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Early Prone Positioning in Acute Respiratory Distress Syndrome Related to COVID-19: A Propensity Score Analysis from the Multicentric Cohort COVID-ICU network. The ProneCOVID Study.

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Abstract

Background Delaying time to prone positioning (PP) may be associated with higher mortality in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19). We evaluated the use and the impact of early PP on clinical outcomes in intubated patients hospitalized in intensive care units (ICUs) for COVID-19.

Methods All intubated patients with ARDS due to COVID-19 were involved in a secondary analysis from a prospective multicenter cohort study of COVID-ICU network including 149 ICUs across France, Belgian and Switzerland. Patients were followed-up until Day-90. The primary outcome was survival at Day-60. Analysis used a Cox proportional hazard model including a propensity score.

Results Among 2137 intubated patients, 1504 (70.4%) were placed in PP during their ICU stay, and 491 (23%) during the first 24 hrs following ICU admission. One hundred and eighty-one patients (36.9%) of the early PP group had a PaO_2/FiO_2 ratio > 150 mmHg when prone positioning was initiated. Among non-early PP group patients, 1013 (47.4%) patients had finally been placed in PP within a median delay of 3 days after ICU admission. Day-60 mortality in non-early PP group was 34.2% vs. 39.3% in the early PP group (p = 0.038). Day-28 and Day-90 mortality as well as the need for adjunctive therapies were more important in patients with early PP. After propensity score adjustment, no significant difference in survival at Day-60 was found between the two-study groups (HR 1.34 [0.96-1.68], p=0.09 and HR 1.19 [0.998-1.412], p=0.053 in complete case analysis or in multiple imputation analysis, respectively).

Conclusions In a large multicentric international cohort of intubated ICU patients with ARDS due to COVID-19, PP has been used frequently as a main treatment. In this study, early PP started within 24 hrs after ICU admission was not associated with a survival benefit compared to PP after day 1.

Introduction

Since 2020, the world has been facing a global threat due to the COVID-19, overwhelming hospitals and intensive care units (ICUs) as never before. To date, the World Health Organization has reported 158 millions confirmed COVID-19 cases and more than 3 millions of deaths (1). Patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and hospitalized for a severe pneumonia may develop acute respiratory distress syndrome (ARDS), which is associated with high mortality (2–4). Therefore, an extensive burden brought upon the intensive care units (ICUs) to provide invasive mechanical ventilation and other advanced forms of life support (5).

Before the COVID-19 pandemic, the Proseva trial (6) demonstrated an improvement in survival from prone position (PP) used as cycles of more than 16 consecutive hrs in selected ARDS patients, i.e. those with a PaO2/FIO2 ratio < 150 mmHg after 12 to 24 hrs-stabilization period. Though experts recommended PP in this setting (7), in the daily practice the rate of use of PP was lower than expected (8). Since the beginning of the COVID-19 pandemia, the surviving sepsis campaign (SSC) recommended PP in COVID-19 presenting with ARDS (9), a treatment widely adopted even though the level of evidence was similar as

before the pandemia (4, 10). In this recommendation, no timing to start prone position was proposed. Owing to the very large number of COVID-19 related ARDS treated with PP it was reported that an early application of PP (11) and the response to PP in terms of oxygenation (12, 13) were both possibly associated with a better outcome. Even if some studies of patients report interesting results (11–13), the impact of early PP on mortality remains unclear in COVID-19 patients in the ICU.

The objective of present ancillary study was to analyze the use of early PP in the ICU management of ARDS patient due to COVID-19 and to evaluate the impact of an early PP on survival, as well as on respiratory system mechanics and oxygenation, using a large international cohort of COVID-19 ARDS patients (4).

Methods

Study design and patients

This study was an secondary analysis of the COVID-ICU study (4). COVID-ICU was a prospective, multicenter observational cohort study of 149 ICUs from 138 hospitals conducted across three European countries (France, Belgian and Switzerland). The ethical committees of Switzerland (BASEC #: 2020 – 00704) and the French Intensive Care Society (CE-SRLF 20–23) approved this study and all patients or relatives had given their consent to be included in the COVID-ICU cohort. It recruited 4,643 patients between February and May 2020 with 80% of patients receiving invasive mechanical ventilation during their ICU stay.

All consecutive patients over 16 year-old included from February 25, 2020, to May 4, 2020, in the COVID-ICU study with an available vital status at Day-90 were eligible. Patients who met the following criteria in the first 24 hrs after admission were included: intubated and mechanically ventilated, $PaO_2/FiO_2 < 300$ mmHg with PEEP > 5 cmH_2O, and no therapeutic limitations. Laboratory confirmation for SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay from either nasal or pharyngeal swabs, and/or lower respiratory tract aspirates. Patients without laboratory-confirmed COVID-19 were not included, even if they presented with a typical radiological pattern.

