Prone positioning for patients with SARS-CoV-2-related respiratory failure in non-intensive care unit

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Abstract

Background Prone positioning (PP) is an established and commonly used lung recruitment method for intubated patients with severe acute respiratory distress syndrome, with potential benefits in clinical outcome. The role of PP outside the intensive care unit (ICU) setting is debated.

We aimed at describing the use and potential benefits of PP in non-intubated patients with acute respiratory failure related to COronaVIrus Disease-19 (COVID-19)-pneumonia.

Methods Consecutive adult patients with COVID-19-related respiratory failure were included in a prospective collaborative cohort and classified based on the severity of respiratory failure by the partial arterial oxygen pressure to fraction of inspired oxygen ratio (PaO2/FiO2) and on clinical severity by the quick Sequential Organ Failure Assessment (qSOFA) score. Primary study outcome was the composite of in-hospital death or ICU admission within 30 days from hospitalization.

Results PP was used in 114 of 536 study patients (21.8%), more commonly in patients with lower PaO2/FiO2 or receiving non-invasive ventilation and less commonly in patients with known comorbidities. A primary study outcome event occurred in 163 patients (30.4%) and was in-hospital death in 129 (24.1%). PP was not associated with death or ICU admission (HR 1.15, CI 95% 0.78-1.72) and not with death (HR 1.03, CI 95% 0.62-1.69); PP was an independent predictor of ICU admission (HR 2.55, 95%CI 1.50-4.32). The severity of respiratory failure and non-invasive ventilation were independent predictors of death or ICU admission at 30 days. The lack of association between PP and death or ICU admission was confirmed at propensity score matching analysis.

Conclusion PP is used in a not negligible proportion of non-intubated patients with COVID-19-related severe respiratory failure and is not associated with death but with ICU admission. The role of PP in this setting requires evaluation in randomized studies.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)-related disease (COVID-19) is characterized by a wide spectrum of respiratory manifestations, ranging from no or flu-like syndromes to severe acute respiratory distress syndrome (ARDS)[1-4]. ARDS, as defined by the Berlin criteria, develops in about 42% of not vaccinated patients presenting with COVID-19 pneumonia, with rate as high as 61–81% in those with critical disease[5] and is associated with a mortality rate nearing 50%[6]. In vaccinated patients these rates are probably lower but still not negligible[7].

The severity of hypoxemia and the high mortality reported in patients with COVID-19 that required early intubation, have led many clinicians to adopt lung recruitment methods to improve oxygenation, gas exchange and, potentially, clinical outcome[8]. Prone positioning (PP) is an established and commonly used lung recruitment method for intubated patients with severe non COVID-19-related ARDS, with potential benefits in clinical outcome[9]. Based on the pathophysiological rationale and the observed

clinical benefits in patients with severe ARDS, the use of PP was extended to both, intubated and not intubated COVID-19 patients in whom the presence of respiratory failure and the lack of effective treatment suggested a poor prognosis[10]. In some patients, PP was used to avoid intubation and overcome intensive care unit (ICU) surge capacity during the COVID-19 outbreak. However, the clinical benefit of PP in non-intubated COVID-19 patients is controversial[11].

This multicenter non-intervention study aims at describing the use and potential benefits of PP with respect to death or admission to ICU at 30 days, in non-intubated patients with acute respiratory failure related to COVID-19-pneumonia.

Methods

Study design and population

Consecutive adult patients with acute respiratory failure related to COVID-19 pneumonia who were admitted at the Department of Internal and Cardiovascular Medicine – COVID-19 of the University Perugia or at the Department of Medicine at the Azienda Ospedaliero-Universitaria Pisana from October 2020 to May 2021 were included in prospective non-interventional cohorts; these cohorts were subsequently merged in a collaborative database. Patients were considered for inclusion in the present study if they had: i) diagnosis of COVID-19 confirmed by real time-Polymerase Chain Reaction testing, ii) pneumonia at chest X-ray, computed tomography (CT) or lung ultrasonography and iii) new onset respiratory failure.

Exclusion criteria were I) contraindication to PP (recent abdominal or thoracic surgery or trauma, facial, pelvic or spine fracture, skeletal deformities such as severe kyphoscoliosis and severe limb contractures, neurological issues making PP impossible or life-threatening); II) need for intubation at hospital admission; III) hemodynamic instability requiring vasopressor; IV) pregnancy.

