoms to ICU admission (10 days vs 8 days, p = 0.002). Moreover, patients in HFNO group were more severely ill at the time of ICU admission as attested by a higher flow rate of oxygen before ICU admission (9 l/min vs 6 l/min, p = 0.003), and a higher respiratory rate (33 per minute vs 30 per minute, p = 0.018). Covariate balances before and after weighting are reported in figure 2. HFNO was associated with a significantly lower rate of intubation after standard logistic regression and after propensity score application (OR [IC-95%] 0.37 [0.18 – 0.76] p = 0.007 and OR [IC-95%] 0.31 [0.14-0.66] p = 0.002 respectively) (Table 2). The two sensitivity analyses performed for the primary outcome using a truncated IPTW excluding patients with an extreme IPTW (5th-95th percentile) and excluding HFNO patients with oxygen flow < 50L/min did not change these results (see supplementary Table 1, additional file 1).

Secondary endpoints:

Mortality at day 28 and day 60 did not significantly differ between HFNO group and standard-oxygen group (12% vs 24%; OR [IC-95%] 0.52 [0.2-1.34], p = 0.17 and 16% vs 26%; OR [IC-95%] 0.75 [0.32-1.8], p = 0.52 respectively) even after propensity score application. The mean length of ICU stay did not differ after propensity score application in HFNO group compared to the standard oxygen therapy group (11.0 days vs 12.5 days; difference [IC-95%] -0.23 [-0.54 - -0.08] p = 0.14). In the univariate model, the number of ventilator-free days at days 28 was higher in HFNO group compared to the standard oxygen therapy group (21 days vs 10 days, p=0.005). Finally, the number of patients with ventilator free-days > 14 days was higher in HFNO group compared to standard oxygenation group after propensity score application (66% vs 39%; OR 3.91[1.91-7.99], p=0.0002). (Table 2)

We did not find any parameter associated with the success or failure of HFNO (see supplementary Table 2, additional file 2).

During the first period (before March 27), 5 patients received HFNO. After the decision to not to restrict the use of HFNO (second period), 71 patients received HFNO. Among the 172 health-care workers, 14 (8%) had clinical signs of SARS-CoV-2 infection and 6 (3%) had a positive PCR SARS-CoV-2 during the first period. These figures were 4 (2%) and 0 during the second period.

Conclusion

The use of HFNO in COVID-19 patient with ARF reduces the rate of endotracheal intubation and may reduce the workload in ICUs, which is crucial in the context of a sanitary crisis.

Abbreviations

- SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
- COVID-19: Coronavirus disease 2019, with acute respiratory distress syndrome
- HFNO: high flow nasal canula oxygen
- ICU: Intensive care unit
- ARF: Acute respiratory failure
- CT: Computed tomography
- FiO2: fraction of inspired oxygen
- IPTW: inverse probability of treatment weighting
- SOT: Standard oxygen therapy
- IMV : Invasive mechanical ventilation

Declarations

Ethic approval and consent to participate

The study was approved by the Medical Ethics Committee of the Hôpital Avicenne with the reference number: CLEA-2020-146

Consent for publication:

Informed written consent was obtained from the patients for publication of this article and any accompanying images.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

JRZ reports personal fees from Pfizer, personal fees from Correvio, personal fees from Eumedica, personal fees from Merck Sharp and Dohme, outside the submitted work.

NB, OM, MB, VL, NE, PK, YTL, GVDM, JO, MS, MG, AW, PA, SG ang YC report no conflict of interest

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Author's contribution

NB was responsible of the conception and design of the study, drafted the manuscript, reviewed and analyzed the literature and was responsible for the manuscript's revision. OM and NE collected data and analyzed the literature. VL and MB made all data and made a significant intellectual contribution. JRZ, JO, GVDM, MS, MG, AW, and YTL made a significant intellectual contribution. SG and YC made a significant intellectual contribution, were responsible for the conception and design of the study, reviewed and analyzed the literature, and were responsible for the manuscript's revision. All authors issued final approval for the version to be submitted