Patients were classified according to the fact that they had been subjected to PP at Day-1 or later. Day-1 was defined as the first day in ICU at 10 am following the COVID-ICU study. All patients placed in PP during their first day in ICU constituted the early PP group. All patients placed in PP after Day-1 or non-placed in PP during their ICU stay were categorized in the non-early prone position group. Patients placed in PP later in their ICU course were included in the non-early proning group to reduce the potential for immortal time bias and to emulate an intention-to-treat strategy of a randomized trial.

Data collection

A standardized electronic case report form was completed each day at 10 am by the study investigators. Baseline characteristics were collected at ICU admission: age, sex, body mass index (BMI), active smoking, Simplified Acute Physiology Score (SAPS) II score, Sequential Organ Failure Assessment (SOFA), treated hypertension, diabetes, long term corticosteroids, immunodeficiency, Clinical Frailty Scale, the date of the first symptom, and dates of the hospital and ICU admissions. All investigators were asked to provide the lowest arterial partial pressure of oxygen (PaO_2) during last 24 hrs and fraction of oxygen inspired (FiO_2) to calculate PaO_2/FiO_2 ratio, and categorized according to the ARDS Berlin definition (14). Static compliance was defined by dividing the tidal volume by the driving pressure. The driving pressure was calculated by subtracting plateau pressure from positive end-expiratory pressure (PEEP). All biological data were collected at ICU admission. Proved concurrent bacterial pneumonia was defined by a positive bacterial culture at ICU admission in either a bronchoalveolar lavage sample, or in a blind protected specimen brush distal, or in endotracheal aspirates. The main outcome was Day-60 survival. Secondary outcomes included Day-28 and Day-90 mortality, ventilator free-days until Day-28, extracorporeal membrane oxygenation (ECMO) requirement, extracorporeal CO_2 removal ($ECCO_2R$) requirement, and inhaled nitric oxide. The ventilatory free days were computed as the number of days that a patient was alive and free of invasive ventilation, calculated from ICU admission until Day-28. Patients who died before Day-28 or received invasive ventilation for more than 28 days were considered to have 0 ventilator-free days (15). The static compliance, the SOFA score and the PaO_2/FiO_2 ratio were also evaluated at Day-3, Day-5, Day-7 as secondary outcomes.

Statistical analysis

Characteristics of patients were described as counts and percentages for categorical variables, and as mean and standard deviation or median and interquartile range for quantitative variables. Categorical variables were compared by Chi-square or Fisher's exact test, and quantitative variables were compared by Student's t-test or Wilcoxon's rank-sum test. Kaplan-Meier overall survival curves until Day-28, Day-60 and Day-90 were computed.

The primary endpoint was the Day-60 survival according to prone positioning at Day-1 of ICU stay. To assess prone positioning at Day-1 effect on Day-60 survival, we used a Cox proportional hazard model weighted on inverse probability of treatment weighting (IPTW) using propensity score (PS) defined as the predictive probability of prone positioning conditional on measured baseline covariates (16). The variables used to estimate propensity score were: age, gender, clinical frailty scale, SOFA cardiovascular, SOFA renal, SOFA coagulation, SAPS II score, immunodepression, long-term corticosteroids, treated hypertension, diabetes, BMI, delay between first symptoms and ICU admission, bacterial coinfection, ICU admission period (March 29 or after vs. March 28 or before), PaO2/FiO2 ratio and static compliance. A multivariate logistic regression model was performed to estimate the PS for each patient. To assess the balance of measured covariates between treatment groups, we used the standardized mean differences before and after PS weighting (17). Then, a Cox proportional hazard model weighted on IPTW was performed to estimate the average treatment effect in the entire eligible population (16). Hazard ratio and its 95% confidence interval were then estimated for the Day-60 mortality associated with prone

positioning at Day-1. This analysis was performed on the complete cases data set, and a sensitivity analysis was performed using multiple imputations due to missing data. Imputation method, missing data were realized according to Vesin et *al.* (18). Proportional hazard assumption was assessed by inspecting the scaled Schoenfeld residuals and Harrel's test (19). Multicolinearity was checked using variance inflation factor.

The secondary endpoints were: Day-28 survival, Day-90 survival, number of days free of mechanical ventilation up to Day-28, the need for extracorporeal life support, the need for inhaled nitric oxide, static compliance (at Day-3, 5, and 7), PaO2/FiO2 (at Day-3, 5, and 7), SOFA score (Day-7, 21, and 28).

All analyses were performed at a two-sided α level of 5% and conducted with R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of ICU patients

COVID-ICU study enrolled 4,244 patients. In this secondary study, 2,137 patients met the inclusion criteria and were included in the analysis (Fig. 1). The median [interquartile range] age was 63 [55–70] years, 1598 (75.1%) of patients were male, the median BMI was 29 [26–33] kg/m^2, the median SAPS II, SOFA and Frailty score were 43 [32–56], 7 [4–10] and 2 [2–3] respectively. The main comorbidity was hypertension (49.9%), followed by diabetes (28.4%) and immunosuppression (7.3%). All patients were rapidly intubated after ICU admission with a median delay inferior to 3 hrs approximately. Regarding the ARDS severity at Day-1, the median static compliance was 32.8 [26.3–41.7] ml/cmH_2O, and the PaO_2/FiO_2 ratio was 145.7 [101.7–200] mmHg including 1106 (51.8 %) patients with a ratio less than 150 mmHg. All others characteristics of patients are summarized in Table 1.