Decision on the use of PP, respiratory support and drug therapy were at discretion of the attending physician. For the purpose of this study, non-invasive ventilation (NIV) included continuous positive airway pressure (CPAP), standard NIV or a combination of the two methods. NIV was initially set with the aim to provide a tidal volume on predicted body weight ratio varying between 6-8 ml/kg with a combination of positive end-expiratory pressure and inspired oxygen fraction (FiO2) to get a peripheral oxygen saturation between 92-98%. NIV was delivered through full face or oro-nasal facial mask connected via a double-tube circuit to a life-support ventilator (VIVO60 or VIVO65 Breas Medical, Sweden). High-flow nasal oxygen (HFNO) was not considered as NIV.

Patients were classified based on the severity of respiratory failure at admission. Acute hypoxaemic respiratory failure was defined by the ratio of partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen (FiO2) (PaO2/FiO2) ≤300 mmHg and stratified into four categories (PaO2/FiO2: > 300 mmHg, 300-200 mmHg, 200-100 mmHg, <100 mmHg).

Diagnosis of COVID-19 -related ARDS was made when patients met the Berlin criteria[4].

Patients were classified based on clinical severity according to the quick Sequential (sepsis-related) Organ Failure Assessment (qSOFA) score into two classes (<2 and ≥2)[12].

Tis study is reported according to the “Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)” statement guidelines for observcohort studies (Additional fle 1) and was approved by the local ethic review boards (Comitato Etico Regione Umbria, University of Perugia, protocol n. 20-05 SARS-CoV2). According to local regulations, the need for informed consent from individual patients was waived owing to the retrospective and observational nature of the study.

Study outcomes

The primary study outcome was the composite of in-hospital death or ICU admission occurring within 30 days from hospitalization. Secondary study outcomes were the individual components of the primary outcome: death or ICU admission both at 30 days from hospitalization. Decision concerning the need for ICU admission was in charge of the attending physician.

Study procedures

Proning maneuver was performed by trained staff of nurses and physicians, in fully awake or consciously sedated patients. The duration of pronation varied from a minimum of 4 to a maximum of 10 hours; pronation was repeated for 2-3 times a day – depending on the duration of the individual PP periods - after a period of supine positioning. For patients that were uncompliant to awake PP or severely tachypnoic (respiratory rate over 30 breaths per minute), sedation was applied by the attending physician. Conscious sedation was performed by the use of dexmedetomidine, morphine and/or benzodiazepine in multiple bolus or continuous infusions.

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Data collection

For all included patients the following were collected: age, sex, comorbidities, vital parameters, the PaO2/FiO2 ratio at admission, partial oxygen pressure (PaO2) and partial carbone dioxide pressure (PaCO2) before oxygen therapy, clinical signs and symptoms, laboratory findings, use of supplemental oxygen therapy or non-invasive respiratory support (NIV or CPAP) at admission and during observation.

Statistical analysis

This is a hypothesis generating study as few data exist on the use of PP outside the ICU. Assuming an incidence of death or ICU admission within 30 days of 20% and the intention to adjust the analysis for age, the severity of respiratory failure and clinical severity, we estimated a sample size of at least 500 patients to get powered information on the role of PP in the risk for the study outcome.

Frequency data are presented as proportions with 95% confidence intervals (CI). Continuous data are shown as means with standard deviations (SD). Students t-test and the $\chi 2$ test or Fisher exact test were used for comparisons of continuous and nominal variables, respectively.

Cox proportional regression model was used to assess independent predictors of death or ICU admission during the hospital stay and within 30 days from admission. Multivariable analyses were constructed from the set of significant ($p<0.10$) univariable predictors at entry and with PP as variable of clinical interest. PaO2/FiO2 and qSOFA were considered as ordinal variables with the category of milder disease as the reference group (PaO2/FiO2 >300mmHg and qSOFA =0). Multivariable analyses are reported as hazard ratio (HR) with 95% CIs and P values.

A propensity score matching analysis was performed to create similar treatment groups (PP vs no PP) with respect to observed patients' features. The propensity score was calculated on characteristics significantly different between patients managed with or without PP[13]. One patient treated with PP was matched to one patient not treated through optimal matching, determining matched samples with the smallest average within-pair absolute difference in propensity score[14-15-16] .The balance of measured covariates between matched cohort was assessed using standardised mean differences. Cox models with robust estimates was used to account for the clustering within matched sets. HRs and their 95% CI were reported for the study outcomes[17]. A two-sided p value <0.05 was considered statistically significant.

