OPEN

Association Between Early Invasive Mechanical Ventilation and Day-60 Mortality in Acute Hypoxemic Respiratory Failure Related to Coronavirus Disease-2019 Pneumonia

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OBJECTIVES: About 5% of patients with coronavirus disease-2019 are admitted to the ICU for acute hypoxemic respiratory failure. Opinions differ on whether invasive mechanical ventilation should be used as first-line therapy over noninvasive oxygen support. The aim of the study was to assess the effect of early invasive mechanical ventilation in coronavirus disease-2019 with acute hypoxemic respiratory failure on day-60 mortality.

DESIGN: Multicenter prospective French observational study.

SETTING: Eleven ICUs of the French OutcomeRea network.

PATIENTS: Coronavirus disease-2019 patients with acute hypoxemic respiratory failure ($Pao_2/Fio_2 \leq 300$ mm Hg), without shock or neurologic failure on ICU admission, and not referred from another ICU or intermediate care unit were included.

INTERVENTION: We compared day-60 mortality in patients who were on invasive mechanical ventilation within the first 2 calendar days of the ICU stay (early invasive mechanical ventilation group) and those who were not (nonearly invasive mechanical ventilation group). We used a Cox proportional-hazard model weighted by inverse probability of early invasive mechanical ventilation to determine the risk of death at day 60.

MEASUREMENT AND MAIN RESULTS: The 245 patients included had a median (interquartile range) age of 61 years (52–69 yr), a Simplified Acute Physiology Score II score of 34 mm Hg (26–44 mm Hg), and a Pao_2/Fio_2 of 121 mm Hg (90–174 mm Hg). The rates of ICU-acquired pneumonia, bacteremia, and the ICU length of stay were significantly higher in the early ($n = 117$ [48%]) than in the nonearly invasive mechanical ventilation group ($n = 128$ [52%]), $p < 0.01$. Day-60 mortality was 42.7% and 21.9% in the early and nonearly invasive mechanical ventilation groups, respectively. The weighted model showed that early invasive mechanical ventilation increased the risk for day-60 mortality (weighted hazard ratio =1.74; 95% CI, 1.07–2.83, p=0.03).

CONCLUSIONS: In ICU patients admitted with coronavirus disease-2019-induced acute hypoxemic respiratory failure, early invasive mechanical ventilation was associated with an increased risk of day-60 mortality. This result needs to be confirmed.

KEY WORDS: acute hypoxemic respiratory failure; coronavirus disease 2019; critically ill; invasive mechanical ventilation; mortality; noninvasive oxygen support

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Around 5% of coronavirus disease-2019 (COVID-19) patients develop a critical form of the disease leading to ICU admission (1, 2). The main manifestation of COVID-19 is acute hypoxemic respiratory failure (AHRF) requiring respiratory support. The optimal supportive treatment for AHRF related to COVID-19 (COVID-AHRF) is not yet established.

Initial guidelines advised against the use of noninvasive positive pressure ventilation (NIPPV) or high-flow nasal cannula (HFNC) as they are aerosol-generating procedures and, thus, a risk of infection among healthcare workers (3). However, some concerns promptly emerged regarding poor prognosis of patients with COVID-19 pneumonia related to invasive mechanical ventilation (IMV) use (4). In late March 2020, guidelines of the surviving sepsis campaign on the management of critically ill adults with COVID-AHRF advocated using HFNC first over other noninvasive techniques such as NIPPV and over IMV (5).

There is no clear-cut evidence of the greater effect of noninvasive oxygen support (NI-OS), including NIPPV, HFNC, continuous positive airway pressure (CPAP), and oxygen delivered through a nonrebreather face mask, than that of early IMV for COVID-AHRF management. NI-OS can improve patient outcome by avoiding intubation (6–8) and ventilator-associated complications (9) but can also worsen it by delaying intubation and increasing the risk of cardiac arrest before intubation (10). In addition, debate continues about the role of early intubation in preventing the risk of patient self-inflicted lung injury (P-SILI) (11–13). COVID-AHRF encompasses different patient phenotypes and thus, as reported by Gattinoni et al (12) (L = low elastance and H = high elastance), requires different ventilator supports. However, assessing patients to determine their phenotype at an early stage of ICU management is difficult, especially in the event of a massive influx of patients (13). Finally, the COVID-19 pandemic has underlined the need for a comprehensive national approach to ventilatory support management, given that the unprecedented influx of patients leads to a shortage of ICU capacity and a lack of resources such as ventilators (14). In such a context, HFNC could be administered in intermediate care units, thereby reserving ventilators for most needy patients. These complex issues have fueled incentives to conduct studies to provide evidence for improving decision-making processes.