Table 1
Demographic, clinical and ventilatory characteristics of patients according to their proning status at Day-1.

Variable	All patients (*n* = 2137)	Non-early prone position group (*n* = 1646)	Early prone position group (*n* = 491)	*p*
Age (years), median (IQR)	63 (55–70)	63 (55–70)	63 (54–70)	0.393
Sex, *n* (%)				
Men	1598 (75.1%)	1242 (75.7%)	356 (73.1%)	0.238
Women	529 (24.9%)	398 (24.3%)	131 (26.9%)	
Body mass index (kg/m^2), median (IQR)	29 (26–33)	28 (26–32)	30 (27–34)	< 0.0001
>= 30 kg/m^2, *n* (%)	888 (44.4%)	636 (41.4%)	252 (54.8%)	< 0.0001
Comorbidities, *n* (%)				
Active smokers	87 (4.2%)	68 (4.3%)	19 (4%)	0.791
Treated hypertension	1055 (49.9%)	786 (48.3%)	269 (55.2%)	0.005
Known diabetes	601 (28.4%)	446 (27.4%)	155 (31.9%)	0.053
Immunodeficiency	154 (7.3%)	120 (7.4%)	34 (7%)	0.788
Long-term corticosteroids	77 (3.7%)	66 (4.1%)	11 (2.3%)	0.064
SAPS II score, median (IQR)	43 (32–56)	42 (32–56)	44 (32–55)	0.702
SOFA score at ICU admission, median (IQR)	7 (4–10)	7 (4–10)	8 (5–10)	0.033
Clinical frailty score, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	0.112
Time between first symptoms and ICU admission (days), median (IQR)	9 (6–12)	9 (6–12)	9 (6–11)	0.273

Abbreviations: IQR: Interquartile range; SOFA: Sequential organ failure assessment; SAPS II: Simplified acute physiology score II; $PaCO_2$: Arterial partial pressure in carbon dioxide; PaO_2: Arterial partial pressure in oxygen; FiO_2: Fraction inspired in oxygen; CRP: C-reactive protein.

Variable	All patients (*n* = 2137)	Non-early prone position group (*n* = 1646)	Early prone position group (*n* = 491)	*p*
Time between ICU admission and invasive mechanical ventilation (hours), median (IQR)	2.7 (0.7–9.7)	3 (0.7–10.8)	1.8 (0.4–6.3)	0.001
Concomitant bacterial pneumonia, *n* (%)	130 (6.3%)	93 (5.8%)	37 (7.7%)	0.143
Static compliance (mL/cmH_2O), median (IQR)	32.8 (26.3–41.7)	33.6 (26.9–42)	30.7 (24.1–39.9)	0.001
Dynamic compliance (mL/cmH_2O), median (IQR)	16.7 (13.6–21)	17 (14.1–21.4)	15.2 (12.3–19.5)	< 0.0001
Blood gas, median (IQR)				
pH	7.4 (7.3–7.4)	7.4 (7.3–7.4)	7.4 (7.3–7.4)	< 0.0001
$PaCO_2$ (mmHg)	43 (37–49)	42 (37–48)	45 (40–52)	< 0.0001
PaO_2/FiO_2 (mmHg)	145.7 (101.7–200)	152.2 (107–205)	128.3 (87.5-177.5)	< 0.0001
<150 mmHg, *n* (%)	1106 (51.8%)	796 (48.4%)	310 (63.1%)	< 0.0001
HCO_3 (mmol/L)	25 (22–27)	24 (22–27)	25 (22–28)	0.001
Lactate (mmol/L)	1.3 (1-1.7)	1.3 (1-1.7)	1.3 (1-1.8)	0.012
Biology, median (IQR)				
Lymphocyte count (x 10^9/L)	0.8 (0.5–1.1)	0.8 (0.5–1.1)	0.8 (0.6–1.2)	0.294
Thrombocyte count (x 10^9/L)	225 (167-292.5)	223 (165–291)	227 (170.2–296)	0.367
Total bilirubin (mg/dL)	0.58 (0.41–0.89)	0.58 (0.41–0.89)	0.58 (0.41–0.89)	0.245

Abbreviations: IQR: Interquartile range; SOFA: Sequential organ failure assessment; SAPS II: Simplified acute physiology score II; $PaCO_2$: Arterial partial pressure in carbon dioxide; PaO_2: Arterial partial pressure in oxygen; FiO_2: Fraction inspired in oxygen; CRP: C-reactive protein.