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Not applicable

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Tables

Table 1: Characteristics of patients at ICU admission*

	Overall (n=138)	Standard oxygen therapy (n=62)	HFNO (n=76)	p
Demographic and clinical characteristics				
Male – no. (%)	112 (81%)	50 (81%)	62 (82%)	1.00
Median age, years (IQR)	59 (48-67)	60 (51-67)	60 (52-67)	0.64
Immunocompromized patient – no. (%)	20 (14%)	9 (14%)	11 (14%)	1.00
Diabetes – no. (%)	43 (31%)	19 (31%)	24 (32%)	1.00
Hypertension – no. (%)	56 (41%)	19 (31%)	37 (49%)	0.049
Chronic respiratory failure – no. (%)	4 (3%)	2 (3%)	2 (3%)	1.00
Chronic kidney failure – no. (%)	7 (5%)	3 (5%)	4 (5%)	1.00
Median BMI, kg/m² (IQR)	29 (26-33)	27 (26-33)	29 (25-33)	0.59
Median SAPS II (IQR)	36 (26-46)	35 (26-45)	36 (27-47)	0.62
Median time from onset symptoms to ICU admission, days (IQR)	10 (8-13)	8 (8-13)	10 (8-13)	0.002
Respiratory finding				
Median 02 flow, liter/minute (IQR)	9 (4-12)	6 (5-13)	9 (6-15)	0.003
Median PaO2, mmHg (IQR)	71 (64-84)	71 (63-85)	69 (63-82)	0.45
Median respiratory rate, (IQR)	30 (27-35)	30 (26-35)	33 (28-36)	0.018
Median O2 maximal flow rate, Liter/minute, (IQR)	12 (9-15)	12 (9-15)	12 (9-15)	0.049
Laboratory finding				
Median Lymphocyte, G/L (IQR)	0.8 (0.6-1.1)	0.9 (0.6-1.1)	0.8 (0.6-1.0)	0.10
Median Fibrinogen, g/L (IQR)	6.59 (5.9-7.3)	6.57 (6.0-7.3)	6.7 (6.2-7.3)	0.50
Median Phosphor, mmol/L (IQR)	0.82 (0.69-0.95)	0.8 (0.71-0.94)	0.84 (0.70-0.94)	0.29
Median CRP, mmol/L (IQR)	182 (114-263)	182 (106-262)	182 (125-269)	0.64
Median ferritin, µg/L (IQR)	1502 (874-2530)	1137 (880-2495)	1701 (885-2677)	0.036
Chest CT scan finding				
Median ground glass surface, % (IQR)	50 (25-60)	50 (25-60)	50 (25-60)	0.27

Steroids during ICU stay – no.(%)	66 (48%)	25 (40%)	41 (54%)	0.15

*HFNO denotes high flow nasal canula oxygen, SAPS II Simplified Acute Physiology Score, BMI Body Mass Index, CRP C-reactive protein, ICU Intensive Care Unit

Table 2 Primary and secondary outcomes*

Outcomes	Standard oxygen therapy	HFNO	unadjusted		IPTW	
			OR [IC95%]	p	OR [IC95%]	p
IMV – no (%)	46/62 (74%)	39/76 (51%)	0.37 [0.18-0.76]	0.007	0.31 [0.14-0.66]	0.002
Death at D28 – no (%)	15/62 (24%)	9/76 (12%)	0.42 [0.17-1.04]	0.061	0.52 [0.2-1.34]	0.17
Death at D60 – no (%)	16/62 (26%)	12/76 (16%)	0.54 [0.23-1.25]	0.15	0.75 [0.32-1.8]	0.52
Patient with ventilator free days>14 days no(%)	24/62 (39%)	50/76 (66%)	3.04[1.52-6.11]	0.002	3.91[1.91-7.99]	0.0002
Ventilator free days, days (IQR)	10 (0-27)	21(5-28)	-	0.005	-	-
Outcomes	Standard oxygen therapy	HFNO	unadjusted		IPTW	
			Difference [IC95%]	p	Difference [IC95%]	p
Mean length of stay, days (IQR)	12.5 (4-24)	11 (5-20)	-0.04 [-0.35-0.27]	0.78	-0.23[-0.54-0.08]	0.14