In the absence of randomized clinical trials to assess the causal effect of IMV on mortality during the COVID pandemic, analysis of observational longitudinal studies is a suitable alternative (15, 16).

The aim of this study was to assess the effect of early IMV in COVID-AHRF on 60-day mortality, using a large high-quality database and applying an inverse probability of treatment weight (IPTW) weighted Cox-survival model.

MATERIALS AND METHODS

Data Source

The study used data from the French prospective multicenter OutcomeRea database (n = 11 ICUs). The methods of data collection and quality of the database have been described in detail elsewhere (17). In accordance with French law, the OutcomeRea database was approved by the French Advisory Committee for Data Processing in Health Research and the French National Commission for Data Protection and Liberties (registration number 8999262). The database protocol was submitted to the Institutional Review Board of the Clermont-Ferrand University Hospital, France, which waived the need for informed consent (Institutional Review Board number 5891).

Study Population

Patients over 18 years were eligible for inclusion in the analysis if they were admitted to one of the participant ICUs belonging to the OutcomeRea network and had at admission an AHRF related to severe COVID-19 pneumonia defined as the combination of: 1) radiological features compatible with this diagnosis, 2) Pao_2/Fio_2 ratio ≤ 300 mm Hg, and 3) a positive severe acute respiratory syndrome coronavirus-2 test using reverse-transcriptase polymerase chain reaction.

Patients were excluded if they were referred from another ICU or intermediate are unit, when a decision was made to discontinue life-sustaining treatments during the first 2 calendar days after ICU admission, if ICU length of stay was less than or equal to 2 days and if they had a shock or a Glasgow Coma Scale (GCS) less than or equal to 12 on ICU admission.

Data Collection

All data were prospectively collected and comprised those recorded on ICU admission, several variables collected throughout the ICU stay and outcomes (demographics, chronic disease/comorbidities as assessed by the Knaus Scale (18), baseline severity indexes, Simplified Acute Physiology Score [SAPS] II (19), and Sequential Organ Failure Assessment [SOFA] (20) scores; daily throughout ICU stay: clinical and biological parameters, requirement for NI-OS and IMV, other organ support [vasopressors and renal replacement therapy], and occurrence of ICU-acquired pneumonia and bacteremia; ICU and hospital length of stay; and vital status at ICU and hospital discharge, and at day 60 after ICU admission).

Definitions, Group Assignment, and Respiratory Support Modalities

COVID-AHRF was classified into three categories based on the severity of hypoxemia at admission: mild ($200 < Pao_2/Fio_2 \leq 300$ mm Hg), moderate ($100 < Pao_2/Fio_2 < 200$ mm Hg), and severe ($Pao_2/Fio_2 \leq 100$ mm Hg) (21).

The early IMV group comprised all patients who received IMV within the first 2 calendar days in after ICU admission and the nonearly IMV group comprised all other patients who received at least one of these NI-OSs: NIPPV, HFNC, CPAP, and oxygen delivered through a nonrebreather face mask and not earlier than the third day after ICU admission.

Strategies for IMV and descriptions of the NI-OS techniques are given in the **Online Data Supplement** (http://links.lww.com/CCX/A495).

Statistical Analysis

Patient characteristics were expressed as *n* (%) for categorical variables and median (interquartile range [IQR]) for continuous variables. Comparisons were made with exact Fisher tests for categorical variables and Wilcoxon tests for continuous variables.

To estimate the average causal effect of early IMV on day-60 mortality, on longitudinal observational data, we used an IPTW estimator, which is the inverse of the patients' predicted probability of being in the early IMV group on the basis of their baseline covariates.

IPTW estimator is a statistical tool that allows causal inference on observational data. It was developed nearly 20 years ago (22–26) and has been widely used in medical fields. The methodology of IPTW has been fully described elsewhere. It is detailed in the Online Data Supplement (http://links.lww.com/CCX/A495) and briefly presented here. When randomized clinical trials are impossible or difficult to be implemented in the presence of baseline confounding factors, IPTW estimators are a suitable alternative for observational data to estimate the real causal effect of a treatment on outcome. By weighting all patients with their IPTW, two pseudopopulations are created, similar with regard to baseline confounding factors, and their outcomes are compared with survival models.