Analyses were performed with SPSS, version 26 and R 3.6.2 (package MatchIt).

Results

From October 2020 to May 2021, 583 patients with SARS-CoV-2-related respiratory failure were admitted at study centers (Figure 1). After exclusion of 47 patients because of intubation at hospital admission, 536 patients were finally included in the study. Main patients' features are reported in Table 1.

The mean age of study patients was 69±15 years, ranging from 17 to 98 years old. One-hundred-fifty-three patients (28.5%) had no known comorbidities at hospital admission.

Blood gas parameters before the starting of oxygen therapy were available in 284 patients as the remaining were tested on supplemental oxygen.

Overall, 373 patients received steroids treatment during the hospital stay (69.6%). The use of antiviral and immunomodulant therapies was at discretion of the attending physician.

NIV was used for the management of respiratory failure in 187 patients (34.9%) (Table 1).

Use of PP

PP was used in 114 patients (21.3%), 86 males (75.4%) (Table 1). Patients managed by PP more commonly had severe respiratory failure (PaO_2/FiO_2 < 300 mmHg in 83.3% vs 61.3% with vs. without PP, respectively) and less commonly known comorbidities (no known comorbidities in 37.7% vs 22.5% with vs. without PP, respectively) with respect to patients managed without PP. NIV was used in 81 and in 106 patients managed or not managed by PP (43.3% vs 25.1%, respectively).

Death or intubation during the hospital stay and within 30 days from admission

In-hospital death or ICU admission at 30 days from hospitalization occurred in 163 patients (30.4%). Death occurred in 129 patients (24.1%).

In-hospital death or ICU admission at 30 days occurred in 39 patients who underwent PP (34.2%) and in 124 of those who did not underwent PP (29.4%) (Rate Ratio 1.16, 95% CI 0.87-1.56). Death occurred in 23 patients who underwent PP (20.2%) and in 102 of those who did not underwent PP (24.2%) (Rate Ratio 0.83, 95% CI 0.56-1.25).

Increasing age, severity of respiratory failure and the use of NIV were independent predictors of death or ICU admission at 30 days (Table 2). PP was not associated with the risk of death or ICU admission at 30 days (HR 1.17, CI 95% 0.78-1.74). An increased risk for death or ICU admission was observed for patients with PaO_2/FiO_2 between 200 and 100 mmHg and for PaO_2/FiO_2 < 100 mmHg at admission (Table 2 and Figure 2).

Increasing age, severity of respiratory failure, the use of NIV and qSOFA ≥2 were independent predictors of death at 30 days. PP was not associated with the risk of death at 30 days (HR 1.01, CI 95% 0.61-1.67). An increased risk for death was observed for patients with PaO_2/FiO_2 between 200 and 100 mmHg and for PaO_2/FiO_2 < 100 mmHg (Table 2).

The use of NIV (HR 3.16, 95% CI 0.75 6.19 , p 0.001) and PP (HR 2.31, 95%CI 1.35-3.95, p 0.001)(Table2) were independent predictors of ICU admission at 30 days. No association was found between age, severity of respiratory failure and ICU admission.

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Sensitivity analyses

In 353 patients entering the study with ARDS, no association was observed between PP and the risk for death or ICU admission (HR 1.07, 95% CI 0.70-1.65). Mild ARDS (PaO_2/FiO_2 between 200 and 300 mmHg) was significantly associated with reduced risk for death or ICU admission (HR 0.33, 95% CI 0.20-0.56).

In 138 patients with moderate to severe ARDS (PaO_2/FiO_2 ≤200 mmHg), the only independent risk factor for death or ICU admission was age (HR 1.03 per year, 95% CI 1.01-1.04); no association was found with PP or NIV and the risk for death or ICU admission in these patients.

In 187 patients receiving treatment with NIV, no association was found between PP (HR 1.43, 95% CI 0.92-2.22) and the risk for death or ICU admission.

When 418 patients with qSOFA available were considered, increasing age and severity of respiratory failure were independent predictors of death or ICU admission while PP was not (HR 1.21, CI 95% 0.77-1.90) (Table 3 and Figure 2).

When the 114 patients who had PP were considered, the only independent predictor of death or ICU admission at 30 days was NIV (HR 3.20, 95% CI 1.13-9.06) (Table 4).