Variable	All patients (*n* = 2137)	Non-early prone position group (*n* = 1646)	Early prone position group (*n* = 491)	*p*
Serum creatinine (mg/dL)	0.94 (0.71–1.39)	0.92 (0.7–1.38)	0.98 (0.74–1.46)	0.033
D-dimer (µg/L)	1913 (1100–4219)	1844 (1038.5-4212.2)	2220 (1237–4262)	0.158
CRP (mg/L)	186.4 (121.2-266.5)	180 (119-261.4)	202.4 (136.1–276)	0.021
Procalcitonin (ng/mL)	0.7 (0.3–2.2)	0.6 (0.3-2)	0.9 (0.4–2.9)	0.01
hsTroponine T (ng/L)	23 (12-63.2)	22 (11.3–58.6)	31.4 (14.1–95.2)	0.003

Abbreviations: IQR: Interquartile range; SOFA: Sequential organ failure assessment; SAPS II: Simplified acute physiology score II; $PaCO_2$: Arterial partial pressure in carbon dioxide; PaO_2: Arterial partial pressure in oxygen; FiO_2: Fraction inspired in oxygen; CRP: C-reactive protein.

Prone position support

Among the 2,137 patients analyzed, 1,504 (70.4%) patients were subjected to prone positioning during the ICU stay with a median number of 4 [2–6] PP sessions. PP session duration in the first 48 hrs was 20 [16–32] hrs.

At Day-1, 491 patients (23%) were placed in PP, constituting the early PP group. Then, 1013 patients (47.4%) were proned after Day-1 with a median delay of 3 [2–5] days after ICU admission, and 633 (29.6%) were never subjected to PP. Those 1646 patients (77%) were classified as the non-early PP group. Characteristics of both groups at Day-1 are summarized in Table 1.

In the early PP group, patients were more obese (54.8% versus 41,4%, $p < 0.0001$), and had a higher rate of treated hypertension (55.2% versus 48.3%, $p = 0.005$). Median PaO_2/FiO_2 ratio was lower in the early PP group (128.3 [87.5-177.5] mmHg versus 152.2 [107–205] mmHg, $p < 0.0001$) as well as the respiratory static compliance (30,7 [24,1–39,9] ml/cm$H_2$0 versus 33.6 [26.9–42] ml/cm$H_2$0, $p = 0{,}001$). In the whole cohort, 181 (36.9%) patients of the early PP group had a PaO_2/FiO_2 ratio > 150 mmHg when placement in prone position was initiated. On the opposite, 796 (48.4%) patients with PaO_2/FiO_2 ratio < 150 mmHg at Day-1 were not placed in PP.

The median number of prone sessions was 3 [2–6] in the non-early PP group, with a median duration of 17 [16–23] hrs during the first 48 hrs vs 4 [2–7] number of prone sessions with a duration of 20 [16–32]

hrs in the early PP group ($p < 0.0001$)

Outcomes

In unadjusted analysis, mortality at Day-28, Day-60 and Day-90 were 30.5%, 35.4% and 35.9% respectively in the complete cohort study. Mortality was significatively lower in the non-early PP group compared to the early PP group as shown in Table 2. More patients needed adjunctive therapies (ECMO, $ECCO_2R$, inhaled nitric oxide) in the early PP group. The static compliance, the PaO_2/FiO_2 ratio and the SOFA score at Day-3, Day-5 and Day-7 were worse in the early PP group. In the whole cohort, ventilatory parameters did not improve during the first seven days after ICU admission.

Table 2
Primary and secondary outcomes

Outcome	All patients (*n* = 2137)	No early prone position group (*n* = 1646)	Early prone position group (*n* = 491)	*p*
Primary outcome				
Mortality at Day-60, *n* (%)	756 (35.4%)	563 (34.2%)	193 (39.3%)	0.038
Secondary outcomes				
Mortality, *n* (%)				
At Day-28	652 (30.5%)	482 (29.3%)	170 (34.6%)	0.024
At Day-90	767 (35.9%)	574 (34.9%)	193 (39.3%)	0.072
Ventilatory free-days util Day-28, median (IQR)	6 (0–16)	7 (0–17)	0 (0–14)	< 0.001
Extracorporeal membrane oxygenation, *n* (%)	221 (10.4%)	151 (9.2%)	70 (14.3%)	0.001
Extracorporeal CO_2 removal, *n* (%)	10 (0.7%)	7 (0.7%)	3 (0.9%)	0.719
Inhaled nitric oxyde, *n* (%)	412 (19.3%)	286 (17.4%)	126 (25.7%)	< 0.0001
Static compliance (mL/cmH2O), median (IQR)				
At Day-3	33.6 (25.7–42.5)	34.4 (26.7–43.6)	31.4 (23.4–40)	< 0.001
At Day-5	31.4 (24.3–40)	32.3 (24.7–40.8)	29.4 (22.6–39.7)	0.011
At Day-7	31 (22.9–40)	31.4 (23.3–40.4)	29.4 (22.1–38.8)	0.105
SOFA score, median (IQR)				
At Day-7	9 (7–12)	9 (7–11)	10 (8–12)	0.002
At Day-21	8 (6.2–11)	8 (7–12)	8 (5–11)	0.638

Abbreviations: IQR: Interquartile range; SOFA: Sequential organ failure assessment; PaO_2: Arterial partial pressure in oxygen; FiO_2: Fraction inspired in oxygen; ICU: Intensive care unit.