The impact of early IMV on day-60 mortality was estimated by a two-step process: 1) weight estimation by the IPTW estimator and 2) estimation of the impact of early IMV on day-60 mortality by a weighted Cox model. In the first step, the weight model, a nonparsimonious multivariate logistic regression model, was constructed to estimate each patient's predicted probability of being in the early IMV group. We included in the weight model the following baseline covariates, recorded at admission and not affected by study groups: period of admission, time between symptom onset and ICU admission, time between hospital and ICU admission, age, gender, body mass index, comorbidities including presence of chronic liver failure, cardiovascular, respiratory and kidney chronic diseases, immunosuppression, clinical and laboratory features at admission, *T* greater than 39°C, renal SOFA item (> 2), GCS < 15, Pao_2/Fio_2 ratio, respiratory rate, lactatemia, lymphocyte count, ferritin, D-dimer plasma level, C-reactive protein serum level, and treatments received at admission including lopinavir ritonavir, hydroxychloroquine, tocilizumab, anakinra, and corticosteroids received at admission. In the model, continuous variables were kept linearly unless in the absence of log linearity. All variables included in the weight model reflected knowledge available at baseline. To avoid extreme weights, we used stabilized weights, and to ensure the positivity, assumption was respected, weights were truncated at the 1–99th percentile (27) (online data supplement, http://links.lww.com/CCX/A495). In the second step, we used a weighted Cox proportional-hazard model to estimate the risk of death within the first 60 days of the ICU stay of early IMV. A

hazard ratio greater than 1 indicated an increased risk of death. The proportionality of hazard risk for IMV was tested with martingale residuals. Further analyses were performed to confirm the results obtained with the IPTW: 1) a raw (nonweighted) multivariable Cox model with adjustment on severity of the patients at admission and 2) a case-control analysis for which cases (patients who had died at day 60) were matched with controls (survivors) based on age, SOFA without respiratory item, and Pao_2/Fio_2 ratio at admission. Characteristics of the population by centers are reported in **Table E1** (http://links.lww.com/CCX/A495). All models were stratified by centers. To assess the potential effect of early IMV on subgroups of patients, sensitivity analyses were performed in the subgroup of the patients: 1) admitted to hospital within less than 5 days, 2) with a Pao_2/Fio_2 less than 150 mm Hg at admission, and 3) with a Pao_2/Fio_2 greater than 150 mm Hg at admission. These groups were defined prior to the statistical analyses. For all tests, a two-sided α of 0.05 was considered to be significant. Missing baseline variables were handled by median. All statistical analyses were performed with the SAS software, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients and Baseline Characteristics

From February 15, 2020, to May 1, 2020, 400 patients with laboratory confirmed COVID-19 were admitted to ICUs of the OutcomeRea network. Of the 245 included in the study (**Fig. 1**) 187 (76.4%) were male. The overall median (IQR) was 61 years (52–69 yr). The sex distribution and median age of included and excluded patients were similar (**Table E2**, http://links.lww.com/CCX/A495). One or more comorbidities were present in 157 patients (64%), with obesity and cardiovascular disease being the most frequently coexisting medical conditions, confirmed in 89 patients (36.4%) and 61 patients (24.8%), respectively. The median duration from the onset of symptoms to ICU admission was 10 days (7–12 d), and between hospital and ICU admission, 2 days (1–4 d). At admission, the median (IQR) SAPS II score was 34 (26–44). Median (IQR) Pao_2/Fio_2 ratio was 121 mm Hg (90–174) and 206 patients (84%) had moderate-to-severe AHRF. Overall, 117 patients (47.8%) received IMV (early IMV group), oxygen by mask or nasal prongs 16 (6.6%), HFNC 85 (34.6%), CPAP 18 (7.4%), and NIPPV 9 (3.6%). After intubation, their median (IQR) tidal volume was 6 mL/kg (5.9–6.4 mL/kg) with a median (IQR) compliance of 36.7 mL/mm Hg (27.6–53.3 mL/mm Hg). Ninety-five patients (38.8%) received lopinavir-ritonavir, 21 patients (8.6%) hydroxychloroquine, 22 patients (9%) tocilizumab, 22 patients (9%) anakinra, and 68 patients (28%) corticosteroids. The comparison of baseline characteristics between the early and the nonearly IMV groups is shown in **Table E3** (http://links.lww.com/CCX/A495). The rates of ICU-acquired pneumonia, bacteremia, and the ICU length of stay were higher in the early than in the nonearly IMV group ($p < 0.01$, $p < 0.01$, and $p < 0.01$, respectively).