Propensity score matching analyses

Among patients' caracteristics reported in Table 1, age, sex, PaO2/FiO2 levels, number of comorbitidies and treatment with NIV differed between patients managed with or without PP. Propensity score matching was used to balance patients' characteristics between the cohort including the 114 patients managed by PP and a control cohort including 114 matching patients managed without PP. The final propensity score matching sample comprised 228 subjects.

The balance of measured covariates showed negligible difference between matched cohorts (standardised mean differences were all ≤ 0.1).

In the propensity score matching population, PP was not associated with death or ICU admission at 30 days (HR 1.33, 95% CI 0.83-2.14; p=0.193) and not with death at 30 days (HR 1.26, 95% CI 0.70-2.20; p=0.403). An association was confirmed between PP and ICU admission

(HR 2.29, 95% CI 1.29-3.86; p=0.004) (Table 5)

Discussion

In our study in patients with SARS-CoV-2-related respiratory failure managed outside the ICU setting, PP was used mainly in presence of severe respiratory failure and reduced bulk of comorbidities. PP was not associated with the risk of death or ICU admission in the overall study population and after propensity score matching; PP was an independent predictor of ICU admission.

PP is an established evidence-based practice in patients with non COVID-19-related ARDS undergoing invasive mechanical ventilation[18]. In this setting, PP has been shown to effectively reduce lung shunting, thanks to improvements in ventilatory homogeneity and relatively constant perfusion patterns[19]. PP decreases the pleural pressure gradient between dependent and non-dependent lung regions as a result of gravitational effects and conformational shape matching of the lung to the chest cavity. This is believed to generate more homogenous lung aeration and strain distribution, thus enhancing recruitment of dorsal lung units[20]. However, a recent study in 20 COVID-19 critically ill patients assisted by NIV in ICU showed that PP improved oxygenation with the counterbalance of a greater thickening diaphragmatic fraction compared to supine position. These results suggest an increase in inspiratory effort during PP[21].

Overall, these data suggest that despite PP initially improves oxygenation, it may produce controversial effects in terms of respiratory effort.

In our study outside the ICU, PP was used in about 20% of the patients, more commonly in patients with severe respiratory failure. In this view, it should be taken into account that during the COVID-19 pandemia a role for PP was advocated in patients with non-severe respiratory failure to improve oxygenation and potentially relieve dyspnea[22]. However, when PP is used in patients with respiratory failure, it can be not well tolerated due to the discomfort related to increased abdominal pressure, to devices for respiratory support and panic. Moreover, for older patients with spondylopathies PP may produce pain that reduces compliance. These issues are particularly relevant in awake patients and can be partially faced by sedation or analgesia but may finally reduce PP standardization. It is conceivable that in these patients the benefit of improved oxygenation is overcome by the increase in respiratory effort.

In our study, we were not able to show a clinical benefit in terms of reduction in mortality or ICU admission by the use of PP neither in the overall population and nor after propensity score matching. Propensity score matching method was used to balance patients' characteristics between patients managed with and without PP. Recent randomized studies confirmed a clinical benefit of PP in intubated COVID-19 patients[23] and in awake patients at early stages of respiratory failure requiring HFNO[24]. However, it should be noted that the mean age of patients included in these studies is more than 10 years lower than that of patients included in our study. Overall, these data suggest that PP may have a role in otherwise 'fit' non-old patients with mild respiratory failure. In patients with severe respiratory failure treated with NIV it is debated whether PP may delay appropriate intubation. For these reasons, awake PP should be proposed to selected patientswith the caution not to delay appropriate intubation and not to increase respiratory effort. When tolerance is not obtained with mild sedation either interruption of PP or endotracheal intubation should be considered. Previous studies suggested a role of PP in reducing mortality in severe ARDS requiring mechanical ventilation[25]. However, PP seems of clinical benefit when it lasts for at least 12 hours daily. Maintaining PP for 12 hours in awake patients maybe problematic and may increase anxiety and work of breathing. In our study 64 patients (79,7% of those receiving PP) required sedation to maintain PP. Whether sedation is effective in reducing the work of breathing and self-induced lung injury remains to be defined[26]. As an additional issue, either improved oxygenation and sedation may both contribute to delay protective intubation. In fact, criteria to upgrade to intubation in patients treated with sedation, NIV and PP are undefined. Finally, overall clinical judgement has a pivotal role as PP can help also Do Not Reanimate patients to overcome the critical phase of COVID-19 pneumonia and to relief dyspnea if well tolerated. As for today, whether awake PP may reduce the rate of death or progression to ICU admission in all COVID-19 patients with respiratory failure remains controversial.

