Non-invasive oxygenation support in acutely hypoxemic COVID-19 patients admitted to the ICU: a multicenter observational retrospective study

Pedro David Wendel-Garcia1†, Arantxa Mas2, Cristina González-Isern3, Ricard Ferrer4, Rafael Mányez5, Joan-Ramon Masclans6, Elena Sandoval7, Paula Vera8, Josep Trenado9, Rafael Fernández10, Josep-Maria Sirvent11, Melcior Martínez12, Mercedes Ibarz13, Pau Garro14, José Luis Lopera15, María Bodí16, Joan Carles Yébenes-Reyes17, Carlos Triginer18, Imma Vallverdú19, Anna Baró20, Fernanda Bodí21, Paula Saludés22, Mauricio Valencia23, Ferran Roche-Campo24, Arturo Huerta25, Francisco José Cambra26, Carme Barberà27, Jorge Echevarría28, Óscar Peñuelas29, Jordi Mancebo30*† and for the UCIsCAT study group

Abstract

Background: Non-invasive oxygenation strategies have a prominent role in the treatment of acute hypoxemic respiratory failure during the coronavirus disease 2019 (COVID-19). While the efficacy of these therapies has been studied in hospitalized patients with COVID-19, the clinical outcomes associated with oxygen masks, high-flow oxygen therapy by nasal cannula and non-invasive mechanical ventilation in critically ill intensive care unit (ICU) patients remain unclear.

Methods: In this retrospective study, we used the best of nine covariate balancing algorithms on all baseline covariates in critically ill COVID-19 patients supported with > 10 L of supplemental oxygen at one of the 26 participating ICUs in Catalonia, Spain, between March 14 and April 15, 2020.

Results: Of the 1093 non-invasively oxygenated patients at ICU admission treated with one of the three stand-alone non-invasive oxygenation strategies, 897 (82%) required endotracheal intubation and 310 (28%) died during the ICU stay. High-flow oxygen therapy by nasal cannula (n = 439) and non-invasive mechanical ventilation (n = 101) were associated with a lower rate of endotracheal intubation (70% and 88%, respectively) than oxygen masks (n = 553 and 91% intubated), p < 0.001. Compared to oxygen masks, high-flow oxygen therapy by nasal cannula was associated with lower ICU mortality (hazard ratio 0.75 [95% CI 0.58–0.98), and the hazard ratio for ICU mortality was 1.21 [95% CI 0.80–1.83] for non-invasive mechanical ventilation.

Conclusion: In critically ill COVID-19 ICU patients and, in the absence of conclusive data, high-flow oxygen therapy by nasal cannula may be the approach of choice as the primary non-invasive oxygenation support strategy.
Keywords: COVID-19, Intensive care, Non-invasive oxygenation, Acute hypoxemic respiratory failure

Background
The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has generated an unprecedented demand for intensive care resources to deliver supportive care using non-invasive oxygenation support and invasive mechanical ventilation [1]. Large studies have provided data regarding baseline clinical characteristics of patients admitted to intensive care units (ICU), the need for invasive mechanical ventilation, and outcomes of mechanically ventilated patients [2–10].

During the pandemic, patients with acute hypoxemic respiratory failure admitted to the ICU and not in need of emergent intubation of the trachea have mainly been treated with non-invasive oxygenation strategies [1]. These methods include standard non-rebreather oxygen masks (oxygen mask), high-flow oxygen therapy administered through large-bore nasal cannulas (HFT), and non-invasive positive pressure ventilation (NIV) techniques [1, 2, 11]. The choice for using one type of oxygenation support over another has likely been based on local recommendations, personal experience, and availability of devices.

The difference of opinions regarding the optimal technique for non-invasive oxygenation support is ample, but the consequences and relevant clinical outcomes of the various usual care strategies in critically ill COVID-19 patients admitted to an ICU remain unclear [12–15]. Thus, our main objective was to evaluate the impact of three stand-alone non-invasive oxygenation strategies on intubation rates and ICU mortality at 90 days after admission of critically ill patients with COVID-19-associated acute hypoxemic respiratory failure. We hypothesized that the various non-invasive oxygenation support strategies had no impact on intubation and ICU mortality rates.

Methods
We retrospectively analysed a cohort of patients admitted to ICUs in the Spanish autonomous community of Catalonia between March 14 and April 15, 2020. The official census population of Catalonia at the time was 7,780,479 inhabitants. At the start of the pandemic, the Catalonian public health system had approximately 500 adult ICU beds in its 26 hospitals, and 13 private hospitals had an additional 100–120 ICUs beds for adults. An invitation to participate in the study was sent to the head of department at all the intensive care medicine departments in Catalonia at the end of April 2020. In view of the nature of the study, the ethics committee at the coordinating centre (Hospital Universitari de la Santa Creu i Sant Pau, Barcelona) approved the study protocol (UCIS-CAT 20/151 OBS) and waived the need for informed consent. Participating centres complied with all local requirements.