Propensity Score Model Development

Propensity scores ranged from 0.01 to 0.92 and from 0.02 to 0.97 in the no-early IMV and in the early IMV groups, respectively, with 93.8% in the region of common support (0.02–0.92) (**Fig. E1**, http://links.lww.com/CCX/A495). All the covariates in the planned propensity score were kept in the final model. After applying IPTW, all covariates in the planned propensity score had weighted standardized differences below 10%, which is in favor of an equilibration of the covariates between the subgroups and ensure the exchangeability at baseline for these confounders (**Table E4** (http://links.lww.com/CCX/A495); and **Fig. 2**).

Follow-Up and Outcomes

The day-60-mortality in the whole study population was 31.8%. It was higher in the early than in the nonearly IMV group: 42.7% versus 21.9% (pval < 0.01), respectively.

After weighted Cox model analysis, the risk of death at day 60 was higher in patients receiving early IMV (HR_w= 1.74, 95% CI, 1.07–2.83; p = 0.03). Similar results were observed in a sensitivity analysis using truncated HR_w (**Table E5**, http://links.lww.com/CCX/A495). In all subgroup analyses, early IMV was or tended to be associated with an increased risk of day-60 mortality (**Fig. 3**).

In other sensitivity analyses, early IMV was also associated with day-60-mortality (**Tables E6** and **E7**, and **Fig. E2**, http://links.lww.com/CCX/A495).

In addition, we found that in the case of delayed intubation, that is, intubation after the first 2 calendar