PP may also play a role in reducing systemic inflammation by increasing alveolar fluid drainage. Inflammatory responses related to ARDS or secondary to ventilator-induced lung injury may be attributed

to pulmonary and extra-pulmonary organ dysfunction and strategies to reduce inflammation was shown lead to increased survival[27].

In our study age, the severity of respiratory failure and the use of NIV were associated with increased risk for death or ICU admission. While the role of age and severity of respiratory failure as predictors is intuitive and plausible, the role of NIV in the management of patients with COVID-19 pneumonia is controversial[28]. The use of positive end-expiratory pressure via NIV in the management of ARDS prevents alveolar derecruitment but may also result in overdistension of previously well-ventilated alveoli[29]. The overall in-hospital mortality of patients treated with NIV outside the ICU was shown to be as high as 36% in COVID-19 patients[28]. Mortality in COVID-19 patients may be related to higher incidences of barotrauma and ventilator-induced lung injury. With this purpose, the use of protective ventilation may result in clinical benefit. In addition to ventilator induced lung injury, the use of NIV may delay appropriate intubation as it is the case for PP.

As it is common in studies in patients with COVID-19 also including DNR patients[30], ICU admission was a component of the primary outcome ICU admission is an operator- and resource-dependent outcome. In our study clinical severity as assessed by the qSOFA was a predictor of death despite it was not a predictor of ICU admission. PP was associated with ICU admission in the overall study population as well as in the propensity score matching analysis.

Our study has several limitations. First, PP was not uniformly performed in all patients mainly concerning the duration and this may limit the generalizability of our results. Second, the ventilation strategy was left at the discretion of the treating physicians. Third, the use of qSOFA instead of a specific risk-scoring system for COVID-19 is not routine practice. However, qSOFA is made of simple, rapid and practical items that makes it widely used for risk stratification in critically ill patients[12]. Our study has also some strengths, mainly related to the large sample size and the possibility to perform a propensity score matching analysis.

Conclusion

In conclusion PP seems not to be associated with clinical benefit when used outside the ICU in patients with severe respiratory failure related to COVID-19 pneumonia. Randomized studies are required to definitively assess the clinical benefit of PP in awake and non-intubated patients with SARS-CoV-2-related respiratory failure.

Abbreviations

ARDS (severe acute respiratory distress syndrome),

CPAP (continuous positive airway pressure), HFNO (High-flow nasal oxygen),

ICU (Intensive Care Unit),

PaCO2 (partial pressure of arterial carbon dioxide),

PaO2(partial pressure of arterial oxygen),

ratio of partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen (FiO2) (PaO2/FiO2),

PP (prone positioning),

RT-PCR (real time-Polymerase Chain Reaction),

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2).

Declarations

Acknowledgements:

Not applicable.

Authors' contributions

CB, MG, and LG conceived and designed the study; GB,AF,KS, FC,GN CS and MG contributed in data management; CB,MG and GM collected and analysed the data.

CB and MG contributed in data analysis, interpretation of the data and drafting the manuscript. All authors read and approved the fnal manuscript.

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Availability of data and materials

The dataset used and/or analysed during the current study is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the local Ethic review boards (Comitato Etico Regione Umbria, University of Perugia, protocol n. 20-05 SARS-CoV2).

According to local regulations, the need for informed consent from individual patients was waived owing to the retrospective and observational nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Characteristics of study patients overall and by use of prone positioning