*IMV denotes invasive mechanical ventilation, HFNO high flow nasal canula, IPTW inverse probability of treatment weighting, IQR interquartile

Figures

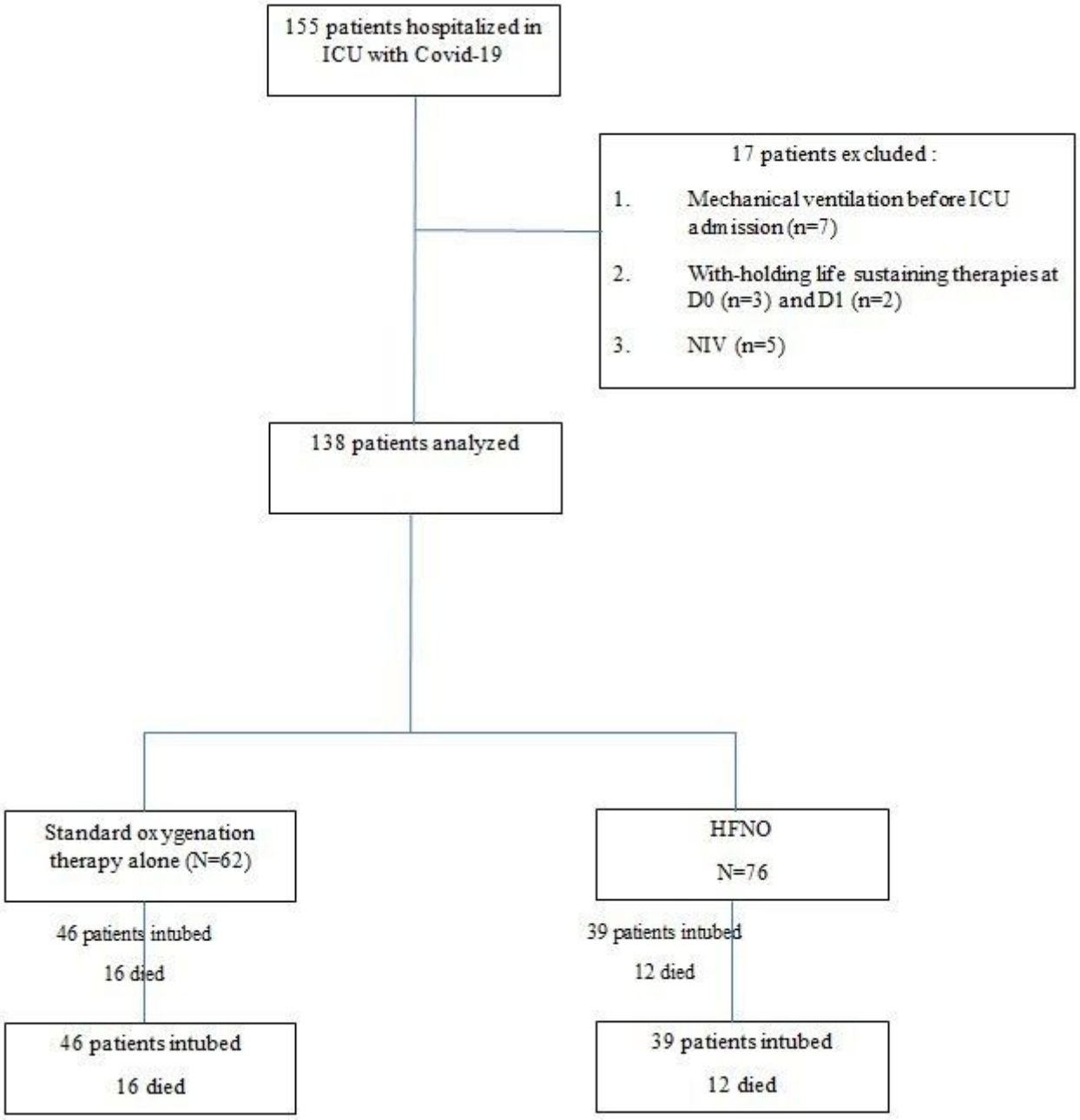

Figure 1