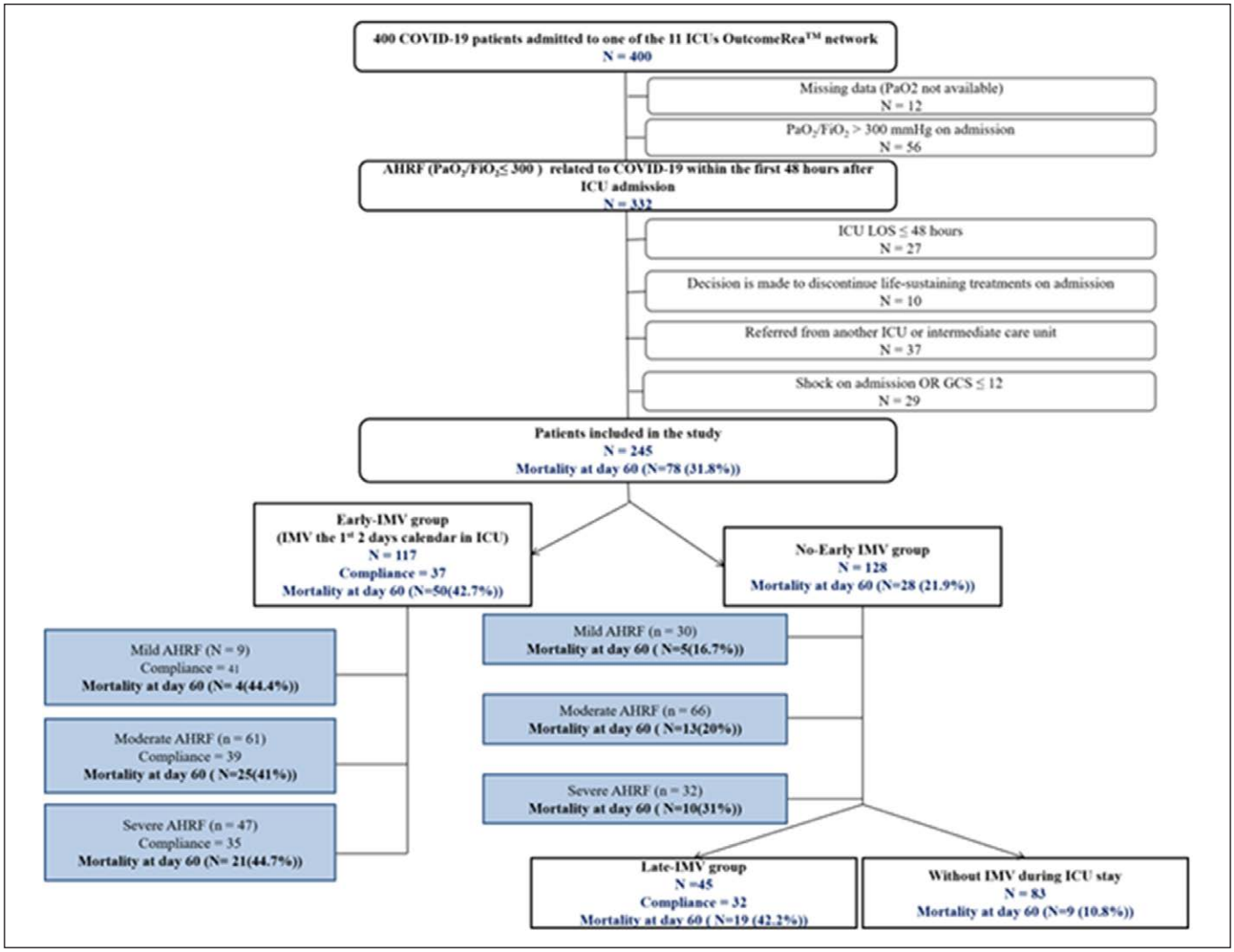

Figure 1. Flowchart. AHRF = acute hypoxemic respiratory failure, COVID-19 = coronavirus disease 2019, GCS = Glasgow Coma Scale, IMV = invasive mechanical ventilation, LOS = length of stay.

days after ICU admission, the patients in the late-IMV group ($n = 45$, 18.4%) had a similar outcome to those in the early IMV group, with a day-60-mortality of 42.2% and 42.7%, respectively. Patients without any IMV ($n = 83$, 33.9%) had the best survival rate during the ICU stay, with a day-60 mortality of 10.8% (**Table E8**, http://links.lww.com/CCX/A495).

DISCUSSION

Our study adds to current knowledge on the management of COVID-19 patients. It shows that using IMV during the first 2 calendar days after ICU admission in critically ill COVID-19 patients with AHRF was associated with increased day-60 mortality as compared to initial use of NI-OS. It also shows that patients intubated later because of failure of the noninvasive oxygenation strategy had a similar outcome to those ventilated early. The day-60 survival of patients with this successful conservative noninvasive strategy was better.

Deciding when to initiate IMV in critically ill patients with AHRF is challenging. The benefits of IMV must be weighed against its inherent risks (9). Since IMV is associated with adverse events entailing substantial morbidity and mortality, physicians have developed multiple means of NI-OS that avoid endotracheal intubation, such as NIPPV, HFNC, and CPAP. In de novo AHRF, the safety of NI-OS is debated. European Guidelines do not recommend CPAP and NIPPV, because they can postpone endotracheal intubation and increase the risk of hypoxic cardiac arrest (28). However, HFNC has recently shown clinical benefits in de novo AHRF (29). In COVID-19 patients