Characteristic	Patients		
	Overall Study patients (N=536)	PP	
		YES (N=114)	NO (N= 422)
Age, mean±SD	69±15 (17-98)	63.2±13	70.4 ±15
Male, no. (%)	334(62.3%)	86 (75.4%)	174 (41.2%)
PaO2/FiO2 categories			
PaO2/FiO2,mean±SD	260 ±95	225 ±78	270±97
>300 mmHg	182 (34.6%)	19 (16.7%)	163 (38.7%)
300-200 mmHg	215 (40.1%)	55 (48.2%)	160 (38.0%)
200-100 mmHg	110 (20.5%)	31 (27.2%)	79 (18.8%)
<100 mmHg	28 (5.2%)	9 (7.9%)	19 (4.5%)
Comorbidities			
COPD, no(%)	63 (11.8%)	7 (6.1%)	56 (13.3%)
Diabetes, no.(%)	104 (19.4%)	17 (15.0%)	87 (20.6%)
Systemic hypertension, no. (%)	299 (55.8%)	66 (57.9%)	233 (55.2%)
Cardiovascular disease, no. (%)	178 (33.2%)	26 (22.8%)	152 (36.0%)
Cerebrovascular disease, no. (%)	54 (10.1%)	6 (5.3%)	48 (11.4%)
Chronic Kidney disease, no. (%)	49 (9.1%)	5 (4.4%)	44 (10.4%)
Cancer, no. (%)	70 (13.1%)	11 (9.6%)	59 (14.0%)
N°of comorbitidies,no.(%)			
0	153(28.5%)	43 (37.7%)	110(26.0%)
1-2	236 (44.1%)	48 (42.1%)	188 (44.5%)
>2	147 (27.4%)	23 (20.2%)	124 (29.4%)
NIV, no. (%)	187 (34.9%)	81 (71.0%)	106 (25.1%)
qSOFA (n=419)			
0 items	232 (43,2%)	49 (43.0%)	183 (43.3%)
1 item	162 (30.2%)	127 (89.7%)	35 (8.29%)
2 items	20 (3,7%)	19 (16.6%)	1 (0.2%)

3 items	4 (0.7%)	2 (1.7%)	2 (0.4%)

SD= standard deviation, COPD= chronic obstructive pulmonary disease.

Table 2. Independent predictors of clinical course at 30 days in the overall study population

Table 3. Multivariable analyses for predictors of clinical course at 30 days in specific patient

Table 4. Multivariable analyses for predictors of clinical course at 30 days in patient who underwent PP (n=114)

Table 5. Characteristics of the Patients After Propensity Score Matching

Figures

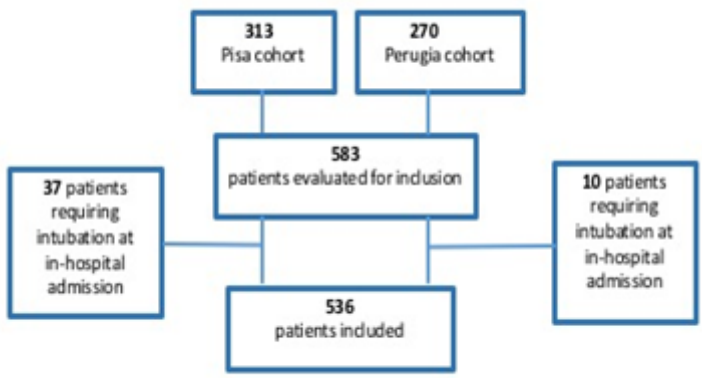

Figure 1

Study Flow Diagram

		HR	95% CI		p value
			Lower limit	Upper limit	
In Hospital death or Intensive care unit admission					
Age per year		1.03	1.02	1.05	<0.001
Gender,male		0.83	0.59	1.18	0.318
Comorbitidies ³ 1		1.22	0.78	1.90	0.373
PaO2/FiO2	>300 mmHg	Ref	--	--	--
	300-200 mmHg	1.38	0.85	2.24	0.191
	200-100 mmHg	2.59	1.57	4.28	<0.001
	<100 mmHg	4.08	2.17	7.67	<0.001
NIV		1.45	1.01	2.10	0.043
Prone positioning		1.17	0.78	1.74	0.440
qSOFA	0	ref	--	--	
	1	1.60	0.88	2.93	0.122
	Unknown	0.90	0.60	1.32	0.587
In Hospital death					
Age per year		1.07	1.05	1.09	<0.001
Gendere, male		0.75	0.51	1.11	0.152
Comorbitidies	³ 1	1.42	0.80	2.50	0.225
PaO2/FiO2	>300 mmHg	Ref	--	--	--
	300-200 mmHg	1.33	0.78	2.35	0.306
	200-100 mmHg	2.43	1.38	4.28	0.002
	<100 mmHg	3.96	1.93	8.13	<0.001
NIV		1.50	0.98	2.28	0.057
Prone positioning		1.01	0.61	1.67	0.952
qSOFA	0	ref	--	--	
	1	1.94	1.07	3.51	0.028
	Unknown	0.77	0.48	1.23	0.275
ICU admission					

Age per year		0.98	0.96	1.00	0.180
Gender,male		1.03	0.57	1.85	0.916
Comorbitidies ³ 1		1.40	0.75	2.61	0.278
PaO2/FiO2	>300 mmHg	Ref	–	–	–
	300-200 mmHg	1.11	0.51	2.41	0.779
	200-100 mmHg	1.55	0.68	3.54	0.290
	<100 mmHg	1.89	0.70	5.06	0.203
NIV		3.16	1.61	6.19	0.001
Prone positioning		2.31	1.35	3.95	0.001