Inclusion and exclusion criteria
The inclusion criteria were age 18 years or older, patient admitted to a ICU, clinical signs and symptoms compatible with COVID-19 pneumonia, a positive real-time reverse-transcriptase polymerase chain reaction test for SARS-CoV-2 obtained from a nasopharyngeal swab, bilateral infiltrates in the chest X-ray, need for supplemental oxygen to keep arterial oxygen saturation measured with a pulse oximeter (SpO₂) above 90%, and admission at one of the participating centres’ ICU between March 14 and April 15, 2020. All patients were candidates for intubation and mechanical ventilation at the time of ICU admission. Decisions regarding intubation of the trachea were based on clinical grounds and judgment of the intensivist in charge.

Only patients who had been treated exclusively with a single non-invasive oxygenation technique during their ICU stay were included in this analysis: oxygen mask at a rate of more than 10 L oxygen/minute, HFT administered through a heated humidifier at a gas flow rate above 30 L/minute and a fraction of inspired oxygen (FiO₂) of at least 0.5, or NIV with a FiO₂ of at least 0.5 (irrespective of interface, mode and ventilator type used). The choice of non-invasive oxygenation technique was at the discretion of each participating ICU and was based on local recommendations and availability of devices. The day of ICU admission was defined as day 0. Patients were excluded from our analysis in three situations: first, they were intubated and mechanically ventilated before ICU admission because the context and conditions of intubation were unknown; second, they were intubated immediately after ICU admission (within 3 h) because the attempt at non-invasive oxygenation support was considered clinically unsuccessful; and third, they received oxygen supplementation either by nasal prongs or by any combination of oxygen mask, HFT and NIV (Fig. 1). Patients receiving a combination of multiple non-invasive oxygenation support techniques were not analysed as the order of administration and the reasons for change could not be precisely elucidated, thus introducing an unquantifiable allocation bias into the analysis.
Data collection

The principal investigator at each centre filled in a standardized case report form for each patient included in the study. Data regarding demographic variables, laboratory data at admission, type of non-invasive and invasive oxygenation support, variables related to gas exchange and respiratory system mechanics obtained shortly after endotracheal intubation, and ICU outcome status at 90 days from ICU admission were processed from the independent case report forms and stored in a single master file. Patients were followed in the ICU until day 90 post-admission or until ICU discharge, whichever occurred first. This file was reviewed independently by three investigators (PDWG, CGI and JM). The principal investigators at each centre were contacted to solve any errors or missing data. Following this process, the master file was closed.

Once intubated, patients who met acute respiratory distress syndrome (ARDS) criteria were classified in mild, moderate and severe oxygenation phenotypes, as described [16]. Driving airway pressure was calculated as the difference between plateau airway pressure and set positive end-expiratory pressure (PEEP). Compliance of the respiratory system was calculated as tidal volume divided by driving airway pressure. The ventilatory ratio and estimated physiological dead-space fraction were calculated as previously described by Sinha et al. [17] and Morales-Quinteros et al. [18], respectively.

Missing data

To account for missing data (Additional file 1: Table s1), we performed multiple imputations by fully conditional specification with predictive mean matching under the missing at random assumption [19]. Further details regarding the imputation method used are presented in Additional file 1: Appendix 1, Additional file 1: Fig. s1, Additional file 1: Fig. S2 and Additional file 1: Table s2.
Statistical analysis
To enable causal inference of the average treatment effect associated with each oxygenation support strategy, we evaluated the baseline covariate balance at ICU admission. Covariate balancing refers to a group of statistical methods used to enable exchangeability of exposed and unexposed subjects to one or multiple treatments in order to minimize confounding. Applying a weight on each individual subject generates a standardized pseudo-population, in which causal treatment effect inference is possible. Nine covariate balancing methods considering all baseline covariates at ICU admission were tested against each other (see Additional file 1: Appendix 2). The best covariate balancing method (standardized mean deviation < 0.1 and variance ratio < 2) was used for all subsequent analyses [20]. A detailed description on the covariate balancing method selection is also shown in Additional file 1: Appendix 2 and Additional file 1: Figs. s3 and s4.

Univariable and multivariable Cox proportional hazards models coupled to the Kaplan–Meier estimator, with and without random frailty terms for between-centre variability effect, were used to analyse the effects of the different oxygenation support strategies on the incidence of intubation and ICU mortality. The effects are represented by hazard ratios and their 95% confidence interval (CI). A time-varying Cox proportional hazards model was used to investigate the effect of time between ICU admission and intubation on 90-day ICU mortality. Patients discharged alive from the ICU were considered to be alive at day 90. Survival distributions among the various oxygenation support strategies were compared using the log-rank test. Proportional hazard assumptions were assessed by inspection of Schoenfeld residuals.