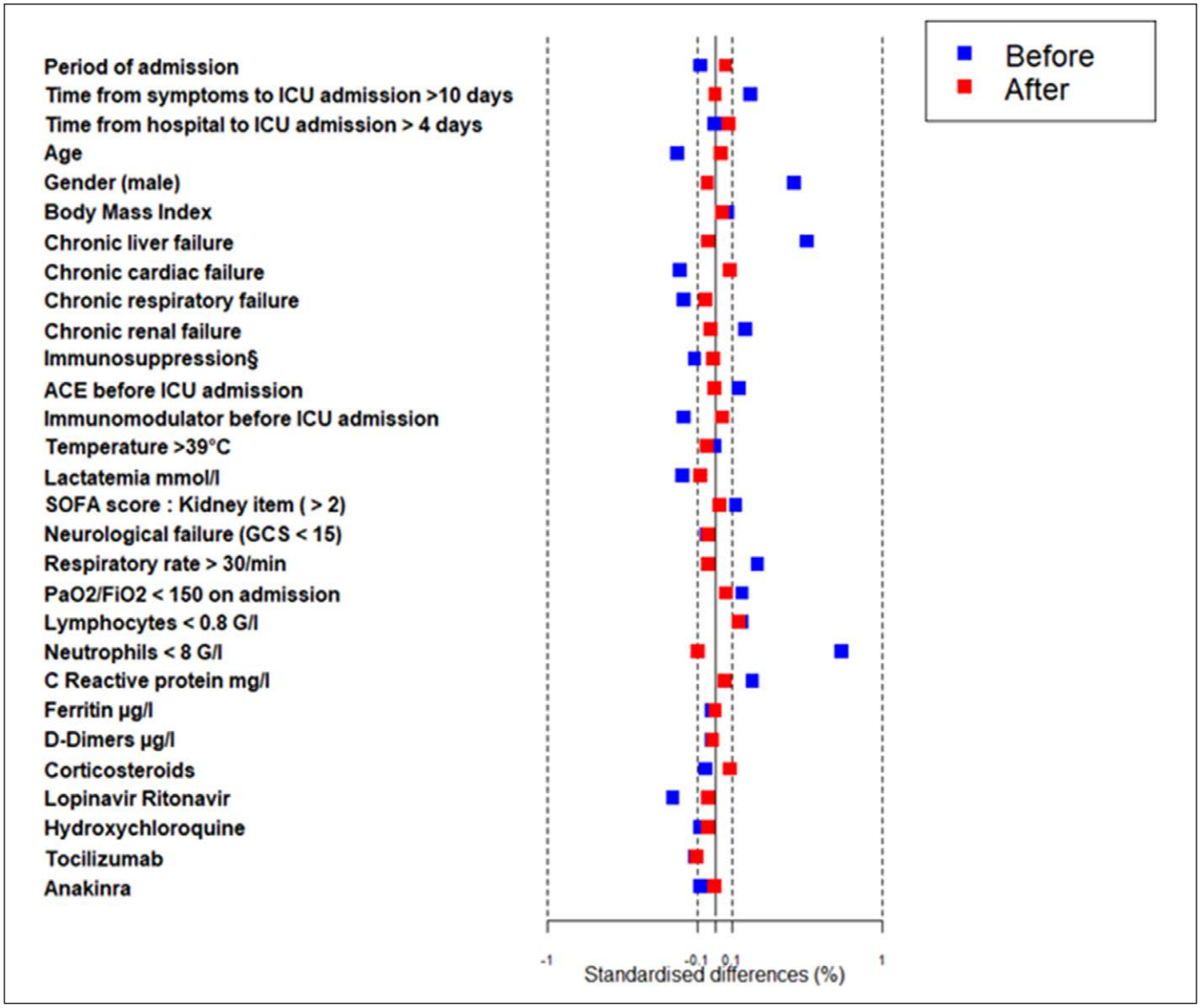

Figure 2. Standardized differences of variables used to generate the propensity score before and after proportional-hazard model weighted by inverse probability (IPTW). Propensity scores ranged from 0.01 to 0.92 and from 0.02 to 0.97 in the no early invasive mechanical ventilation (IMV) and in the early IMV groups, respectively, with 93.8% in the region of common support (0.02–0.92). All the covariates in the planned propensity score were kept in the final model. After applying IPTW, all covariates in the planned propensity score had weighted standardized differences below 10%, which is in favor of an equilibration of the covariates between the subgroups and ensures the exchangeability at baseline for these confounders. ACE = angiotensin-converting-enzyme inhibitors, SOFA = Sequential Organ Failure Assessment.

with AHRF or ARDS, the question is even more complex, especially in the early phase of the illness, because these patients may have normal lung mechanics and elastance (11, 12, 30). Thus, several experts have argued that protective IMV with effective sedation and paralysis should be implemented early to prevent delays in endotracheal intubation with the subsequent risk of increased mortality, barotrauma, volotrauma, and P-SILI due to large respiratory effort during noninvasive ventilatory support (12). The risk of aerosolization of viral particles and contamination of healthcare workers has also been cited to warrant early intubation instead of using NI-OS (31, 32). To date, no studies related to COVID-19 have directly evidenced this risk. Furthermore, findings with regard to droplet dispersion and aerosol generation with HFNC are uncertain and the increased risks of aerosolization with NIPPV compared with HFNC are largely unknown (33–35).

The need for IMV varied widely, from 29.1% to 89.9%, among patients admitted to the ICU with COVID-AHRF. IMV is invariably associated with high mortality ranging from 16% to 78% (2, 4, 31, 36, 37).