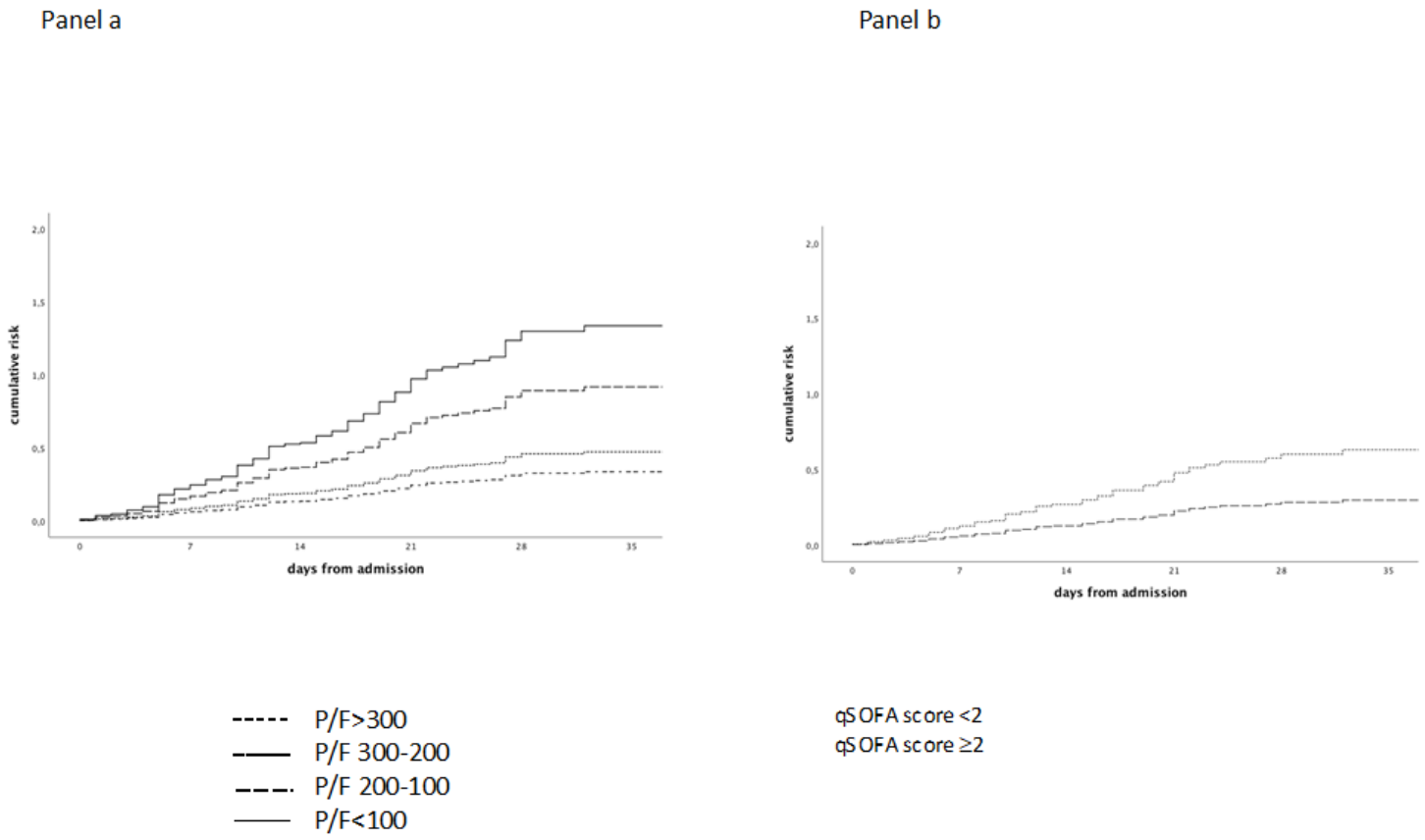

Figure 2

Risk of death or ICU admission by severity of respiratory failure (panel a) and by clinical severity (panel b)