Flow-chart

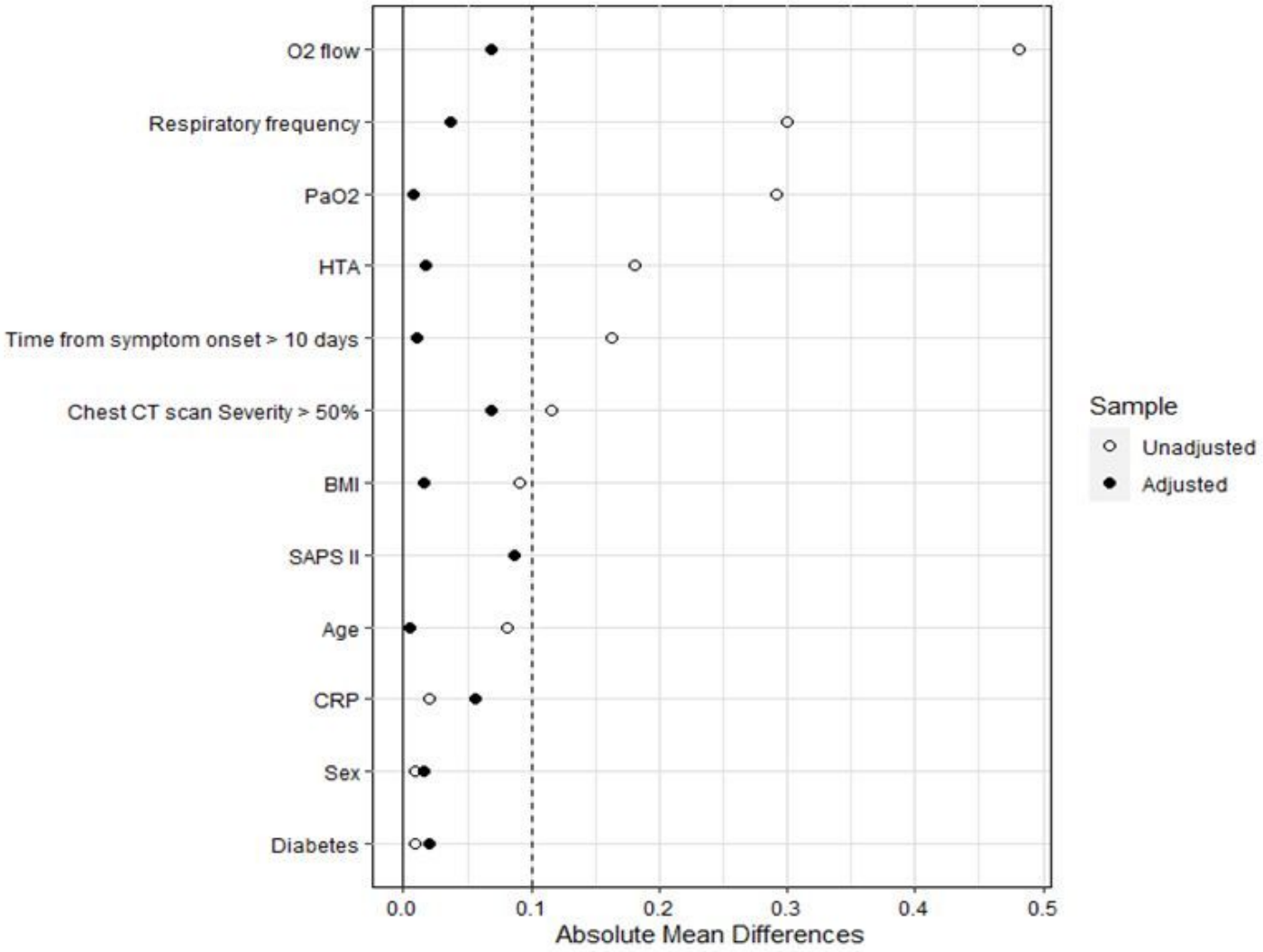

Figure 2

Mean difference of covariate balances before and after weighting

Supplementary Files

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