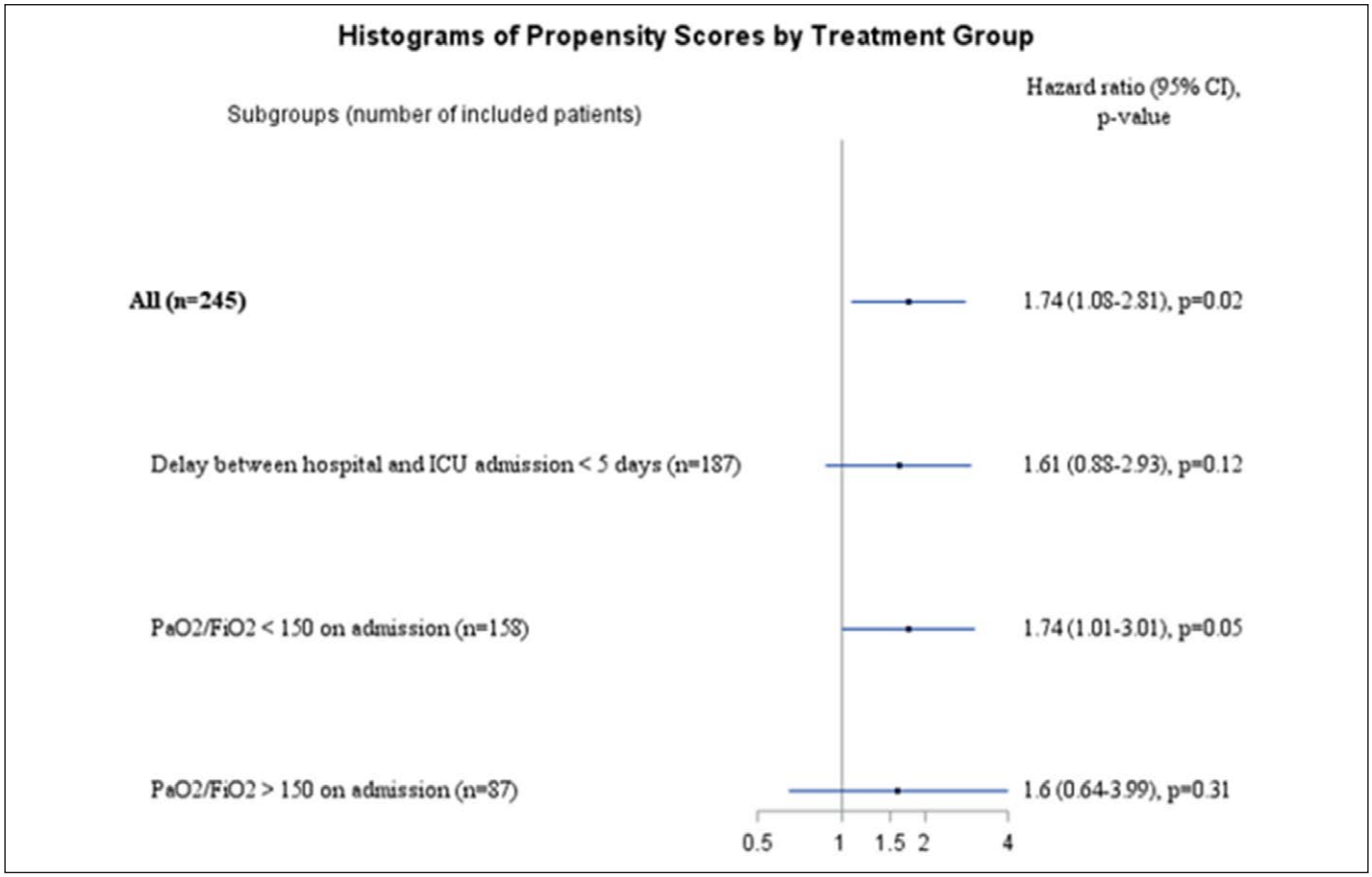

Figure 3. Effect of early invasive mechanical ventilation on ICU death of patients in the main cohort and in different subgroups (sensitivity analyses).

Very few studies have assessed the impact on the mortality of the mode of respiratory support in severe forms of COVID-19 pneumonia. In a cohort from Lombardy (36) of 3,940 ICU COVID-19 patients, 2,929 (87.3%) underwent intubation. The patients initially treated with NI-OS had a lower risk for mortality (heart rate [HR], 0.62; 95% CI, 0.52–0.75; $p < 0.01$) than those treated with IMV. Two recent retrospective cohort studies were not able to show a deleterious effect of intubation and subsequent IMV. Demoule et al (38) showed that HFNC significantly reduced intubation and subsequent IMV—55% (95% CI, 46–63) in the HFNC patient group ($n = 146$) versus 72% (95% CI, 64–79%) in patients without HFNC ($n = 233$)—but did not affect case fatality. Hernandez-Romieu et al (39) showed that mortality among 231 patients was neither associated with time from ICU admission to intubation nor with HFNC use.