Ventilator-free survival days were defined as the cumulative time in the first 30 days of ICU admission without the need for invasive mechanical ventilation. Patients who died within the first 30 days were assigned 0 ventilator-free days. Population characteristics were compared using analysis of variance or the Kruskal–Wallis test, as appropriate, and the chi-squared test for categorical variables. Statistical analysis was performed through a fully scripted data management pathway using the R environment for statistical computing version 4.1.0. No power calculations were performed due to the observational nature of this cohort study. A two-sided \( p < 0.05 \) was considered statistically significant. Values are given as medians and [interquartile ranges] or counts and percentages as appropriate.

Results
Twenty-six centres participated in the study, 20 of the 26 public health system hospitals in Catalonia and 6 of 13 private care centres. The study thus reflects the care provided to patients in 438 of the 620 adult ICU beds available in Catalonia at the beginning of the pandemic, 370 pertaining to the public system and 68 to the private health system (see Additional file 1: Appendix 3).

A total of 1703 critically ill COVID-19 patients were admitted to the participating ICUs between March 14 and April 15, 2020. Figure 1 shows the study flowchart and Additional file 1: Table s3 shows the main characteristics and outcomes for the overall unbalanced population. Three-hundred and nine patients were treated with combinations of non-invasive respiratory support techniques and were excluded from the analysis to allow a clear differentiation between individual therapies. Overall, these patients had a 72% intubation rate (222/309) and the ICU mortality rate up to day 90 post-admission was 27.5% (85/309).

Population analysed and matching analysis
The final analysis included 1093 patients treated with a non-invasive oxygenation support strategy during their ICU stay: 553 (51%) with oxygen mask, 439 (40%) with HFT, and 101 (9%) with NIV. Their main characteristics and outcomes are shown in Additional file 1: Table s4.

Among the various balancing algorithms tested, we employed the targeted stable balancing weights using the optimization algorithm. This algorithm minimized standard mean deviation (< 0.0001) and variance ratios (≤ 1.7) between oxygenation support strategies for all variables and presented consistent and moderate weights (1 ± 0.35) for all patients (Additional file 1: Fig. s5, Additional file 1: Fig. s6, Additional file 1: Fig. s7).

Characteristics of the analysed population
Baseline characteristics across oxygenation support strategies were identical after covariate balancing (Table 1). Patients were mainly male (68%) with a median age of 63 [54–70] years. The median time between hospital and ICU admission was 1 day [0–3 days]. The overall intubation rate was 82% (897/1093). A total of 501 out of 553 (91%) patients treated with oxygen mask were eventually intubated and mechanically ventilated as opposed to 307 out of 439 (70%) of those treated with HFT and 89 out of 101 (88%) of those treated with NIV \( (p < 0.001) \). The number of ventilator-free days was higher in the HFT group than in the oxygen mask and NIV groups \( (p < 0.001) \).

Table 2 shows the characteristics of patients who eventually required intubation and mechanical ventilation, after covariate balancing. The median time from ICU
admission to endotracheal intubation was 0 [0–0] days in the oxygen mask group, 0 [0–1] days in the HFT group, and 0 [0–1] days in the NIV group (\(p<0.001\)). Among the 897 intubated patients, 824 (92%) had an ARDS and this was moderate-to-severe in 571 (69%).

Figure 2 shows the cumulative proportion of intubation over time according to the various non-invasive oxygenation support techniques. As compared to oxygen mask, the hazard ratio for intubation in HFT treated patients was 0.45 (95% CI 0.39–0.53) and 0.67 (95% CI 0.53–0.85) for NIV treated patients.

**Mortality**

The cumulative proportion of ICU survival, evaluated up to 90 days of ICU admission, differed significantly according to the initially chosen non-invasive oxygenation strategy (\(p=0.02\)) (Fig. 3a). As compared to patients treated with an oxygen mask, the hazard ratio for ICU mortality was 0.75 [95% CI 0.58–0.98] for HFT ventilated patients, and 1.21 [95% CI 0.8–1.83] for NIV treated patients.

In intubated and mechanically ventilated patients, the 90-day ICU mortality did not differ (\(p=0.2\)) between groups (Fig. 3b).

**Secondary analyses**

The time from ICU admission to intubation showed no influence on static respiratory system compliance, driving airway pressure, or \(\text{PaO}_2/\text{FiO}_2\) ratio as measured shortly after intubation (Additional file 1: Fig. s8, Table s1).
Additional file 1: Fig. s9, Additional file 1: Fig. s10. However, it was associated with an elevated ICU risk of mortality in a time-varying Cox regression model (Additional file 1: Fig. s11).