Outcome	All patients (*n* = 2137)	No early prone position group (*n* = 1646)	Early prone position group (*n* = 491)	*p*
At Day-28	8 (6.5–11)	8 (6–11)	9 (7–11)	0.905
PaO_2/FiO_2 ratio (mmHg), median (IQR)				
At Day-3	158.3 (118.3-213.3)	162.9 (121.2–220)	148 (108.7-192.5)	< 0.0001
At Day-5	155 (113.3-205.5)	158.3 (115-208.6)	140 (106-191.4)	0.001
At Day-7	157.1 (114–205)	158.3 (116-209.3)	150 (104.4-187.5)	0.002
Number of prone sessions during ICU stay, median (IQR)	3 (2–6)	3 (2–6)	4 (2–7)	< 0.0001
Delay between ICU admission and 1st prone position, days, median (IQR)	2 [0–4]	3 [2–5]	0 [0–0]	

Abbreviations: IQR: Interquartile range; SOFA: Sequential organ failure assessment; PaO_2: Arterial partial pressure in oxygen; FiO_2: Fraction inspired in oxygen; ICU: Intensive care unit.

After propensity score adjustment, results were analyzed in both complete case analysis including 944 patients and in multiple imputation analysis with all baseline population of 2137 patients. Baseline characteristics before and after weighted-propensity score analysis are provided in additional Table 1, in the additional file 1.

After weighting, no significant difference in Day-60 mortality was found between the two-study groups, in both analysis (hazard ratio (HR) 1.34 [0.96–1.68], $p = 0.09$ in complete case analysis and 1.19 [0.998–1.412], $p = 0.053$ in multiple imputation analysis) shown in Fig. 3. Mortality at Day-28 and Day-90 were also similar between the two study groups after weighted-propensity score analysis.

In the subgroups of ARDS patients according to their PaO_2/FiO_2 more or less than 150 at Day-1, mortality was higher in patients with PaO_2/FiO_2 less than 150 mmHg (Table 3).

Table 3
Subgroups analysis

Variable	**PaO_2/FiO_2 ratio at Day-1**		***p***
	>= 150 mmHg (n = 1031)	**< 150 mmHg (n = 1106)**	
Mortality Day-28, *n* (%)	271 (26.3%)	381 (34.4%)	< 0.0001
Mortality Day-60	312 (30.3%)	444 (40.1%)	< 0.0001
Mortality Day-90	319 (30.9%)	448 (40.5%)	< 0.0001
Invasive ventilation-free days up to Day-28 (days), median (IQR)	9 (0–18)	0 (0–14)	< 0.0001
Time between ICU admission and first prone session			
	After 24 hours (n = 1013)	**Before 24 hours (n = 491)**	
Mortality Day-28, *n* (%)	339 (33.5%)	170 (34.6%)	0.656
Mortality Day-60	403 (39.8%)	193 (39.3%)	0.86
Mortality Day-90	410 (40.5%)	193 (39.3%)	0.665
Invasive ventilation-free days up to Day-28 (days), median (IQR)	0 (0–13)	0 (0–14)	0.415
Duration of first prone session, Day-1			
	Less than 16 hours (n = 185)	**16 hours or more (n = 250)**	
Mortality Day-28, *n* (%)	76 (41.1%)	75 (30%)	0.016
Mortality Day-60	90 (48.6%)	80 (32%)	< 0.001
Mortality Day-90	90 (48.6%)	80 (32%)	< 0.001
Invasive ventilation-free days up to Day-28 (days), median (IQR)	0 (0–13)	5 (0–14)	0.067

Abbreviations: IQR: Interquartile range; PaO_2: Arterial partial pressure in oxygen; FiO_2: Fraction inspired in oxygen; ICU: Intensive care unit.

Among the 1,504 patients who received prone positioning during their ICU stay, an early PP was not associated with a reduction of mortality nor an increase in ventilator-free-days up to Day-28. Among

patients who subjected to PP at Day-1, a duration of PP session greater than 16 hrs was associated with a reduction of mortality at Day-28, 60 and 90.