Hospital capacity in France was exceeded during the pandemic. Some patients were intubated early to be transferred safely to the ICU and consequently did not undergo HFNC or other techniques to delay intubation. Furthermore, the recommendations, published at the beginning of the pandemic (3), advised against NIPPV and HFNC to avoid virus transmission. Some of our patients, therefore, were intubated before or at admission without having the option of noninvasive procedures.

In our study, higher mortality was observed in the early IMV group. Several factors could have contributed to this result. First, most patients in the nonearly IMV group received HFNC for oxygenation and respiratory support (62.4%) and very few received NIPPV. In de novo AHRF, the impact of HFNC on survival is uncertain (32, 40), but several studies have reported a lower risk of mortality associated with its use (41, 42) and recent meta-analyses have concluded that HFNC reduces the risk for endotracheal intubation (29, 40). The benefit of HFNC over standard oxygen delivered through a facemask or by NIPPV can be explained by its physiologic effects. HFNC provides a high and stable Fio_2, delivers a positive end-expiratory pressure value maintenance around 4 mm Hg, and can adjust independently the amount of Fio_2 and the flow rate in

an attempt to match the patient's oxygenation requirements and inspiratory flow demands. Thus, HFNC seems to improve oxygenation while reducing excessive respiratory efforts, pleural pressure swings, and exacerbation of lung injury (P-SILI) (41).

Second, NI-OS significantly reduced nosocomial infections. Several studies have already shown that NIPPV in critically ill patients with acute exacerbation of chronic obstructive pulmonary disease or severe cardiogenic pulmonary edema was associated with improved survival and reduction of nosocomial infections (43, 44).

One important finding of our study was that patients who ultimately did need IMV according to physicians had a high mortality rate. This underlines again the complexity of the timing of intubation in patients suffering from COVID-AHRF. This finding is consistent with the results from the Lombardy cohort (36), in which the 151 patients who were initially treated noninvasively and subsequently underwent intubation had a lower chance of survival than the 199 patients who underwent NI-OS throughout the ICU stay (HR, 1.69; 95% CI, 1.43–1.98; $p < 0.01$). The mortality of the patients undergoing subsequent intubation was similar to that of patients who were treated with mechanical ventilation at ICU admission: HR for IMV versus NIV failure, 1.20; 95% CI, 0.95–1.53; $p = 0.12$). Tools have been developed to avoid a deleterious delayed intubation in patients suffering from COVID-AHRF (45, 46). In pneumonia patients with AHRF under HFNC, the ratio of oxygen saturation as measured by pulse oximetry/Fio_2 to respiratory rate is an index that can help to identify those with low and those with high risk for intubation (47).

Our study has certain limitations. First, although the question of whether noninvasive oxygenation techniques can be administered outside ICUs is crucial in the case of limited ICU capacity and lack of ventilators, we focused on the impact of early IMV in ICU patients. Consequently, the study does not address the potential role of NI-OS in intermediate care units or wards. However, if hospitals and physicians cannot do otherwise, NI-OS could be an alternative in such a pandemic context, provided that strict protocols are discussed beforehand among the various hospital stakeholders involved. Second, most of our patients were managed with HFNC, and none were under Helmet, which limits the external validity of our results. Third, we pooled all the noninvasive ventilation procedures and could not compare HNFC with either NIPPV or CPAP. Fourth, several data could not be collected or determined retrospectively, including the phenotype (L or H) of the COVID-AHRF, the tidal volume in patients under noninvasive oxygenation techniques, and the medical reasons leading physicians to intubate or not the patients and the timing of the procedure. Finally, our study was only observational. As a result, although we tried to consider most confounding factors, our model could still be biased mostly because of unmeasured confounding. Then, to avoid selection bias and bias due to immortal time, we excluded all the patients transferred from another ICU or intermediate care unit who might have benefitted from NI-OS before ICU admission and also all patients with shock or neurologic failure at admission, for whom intubation is recommended. In addition, all our sensitivity analyses yielded the same results.

CONCLUSIONS

In ICU patients admitted with COVID-19-induced acute hypoxemic respiratory failure, early IMV was associated with an increased day-60 mortality. Those results deserved to be confirmed by randomized controlled trials.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccxjournal).

Drs. and Prs. Dupuis, Bouadma, Bailly, and Timsit had the idea for and designed the study. Pr. Timsit supervised the study. Dr. Dupuis, Mr. Ruckly, and Dr. Bailly did the statistical analysis. All authors contributed to the acquisition, analysis, or interpretation of data. Drs. and Prs. Dupuis, Bouadma, Souweine, and Timsit wrote the article. All authors revised the report and approved the final version before submission.

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