The Cox proportional hazards model, in covariate balanced population analysis, showed that highly predictive variables for ICU mortality were age, body mass index, high levels of C-reactive protein, procalcitonin, ferritin, D-dimers, and the presence of chronic obstructive pulmonary disease (Additional file 1: Fig. s12). Variables that were highly predictive of ICU mortality in patients, who required invasive mechanical ventilation, are shown in Additional file 1: Fig. s13. In mechanically ventilated patients, high D-dimers were significantly associated with mortality independently of the static respiratory system compliance (Additional file 1: Fig. s14).

Sensitivity analyses assessing 90-day ICU mortality risk in the un-balanced population in crude models (Additional file 1: Fig. s15, Additional file 1: Table s6) and multivariable-adjusted models (Additional file 1: Fig. s16, Additional file 1: Fig. s17, Additional file 1: Fig. s18, Additional file 1: Fig. s19), with and without between-centre random effects term, showed the same associations as the covariate balanced population analysis.

Discussion

In this retrospective, baseline covariate balanced, multicentre cohort of 1093 critically ill non-invasively ventilated COVID-19 ICU patients, 897 (82%) eventually required endotracheal intubation and 310 (28%) died during their ICU stay. The need for endotracheal intubation and invasive mechanical ventilation was significantly lower in patients supported by HFT and NIV than in those receiving oxygen mask therapy at ICU admission. Additionally, patients supported by means of HFT had a lower risk of ICU mortality than patients supported with oxygen masks and NIV.
The association between the use of HFT or NIV and a reduction in endotracheal intubation rates compared to oxygen mask has yielded ambiguous results [24–26]. The two largest randomized trials to date did not find reductions in endotracheal intubation rates benefitted patients supported with HFT or NIV compared to those treated with an oxygen mask [27, 28]. These findings may have several explanations: different populations and etiologies of acute hypoxemic respiratory failure, different inclusion and exclusion criteria, non-identical methodological approaches to the use of non-invasive techniques, and different criteria to declare a failed non-invasive oxygenation attempt. Furthermore, the primary outcomes of these studies were not the same.

In SARS-CoV-2-induced hypoxemic respiratory failure, however, the use of HFT and NIV was superior to oxygen mask in limiting progression to invasive mechanical ventilation, supporting our findings [29, 30]. The reason for this efficacy of HFT and NIV is possibly explained by their physiological effects in terms of improvements in gas exchange, decreases in respiratory muscle effort, and a generally ameliorated sensation of dyspnea as

Fig. 2 Kaplan–Meier plot of the cumulative proportion of intubation. Kaplan–Meier curve of the cumulative proportion of intubation stratified according to the initial oxygenation support strategy at ICU admission. Oxygen mask, high-flow oxygen therapy and non-invasive ventilation are plotted in red, blue, and green, respectively. p values were calculated by means of the log-rank test. Hazard ratios (HR) were computed using a Cox proportional hazard model and the risk of intubation in the high-flow oxygen therapy and non-invasive ventilation groups was assessed using the oxygen mask group as reference; 95% confidence intervals (CI) are given in parentheses. Table at the bottom presents the patients at risk per time point.

Fig. 3 Kaplan–Meier plot of the cumulative survival in the intensive care unit. Kaplan–Meier curve of the cumulative intensive care survival was stratified according to the initial oxygenation support strategy at admission to the intensive care unit. Subplot (a) refers to all patients included in the analysis. Subplot (b) considers only patients pending probably intubation and invasive mechanical ventilation. Oxygen mask, high-flow oxygen therapy and non-invasive ventilation are plotted in red, blue, and green, respectively. p values were calculated by means of the log-rank test. Hazard ratios (HR) were computed by means of a Cox proportional hazard model. The risk of intensive care unit mortality in the high-flow oxygen therapy and non-invasive ventilation groups was assessed using the oxygen mask group as reference; 95% confidence intervals (CI) are given in parentheses. Table at the bottom shows the patients at risk per time point.

(See figure on next page.)
**Fig. 3** (See legend on previous page.)
compared to oxygen masks [31–37]. Several mechanisms may explain these beneficial mechanisms. First, the increase in end-expiratory lung volume with some degree of alveolar recruitment induced by PEEP could decrease shunt and consequently improve PaO₂ [32–34]. Second, as compared to facial oxygen masks, HFT generates a dead space washout of the upper airways, allowing a more homogeneous distribution of tidal volume [32]. Third, HFT induces a decrease in respiratory rate with less effort per breath with unchanged tidal volumes, thus suggesting better lung compliance [32]. These effects may help decrease inspiratory muscle effort, reduce the chemical drive to breath and, in turn, decrease the sensation of dyspnea [35]. It is of note, however, that we are dealing with a single disease (COVID-19) that is typically vasculopathic and accompanied by widespread endothelialitis [38, 39]. Such physiopathological derangements may profoundly modify the ventilation/perfusion relationships and hypoxic pulmonary vasoconstriction [40]. In addition, SARS-CoV-2 exerts direct effects on the carotid bodies and the central nervous system [39], which may alter the central respiratory drive [21].