Discussion

In this secondary analysis of a multicenter cohort study, our results show that PP was widely used across European ICUs during the COVID-19 pandemic, with 70% of patients intubated at ICU admission placed in prone position during their ICU stay. This rate contrasts with the results of the Lung Safe study and Apronet studies published before this pandemic, reporting less than 15% use of PP in ARDS of all-causes worldwide (8, 20). Interestingly, our study highlights that prone positioning was not always used according to international guidelines (7, 21). As a result, a large proportion of patients (37%) was placed in PP despite a PaO_2/FiO_2 ratio higher than 150 mmHg. In addition, approximately 50% of patients were not placed in PP at Day-1 despite PaO_2/FiO_2 ratio lower than 150 mmHg. Those findings are consistent with results of previous studies (11, 12). In a recent observational study, Mathews et *al.* reported that 44% of intubated patients with a PaO_2/FiO_2 ratio less than 100 mmHg were not placed in PP during the first 2 days, and only 30% of patients experienced proning during their ICU stay (11). In a large cohort study of more than 1000 patients, 21% of patients were not placed in PP despite a PaO_2/FiO_2 ratio of less than 100 mmHg (12). Those results highlight the difficulty to recognize ARDS and to properly apply international guidelines. Higher number of ICU beds, higher number of patients per physician or per nurse have previously been associated with a more difficult ARDS recognition and a lower use of prone positioning (20). The intervention of prone positioning in intubated patient requiring experimented staff to do it safely. Work overload, the deterioration of work conditions and the hiring of unexperimented staff associated with this pandemic (22, 23) may have contributed to an under-recognition of ARDS and may explain why patients had not been placed in PP or placed in PP disregarding international guidelines.

Our study failed to demonstrate an improvement of survival in intubated patients receiving an early PP at Day-1 compared to non-early PP. Our findings therefore contrast to those reported in another study in mechanically ventilated patients, in which early prone positioning in the first two days of ICU admission was associated with a survival benefit in COVID-19 related ARDS (11). Several reasons may explain these discrepancies. First, definition of treatment group was different between studies. In our study, treatment groups were defined according to their PP status at Day-1 and not according to their PP status in the first 48h after admission. In order to respect the validity of the propensity score using, our study was designed to analyze a potential survival benefit of prone positioning during the first 24 hrs of ICU admission. Although, the median delay between ICU admission and the first prone positioning in the non-early PP group was 3 days, we could have failed to demonstrate a benefit because approximately 25 % of patients in this group had been finally placed in PP during Day-2. Those patients would have been referred as PP group in Mathews et *al*. study (11). Consequently, our results suggest no additional outcomes' improvement supporting very early PP during the first 24 hrs of ICU admission. Second, our study enrolled all intubated ARDS patients and more than a third of patients placed in PP had a PaO_2/FiO_2 ratio higher than 150 mmHg. The Proseva trial showed survival benefit with PP in moderate to severe patients with a

PaO_2/FiO_2 ratio less than 150 mmHg (6). Even if PP is supposed to limit the extent of lung injuries induced by ventilation in ARDS patients with various degrees of severity, the potential survival benefit in patients with PaO_2/FiO_2 ratio higher than 150 mmHg has not been demonstrated and remains unclear mainly due to under-powered previous studies (24). Third, a large proportion of patients in the early PP group were placed in PP for less than 16 hrs in contrast to the Proseva trial showing a benefit in patient placed two time in prone position for at least 16 hrs during the first two days (6). Similar to previous studies (25, 26), the short duration of PP session could also explain the absence of benefit of PP observed in the early PP group. Finally, 660 patients were proned after 48 hrs of ICU admission, representing 43.8% of all proned patients in our cohort, and Guerin et *al*. found a survival benefit when using prone positioning early after endotracheal intubation (within 48 hrs) (6). In Mathews et *al.*'s study a smaller proportion of patients (19.5%) was initiated on proning after 48 hrs of ICU admission (11), which might have contributed to greater difference in patient's care between groups and thus impact mortality. However, impact of timing of prone sessions initiation after endotracheal intubation has not been specifically studied yet and is scarcely described in other randomized control trials assessing proning in ARDS (27–29).

Prone position has been shown to improve blood oxygenation by homogenizing the distribution of pulmonary ventilation/perfusion ratios; preventing ventilator induced lung injury by homogenizing the strain to lung tissue associated with mechanical ventilation on inflamed alveoli, and preserving systemic hemodynamics, particularly right ventricular function (30). However, the clear response to the prone position has remained non-defined. Our results show that patients placed in PP at Day-1 did not improve their ventilatory parameters, including the static compliance and oxygenation during their ICU stay at least until Day-7. In a large cohort of intubated COVID-19 patients, Langer et *al*. found that prone positioning was associated with immediate oxygenation improvement without any increase of respiratory system compliance (12). The lack of oxygenation improvement in our study could be due to the timing of assessment of oxygenation. Indeed, we recorded blood gases results daily independently of patients proning status at that time and did not study blood gases evolution during and just after proning. This could be in line with results reported by Langer et *al*. showing a trend toward worsening of oxygenation after re-supination (12). Our results considering the lack of improvement of static compliance are consistent with those of Langer *et al.* contrasting data on non-COVID-19 related ARDS which showed a reduction of driving pressure and plateau pressure when placed in prone position, suggesting better static compliance (30). This difference of effect of PP on respiratory mechanics between COVID-19 and non-COVID-19 related ARDS possibly highlight different pathophysiologies (31). Those lack of ventilatory parameters improvements could explain why the median duration of invasive mechanical ventilation in ARDS COVID-19 patients is approximately 12–13 days, longer that previously reported in all-causes ARDS patients included in Lung safe study (4,19). It might therefore also be possible that the follow-up of seven days in our study did not allow us to show a potential ventilatory parameters benefits of prone position due to the short time of the follow-up.