	HR	95% CI		p value
		Lower limit	Upper limit	
In Hospital death or Intensive care unit admission in patients in ARDS at admission (n= 353)				
Age per year	1.03	1.02	1.05	<0.001
PaO2/FiO2 300-200 mmHg	ref	–	–	–
200-100 mmHg	1.94	1.33	2.82	<0.001
<100 mmHg	2.97	1.76	4.99	<0.001
NIV	1.22	0.83	1.78	0.313
Proning	1.07	0.70	1.65	0.745
qSOFA 0	ref			
1	1.61	0.86	3.04	0.137
unknown	0.80	0.52	1.23	0.316
In Hospital death in patients in ARDS at admission (n= 353)				
Age per year	1.07	1.05	1.09	<0.001
PaO2/FiO2 300-200 mmHg	ref	–	–	
200-100 mmHg	1.85	1.21	2.83	0.005
<100 mmHg	2.76	1.52	5.02	<0.001
NIV	1.39	0.90	2.15	0.134
Proning	1.01	0.60	1.73	0.960
qSOFA 0	ref			
1	1.99	1.07	3.70	0.030
unknown	0.77	0.46	1.27	0.304
In Hospital death or Intensive care unit admission in patients with qSOFA available (n= 418)				
Age per year	1.04	1.02	1.05	<0.001
PaO2/FiO2 >300 mmHg	Ref	–	–	–
300-200 mmHg	1.58	0.90	2.77	0.112
200-100 mmHg	3.32	1.88	5.89	<0.001
<100 mmHg	5.09	2.54	10.22	<0.001
qSOFA 0	ref	–	–	
1	1.63	0.89	2.99	0.111

NIV		1.31	0.87	1.97	0.185
Proning		1.21	0.77	1.90	0.400
In Hospital death in patients with qSOFA available (n= 419)					
Age per year		1.07	1.05	1.09	<0.001
PaO2/FiO2	>300 mmHg	Ref	–	–	–
	300-200 mmHg	1.35	0.73	2.49	0.334
	200-100 mmHg	2.82	1.53	5.19	<0.001
	<100 mmHg	3.65	1.69	7.92	<0.001
qSOFA	0	ref	–	–	–
	1	2.12	1.17	3.86	0.013
NIV		1.33	0.85	2.10	0.216
Proning		1.22	0.71	2.09	0.462

		HR	95% CI		p value
			Lower limit	Upper limit	
In Hospital death or Intensive care unit admission					
Age per year		1.01	0.99	1.04	0.286
PaO2/FiO2	300-200 mmHg	0.46	0.15	1.34	0.156
	200-100 mmHg	0.87	0.32	2.30	0.777
	<100 mmHg	1.39	0.44	4.34	0.569
NIV		3.20	1.13	9.06	0.003
qSOFA	0	Ref.	–	–	–
	1	2.60	0.30	22.13	0.382
	Unknown	2.66	0.42	2.50	0.935
In Hospital death					
Age per year		1.05	1.01	1.09	0.003
PaO2/FiO2	300-200 mmHg	0.76	0.18	3.28	0.719
	200-100 mmHg	0.96	0.25	3.69	0.952
	<100 mmHg	2.68	0.58	12.2	0.203
NIV		2.95	0.65	13.39	0.161
qSOFA	0	Ref.	–	–	–
	1	1.55	0.16	14.8	0.706
	Unknown	0.46	0.10	2.08	0.313
ICU admission					
Age per year		0.99	0.97	1.04	0.130
PaO2/FiO2	300-200 mmHg	1.21	0.60	2.63	0.626
	200-100 mmHg	1.85	0.81	4.20	0.143
	<100 mmHg	2.36	0.88	6.30	0.085
NIV		3.85	1.98	7.47	<0.001
qSOFA	0	Ref.	–	–	–
	1	0.44	0.06	3.37	0.434
	unknown	1.20	0.68	2.12	0.519

Variables	PP (No.114)	no PP (No.114)	Standardized difference
Age	63.29	63.22	0.054
Males, n (%)	24	27	0.061
P/F >300, n (%)	66	17	0.023
P/F 300-200, n (%)	48	47	0.017
P/F 200-100, n (%)	27	27	0.000
P/F <100, n (%)	7	7	0.000
Comorbitidies ³ 1, n (%)	62	64	0.036
NIV, n (%)	71	72	0.038
Primary and Secondary Outcomes After Propensity Score Matching			
	HR	**95% CI**	**p value**
		Lower limit **Upper limit**	
In Hospital death/ICU	1.33	0.83 2.14	0.193
In-hospital death	1.26	0.70 2.20	0.403
ICU admission	2.29	1.29 3.86	0.003