It is also of interest in our study that we observed lower endotracheal intubation rates in HFT and NIV treated patients than in oxygen mask treated patients. However, only the use of HFT was associated with a reduction in mortality rate. This result is consistent with the landmark trial of Frat et al. [27] but in contrast with the remaining literature [28–30]. Recent data [41] indicate that when compared to early intubation, HFT is associated with an increase in ventilator-free days and no differences in hospital mortality. The lower mortality in the HFT group in our study could directly reflect the lower intubation rate in this population.

In our study, we observed a trend towards higher mortality in the NIV group than in the oxygen mask group despite the lower intubation rate. It has been hypothesized that early endotracheal intubation and lung-protective ventilation in patients failing non-invasive oxygenation support and eventually requiring invasive mechanical intubation is associated with a protective effect. In a large series of ADRS patients, Kangelaris et al. [42] showed that mortality in those who were intubated early (on day 1 of ARDS diagnosis) was significantly lower than in those intubated later (between 2 and 4 days after ARDS diagnosis): the adjusted risk of death was 2.37 times higher for late intubation than for early intubation. Other authors, however, did not observe these effects in COVID-19 patients [43, 44]. More than time per se, several authors have suggested that what occurs during non-invasive oxygenation support is relevant. Carteaux [45] and Frat [46] showed that rather than the time to intubation, large tidal volumes—and thus large transpulmonary pressure swings—during NIV are associated with worse outcomes. Hence, one could argue that the total dose of injury (i.e. size of tidal volume and dissipated pressure times duration of ventilation) may eventually be harmful.

Our data show a clear association between the time from ICU admission to intubation and an increased risk of mortality (see Additional file 1: Fig. s11), possibly explaining the trend towards higher mortality in intubated patients previously undergoing NIV support. Additionally, patient self-inflicted lung injury, through the generation of large swings in transpulmonary pressures with excessive tidal volumes and cycling opening and alveolar collapse phenomena, has been postulated as a primary driver of mortality in NIV supported patients [45–47]. In addition, other relevant phenomena occurring in non-intubated spontaneously breathing subjects with acute hypoxemic respiratory failure include expiratory airway closure [48], pendelluft with regionally large swings of transpulmonary pressure [49] and, possibly bronchiolotrauma [50]. Finally, the large transpulmonary pressure swings during spontaneous breathing, which generate high pulmonary transmural vascular pressures, also enhance pulmonary oedema [47, 51]. However, in our study, shortly after endotracheal intubation and irrespective of the non-invasive oxygenation strategy used, we found that respiratory mechanics and gas exchange were comparable between groups. This observation suggests that, when used for a relatively short period of time, none of these three very different non-invasive oxygenation techniques seem to be worse than the other in terms of magnifying the amount of lung injury (as clinically assessed in terms of gas exchange and basic respiratory system mechanics).

Whether the development of a full-blown patient self-inflicted lung injury requires a time-course threshold, as suggested by the increased mortality in patients intubated after more than 3 days under non-invasive respiratory support (Additional file 1: Fig. s11), or it is governed by another form of time-to-event relationship, is unknown [47]. Conversely, patient self-inflicted lung injury could primarily be biotraumatic, exacerbating pulmonary inflammation. And only secondarily, at a later stage (i.e. invasive mechanical ventilation acting as a “second hit”), would this lead to diffuse alveolar damage and alveolar remodelling, and thus impair respiratory system mechanics [30, 47, 49, 52].

Our results stand in contrast with those from a recent randomized controlled trial that compared HFT and NIV as treatment for hypoxemic respiratory failure. The authors found that mortality rates were comparable in the two groups [53]. Nevertheless, it is of note that the patients in Grieco’s study were treated by means of a helmet rather than a facemask. Recent evidence suggests
that the limitations of NIV in oxygenation support of hypoxemic respiratory failure are inherent to the face-mask interface and that the use of a helmet is associated with fewer air leaks, higher and more stable PEEP levels during prolonged periods of time, improved oxygenation, and reduced inspiratory efforts [31, 54]. Our study has a number of limitations. First, the cohort of patients was collected retrospectively and lacked any degree of randomization, formally impeding an unbiased treatment effect. Nonetheless, the baseline covariate balancing performed enabled mitigation of most objectively assessable confounders. Second, the cohort may be subject to selection bias as during the pandemic outbreak, patients who were treated with the same non-invasive oxygenation techniques but were not admitted into the ICU were not included in the study. Third, in the absence of a study protocol, the choice of oxygenation support strategy and the decision to proceed towards endotracheal intubation and mechanical ventilation were likely variable. It is not known whether the choice of one technique or another was based on clinical decision or equipment availability. Nonetheless, the data presented faithfully represent usual care practice during the pandemic. Fourth, no data on longitudinal inflammatory parameters or pulmonary mechanics data were available, preventing investigation of long-term mechanistic effects associated with the choice of non-invasive oxygenation support strategy. Fifth, neither gas exchange nor other respiratory variables were collected before invasive mechanical ventilation was started. Sixth, mortality was available from the ICU only, impeding analysis of hospital or absolute survival. Nevertheless, the largest proportion of mortality in critically ill patients occurs in the ICU, and our patients were followed for up to 90 days therein. Seventh, no specifications were available regarding the type of NIV interface and settings employed, albeit most probably only face-masks were used. Eighth, the temporal gap between ICU admission and endotracheal intubation was only available on a scale of days, thus impeding a more granular analysis. Ninth, the imbalance in group sizes could have led to a lack of power to recognize higher mortality in the NIV supported group. Tenth, as we do not have data from a more contemporaneous cohort, we cannot assess the dynamic effects of the pandemic—such as changing care practices and new pharmacologic treatments—on the reported effects. Finally, the potential role of unmeasured confounders cannot be excluded.