This study has some limitations. First, it is not a randomized controlled study. We used however a propensity score adjusting on potential confounders. Second, despite of the propensity score weighting adjustment, it might be possible that patients in the early PP group were more severe at ICU admission and required a prone positioning earlier than patients in the non-early PP group, leading to confusion bias. Third, our study design did not allow us to analyze outcomes in patients respecting the PP status in the first 48 hrs and after stabilization according the Proseva trial protocol, but only depending on the PP status at Day-1, in order to carefully respect the methodology of propensity score analysis. Fourth, some patients required up to 20 prone sessions leading to potential complications. Unfortunately, those data were not collected in this study.

Conclusions

Our results suggest that ICUs across European countries have largely adopted prone positioning in ARDS patients due to COVID-19 regardless of their severity. In this study, early prone positioning initiated during the first day of ICU admission did not confer a survival benefit for patients requiring invasive mechanical ventilation, but prone sessions of more than 16 hrs seemed to be associated with better outcome. Further studies are needed to identify subgroups of patients with COVID-19 related ARDS who might benefit from early prone positioning.

Abbreviations

COVID-19
Coronavirus disease 2019; PP:Prone position; ICU:Intensive care unit; ARDS:Acute respiratory distress syndrome; RT-PCR:Real-time reverse transcriptase-polymerase chain reaction; BMI:body mass index; SOFA:Sequential Organ Failure Assessment; PaO_2:Arterial partial pressure of oxygen; FiO_2:Fraction inspired of oxygen; SAPS II:Simplified Acute Physiology Score II; PEEP:Positive end-expiratory pressure; ECMO:Extracorporeal membrane oxygenation; $ECCO_2R$:Extracorporeal CO_2 removal; IPTW:Inverse probability of treatment weighting; PS:propensity score.

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All authors interpreted the data and critically revised the manuscript for important intellectual content and gave approval for the final version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The manuscript's guarantors (CLT and NT) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate: All patients or close relatives were informed that their data were included in the COVID-ICU cohort. Human research ethics committee approval for the study were the ethical committee of Geneva (BASEC #: 2020-00704) and the ethical committee of the French Intensive Care Society (CE-SRLF 20-23) following our local regulations.

Consent for publication: All patients or close relatives were informed that their data might be published.

Competing interests: All authors declare no conflicts of interest.

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Figures

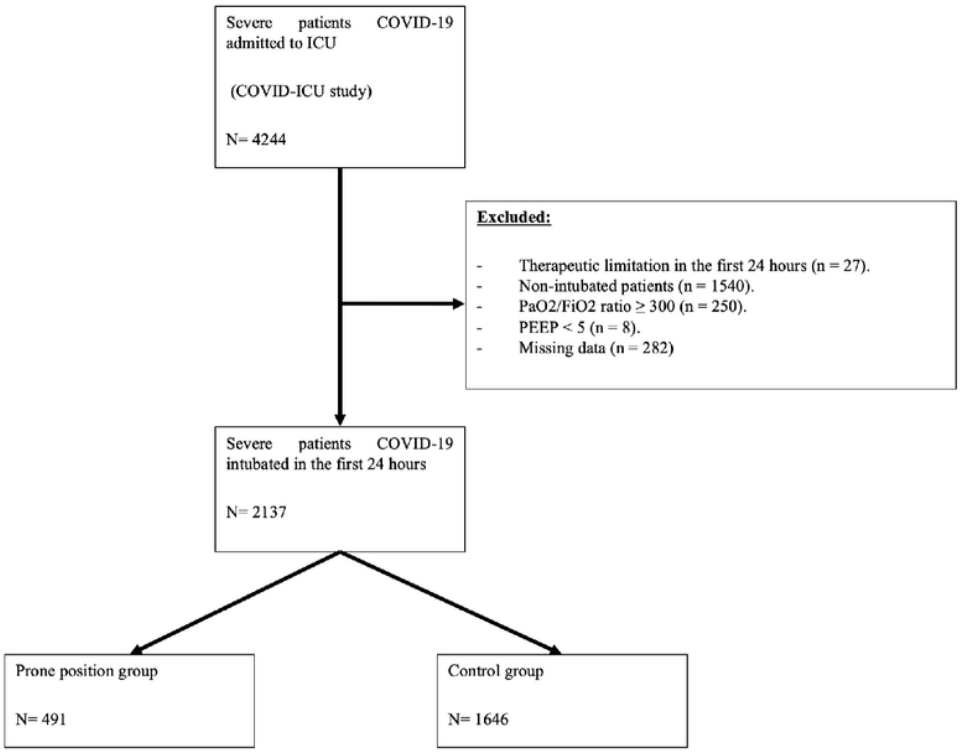

Figure 1

Study flow chart. ICU: intensive care unit; PaO2: Arterial partial pressure of oxygen; FiO2: Fraction inspired of oxygen; PEEP: positive end-expiratory pressure.