Conclusion
In critically ill COVID-19 ICU patients with acute hypoxemic respiratory failure, the use of HFT was associated with lower intubation and ICU mortality rates than those in patients supported by means of oxygen mask and NIV. Given the inconclusive data in the ICU population, the choice of HFT as a primary non-invasive oxygenation support strategy seems warranted.

Abbreviations
COVID-19: Coronavirus disease-2019; ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SpO2: Pulse oximeter oxygen saturation; CI: Confidence interval; ARDS: Acute respiratory distress syndrome; PEEP: Positive end-expiratory pressure; Oxygen mask: Standard non-rebreather oxygen masks; HFT: High-flow oxygen therapy administered through large-bore nasal cannulas; NIV: Non-invasive positive pressure ventilation; CPAP: Continuous positive airway pressure.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13054-022-03930-5.

Additional file 1: e-Table 1: Percentage of missing values. e-Appendix 1: Multiple imputations of missing data and technique break-down. e-Figure 1: Multiple imputation - convergence plots. e-Figure 2: Multiple imputation - distribution plots. e-Table 2: Imputation model fit. e-Appendix 2: Extended Statistical Methodology. e-Figure 3: Covariate balancing models - model fit comparison. e-Figure 4: Covariate balancing models - weights comparison. e-Appendix 3: Study information. e-Table 3: Overall un-balanced population. e-Table 4: Un-balanced study population. e-Figure 5: Final covariance balancing model - model fit. e-Figure 6: Final covariate balancing model - individual variable distributions. e-Figure 7: Final covariate balancing model - model weights. e-Figure 8: Static compliance versus time from ICU admission until intubation. e-Figure 9: Driving pressure versus time from ICU admission until intubation. e-Figure 10: PaO2/ FiO2 ratio versus time from ICU admission until intubation. e-Figure 11: Cox time varying model for influence of time until intubation on ICU mortality. e-Figure 12: Multivariable Cox proportional hazards model for in-ICU mortality (overall and covariance balanced). e-Figure 13: Multivariable Cox proportional hazards model for in-ICU mortality (only intubated and covariance balanced). e-Figure 14: Kaplan-Meier curve for ICU mortality – compliance vs. D-dimers. e-Figure 15: Kaplan-Meier curve for ICU mortality in unbalanced population. e-Table 5: Cox mixed-effects model with between-center random effects term (unbalanced). e-Figure 16: Multivariable Cox proportional hazards model for in-ICU mortality (overall and unbalanced). e-Figure 17: Multivariable Cox proportional hazards model for in-ICU mortality (only intubated and unbalanced). e-Figure 18: Multivariable Cox mixed-effects model with between-center random effects term for in-ICU mortality (overall). e-Figure 19: Multivariable Cox mixed-effects model with between-center random effects term for in-ICU mortality (only intubated – unbalanced). e-Appendix 4: Formulas.

Acknowledgements
The authors thank Carolyn Newey for her assistance in editing the manuscript. In addition to the authors (in bold), the UCICAT study group includes the following collaborators: Hospital Universitari General de la Vall d’Hebron, Barcelona: R. Ferrer, O. Roa, X. Nuñols, J.C. Ruiz, E. Papiol. Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat: R. Mañé, V.D Gumicio. Hospital Clinic i Provincial de Barcelona, Barcelona: E. Sandoval, G. Muñoz, D. Toapanta, P. Castro, J. Osorio. Hospital del Mar, Barcelona: J.R. Masclans, R. Muñoz-Bermúdez, F. Parillà, P. Pérez-Teran, J. Marin-Coral. Hospital de Sant Joan Despí: Despi Moisés Broggi, Sant Joan. Despí: A. Mas, B. Cabcio, S. Hernández-Marin, M.R. Roborzan , C.A Briones. Hospital Mutua de Terrassa, Terrassa: J. Trenado. Althaia (Xarxa Asistencial Universitària de Manresam& Martínez), Manresa: R. Fernández. Hospital Universitari Doctor Josep Trueta de Girona, Girona: J.M. Sirvent, P. Sebastián, X. Saiz. Hospital General De Cataluña, Sant Cugat del Vallès: M. Martínez. Hospital Universitari Sagrat Cor—Grup Quironsalut, Barcelona: M. Ibarz. Hospital General de Granollers, Granollers: P. Garro, C. Pedrós, E. Vendrell. Hospital General de Vic (Consorci Hospitalari de Vic), Vic: J.L. Lopera. Hospital Universitari de Tarragona Joan XXIII, Tarragona: M. Bodí, A. Rodríguez, G.
Authors’ contributions

PDWG, CGI and JM take responsibility for the integrity of the data and the accuracy of the data analysis. PDWG, CGI and JM conceived, designed and coordinated the research. PDWG, CGI and JM were responsible for data acqui-

Authors details

Funding

Availability of data materials

Declarations

Consent for publication

Competing interests

Author details

References

Received: 5 November 2021 Accepted: 26 January 2022

Published online: 08 February 2022

1. Azoulay E, de Waele J, Ferrer R, Staedinger T, Borkowska M, Pirova P, et al. International variation in the management of severe COVID-19 patients. Crit Care. 2020;24:486.

2. Schmidt M, Hajage D, Demoule A, Pham T, Combes A, Dres M, et al. International variation in the management of severe COVID-19 patients. Crit Care. 2020;24:486.

3. Schmidt M, Hajage D, Demoule A, Pham T, Combes A, Dres M, et al. International variation in the management of severe COVID-19 patients. Crit Care. 2020;24:486.

4. Schmidt M, Hajage D, Demoule A, Pham T, Combes A, Dres M, et al. International variation in the management of severe COVID-19 patients. Crit Care. 2020;24:486.

5. Schmidt M, Hajage D, Demoule A, Pham T, Combes A, Dres M, et al. International variation in the management of severe COVID-19 patients. Crit Care. 2020;24:486.