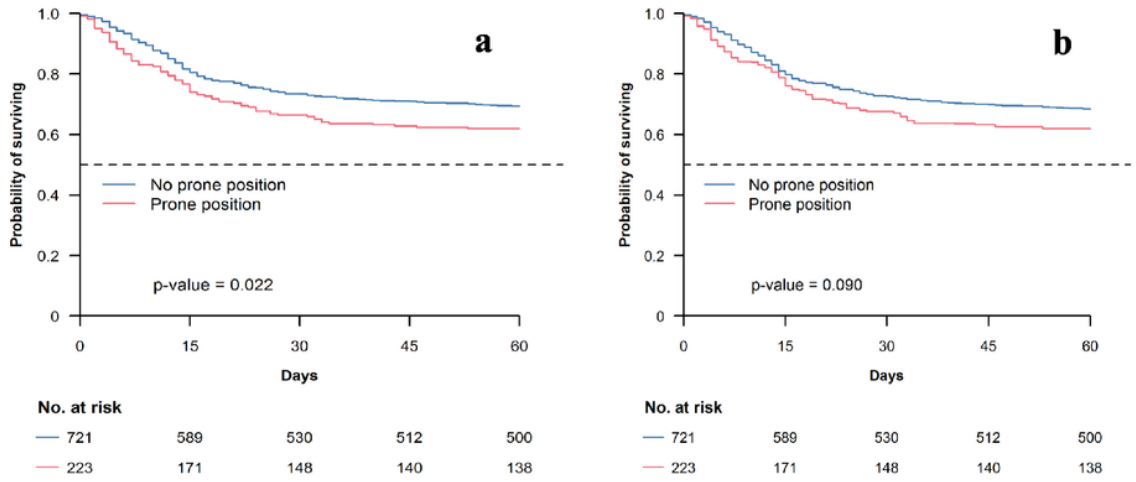

Figure 2

a. Kaplan Meier curves according to prone status in ICU at Day-1 before weighting adjustment in complete case population. b. Kaplan Meier curves according to prone status in ICU at Day-1 after weighting adjustment in complete case population ICU: intensive care unit

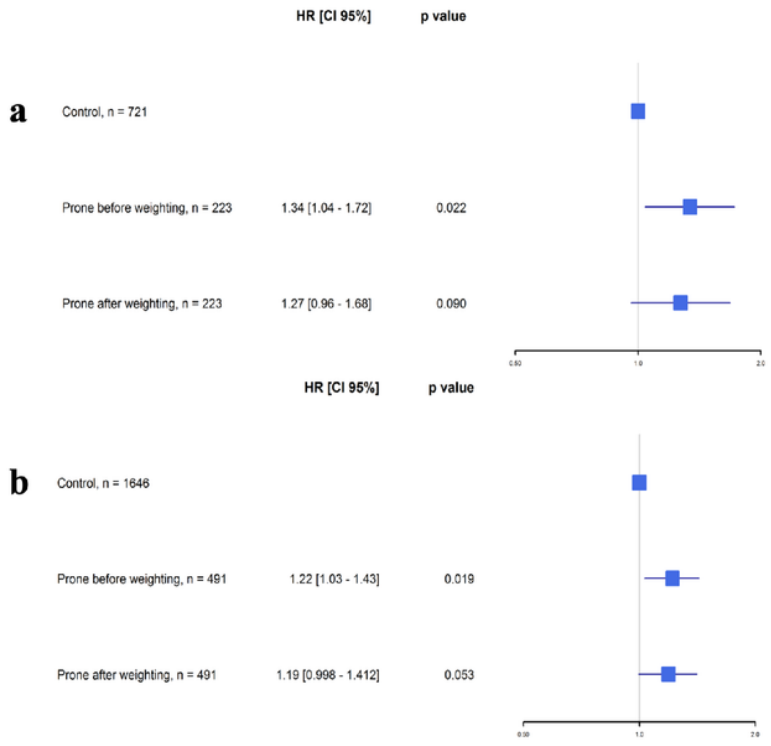

Figure 3

a. Forest plot: Hazard Ratio according to prone status in ICU at Day-1 before and after weighting in complete case population. b. Hazard Ratio according to prone status in ICU at Day-1 before and after weighting in baseline population. ICU: intensive care unit; HR: Hazard ratio.

Supplementary Files

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