6. Schmidt M, Hajage D, Demoule A, Pham T, Combes A, Dres M, et al. International variation in the management of severe COVID-19 patients. Crit Care. 2020;24:486.
With SARS-CoV-2 admitted to ICUs of the Lombardy region Italy. JAMA. 2020;323:1574–81.
7. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395:1763–70.
8. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, Hernández M, GEA A, Arruti E, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. Intensive Care Med. 2020;46:2200–11.
9. Karagiannidis C, Mostert C, Hentscheler C, Voshaar T, Malzahn J, Schilling G, et al. Case characteristics, resource use, and outcomes of 10,021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir Med. 2020;8:853–62.
10. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323:2052–9.
11. Fernández R, González de Molina FJ, Batlle M, Fernández MM, Hernandez S, Villagrá A. Soporte ventilatorio no invasivo en pacientes con neumonía por COVID-19: un registro multicéntrico español. Medicina Intensiva. 2021;45:315–7.
12. Tobin MJ, Jurbani A, Laghi F. Noninvasive strategies in COVID-19: epistemology, randomized trials, guidelines, physiology. Eur Resp J. 2020;2004247.
13. Marin JI, Gattinoni L. Management of COVID-19 respiratory distress. JAMA. 2020;323:2329–30.
14. Gorman E, Connolly B, Couper K, Perkins GD, McAuley DF. Non-invasive respiratory support strategies in COVID-19. Lancet Respir Med. 2021;9:553–6.
15. Fan E, Bittler JR, Brochard L, Caffe SS, Ferguson ND, Slutsky AS, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? Lancet Respir Med. 2020;8:8816–21.
16. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526–33.
17. Sinha P, Caffe SS, Bittler JR, Soni N, Ho K, Mattey MA, et al. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2019;199:333–41.
18. Morales-Quinteros L, Neto AS, Artigas A, Blanch L, Botta M, Kaufman DA, et al. Dead space estimates may not be independently associated with 28-day mortality in COVID-19 ARDS. Crit Care. 2021;25:171.
19. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res. 2007;16:219–42.
20. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score. Stat Med. 2015;34:3661–70.
21. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score. Stat Med. 2015;34:3661–70.
22. Aegerter Y, Dreyfuss D, Brutsche D, Schenker J, Schöni F, Zbinden M, et al. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19-associated acute respiratory failure. Crit Care. 2021;25:10–1.
23. Kangelaris KN, Ware LB, Wang CY, Jann DR, Zhuo H, Mattey MA, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017–32.
24. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiambretti L, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017–32.
25. Aegerter Y, Dreyfuss D, Brutsche D, Schenker J, Schöni F, Zbinden M, et al. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19-associated acute respiratory failure. Crit Care. 2021;25:10–1.
26. Kangelaris KN, Ware LB, Wang CY, Jann DR, Zhuo H, Mattey MA, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017–32.
27. Aegerter Y, Dreyfuss D, Brutsche D, Schenker J, Schöni F, Zbinden M, et al. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19-associated acute respiratory failure. Crit Care. 2021;25:10–1.
28. Azoulay E, Lemaire V, Mokart D, Nseir S, Argaud L, Plene F, et al. Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure: the HIGH randomized clinical trial. JAMA. 2018;320:2099–107.
29. Demoule A, Veillard Baron A, Barón M, Bertron A, Céri G, Voiron G, et al. High-flow nasal cannula in critically ill patients with severe COVID-19. Am J Respir Crit Care Med. 2020;202:1039–42.
30. Wendel Garcia PD, Aguirre-Bermejo H, Buehler PK, Alfaro-Farias M, Yuen B, David S, et al. Implications of early respiratory support strategies on disease progression in COVID-19: a matched subanalysis of the prospective RISC-19-ICU cohort. Crit Care. 2021;25:175.
31. Greico DL, Menga LS, Raggi V, Bongiovanni F, Arzelotti GM, Tanzarella ES, et al. Physiologic comparison of high-flow nasal cannula and helmet noninvasive ventilation in acute hypoxemic respiratory failure. Am J Respir Crit Care Med. 2019;201:303–12.
32. Mauti T, Turini C, Eronia N, Grasselli G, Volta CA, Bellani G, et al. Physiology effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am J Respir Crit Care Med. 2017;195:1207–15.
33. Mauti T, Spinelli E, Mariani M, Guzzardella A, Del Prete C, Carlesso E, et al. Nasal high flow delivered within the helmet: a new noninvasive respiratory support. Am J Respir Crit Care Med. 2019;199:115–7.
34. Mauti T, Albani L, Turini C, Cambiaghi B, Carlesso E, Taccone F, et al. Optimum support by high-flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. Intensive Care Med. 2017;43:1453–63.
35. Lher E, Deye N, Lellouche F, Taille S, Demoule A, Fritaccielli A, et al. Physiologic effects of noninvasive ventilation during acute lung injury. Am J Respir Crit Care Med. 2005;172:1112–8.
36. Tonelli R, Busani S, Tabbi L, Fantini R, Castaniere I, Biagiotti E, et al. Inspiratory effort and lung mechanics in spontaneously breathing patients with acute respiratory failure due to COVID-19: a matched control study. Am J Respir Crit Care Med. 2021;204:725–8.
37. Tonelli R, Fantini R, Tabbi L, Castaniere I, Pisani L, Pellegrino MR, et al. Early inspiratory effort assessment by esophageal manometry predicts noninvasive ventilation outcome in de novo respiratory failure. A pilot study. Am J Respir Crit Care Med. 2020;202:558–67.
38. Ackermann M, Verleden SE, Kruelnhel M, Haeverich A, Welte T, Langer F, et al. Pulmonary vascular endotheliitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383:240–8.
39. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017–32.
40. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiambretti L, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017–32.
41. Mellado-Artigas R, Ferneyro BL, Angriman F, Hernández-Sanz M, Arruti E, Torres A, et al. High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. Crit Care. 2021;25:10–1.
42. Kangelaris KN, Ware LB, Wang CY, Jann DR, Zhuo H, Mattey MA, et al. Timing of intubation and mortality among critically ill Coronavirus Disease 2019 patients: a single-center cohort study. Crit Care Med. 2020;48:e1045–53.
43. Papoutsis E, Giannakoulis VG, Xourgia E, Routsi C, Kotanidou A, Siempos II. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. Crit Care. 2021;25:121.
44. Carrion-Moreno AC, Adelman MW, Hockstein MA, Brochiaux CJ, Edwards JA, Fazio JC, et al. Timing of intubation and mortality among critically III Coronavirus Disease 2019 patients: a single-center cohort study. Crit Care Med. 2020;48:e1045–53.
45. Paciotti G, Giannakoulis VG, Xourgia E, Routsi C, Kotanidou A, Siempos II. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. Crit Care. 2021;25:121.
49. Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa EL, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. Am J Respir Crit Care Med. 2013;188:1420–7.
50. Borges JB. The plausibility of "bronchiolotrauma." Am J Respir Crit Care Med. 2018;197:1086–7.
51. Mancebo J. Noninvasive ventilation in acute hypoxemic respiratory failure: songs of love and hate. Crit Care Med. 2016;44:444–6.
52. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury. Crit Care Med. 2012;40:1578–85.
53. Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, et al. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients With COVID-19 and moderate to severe hypoxemic respiratory failure: the HENIVOT randomized clinical trial. JAMA. 2021;325:1731–43.
54. Patel BK, Wolle KS, Pohlman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA. 2016;315:2435–41.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.