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Study of Prone Positioning to Reduce Ventilator-Associated Pneumonia in Hypoxemic Patients

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Abstract

Question of the study: Whether prone positioning (PP) affects ventilator associated-pneumonia (VAP) and mortality in patients with acute lung injury/adult respiratory distress syndrome.

Patients and methods: 2409 prospectively included patients admitted over 9 years (2000-2008) to 12 French ICUs (OUTCOMEREA®), who required invasive mechanical ventilation (MV) and had PaO_2/FiO_2 ratios <300 during the first 48 hours. Controls were matched to PP patients on the PP propensity score (±10%), MV duration ≥ that in PP patients before the first turn prone, and centre.

Results: VAP incidence was similar in the PP and control groups (24 vs. 13 episodes/1000 patient-days of MV, respectively; *p*=0.14). After adjustment, PP did not decrease VAP occurrence (hazard ratio, 1.64; 95%CI, 0.70-3.84; *p*=0.25) but significantly delayed hospital mortality (HR, 0.56; 95%CI, 0.39-0.79; *p*=0.001), without decreasing 28-day mortality (37% in both groups). Post hoc analyses indicated that PP did not protect against VAP but, when used for >1 day, might decrease mortality and benefit the sickest patients (SAPSII >50).

Answer: In ICU patients with hypoxemic acute respiratory failure, PP had no effect on the risk of VAP. PP delayed mortality without decreasing 28-day mortality. PP for longer than 1 day might decrease mortality, particularly in the sickest patients.

Keywords: acute lung injury, prone position, ventilator-associated pneumonia, mortality.

INTRODUCTION

Nosocomial infections adversely affect patient outcomes, increase healthcare costs, and generate difficult diagnostic and therapeutic challenges [1]. In the intensive care unit (ICU), ventilator-associated pneumonia (VAP) is the most common nosocomial infection, with 8% to 28% of patients on endotracheal mechanical ventilation (MV) being affected [2]. Mortality rates in patients with VAP have ranged from 24% to 50% [3]. Injured lungs are highly susceptible to infection, and acute respiratory distress syndrome (ARDS) is associated with a high rate of VAP [4-6]. Prone positioning (PP) has been used to improve oxygenation [7]. Despite the lack of conclusive evidence that PP improves patient outcomes, PP is used in hypoxemic patients receiving MV for ARDS. No data are available on the rate of PP use in this population, even in the largest recent epidemiological studies [8, 9].

In addition to improving oxygenation, PP was shown in experimental studies to diminish ventilator-induced lung injury [10], and most clinicians agree that turning patients prone improves secretion drainage [11, 12]. Whether these effects protect against VAP is unclear. On the one hand, PP has been shown to enhance alveolar recruitment by avoiding atelectasis [13], which facilitates lung infection in experimental studies [14]; but on the other hand, PP may increase the dissemination of lung pathogens. In randomized controlled trials of PP in patients with ALI/ARDS, VAP rates are inconsistently reported [15] and, when available, vary across studies. Thus, in a study of 136 patients with severe ARDS, PP had no effect on VAP rates [16]; whereas in another study, conducted in 791 patients with hypoxemic acute respiratory failure, VAP was slightly but significantly less common with PP [17].

The primary objective of this study was to clarify the effect of PP on VAP rates in ICU patients with ALI/ARDS. To this end, we used a large prospective database of ICU patients. We also compared mortality with and without PP.

MATERIALS AND METHODS

Study Design and Data Source

We conducted a prospective observational study in the French OUTCOMEREA multicentre database over an 8-year period (2000-2008). The database is specifically designed to record daily disease severity and the occurrence of iatrogenic events and nosocomial infections [1, 17-21]. Inclusion criteria for the study were MV for at least 2 days, started within 48 hours after ICU admission, with a PaO_2/FiO_2 ratio of 300 or less during the first 2 days of MV with bilateral infiltrates with classic absence of clinical evidence of left atrial hypertension according to each ICUs'protocol. Patients ventilated at least once with PP (PP group) were compared to patients who were never turned prone while on MV (supine positioning [SP] group).

Data collection

Senior physicians in each participating ICU collected data daily. For each patient, the investigator entered the data into a computer case-report form using data capture software (RHEA,® Rosny-sous-Bois, France) and imported all records to the OUTCOMEREA® data warehouse. Data collection was approved by the Clermont Ferrand ethics committee. The database is registered with the C.N.I.L., an independent French administrative authority protecting privacy and personal data. All codes and definitions were established prior to study initiation. The following information was recorded for each patient: age and sex, admission category (medical, scheduled surgery, or unscheduled surgery), origin (home, ward, or emergency room), and McCabe score [22]. Severity of illness was evaluated on the first ICU day using the Simplified Acute Physiology Score (SAPS II) [23], Sepsis-related Organ Failure Assessment (SOFA) score [24], and Acute Physiologic and Chronic Health Evaluation (APACHE) II score [25]. Knaus scale definitions were used to record pre-existing chronic

organ failures including respiratory, cardiac, hepatic, renal, and immune system failures [25].

Patient characteristics, treatment modalities (including MV, position, inotropic agents, and antimicrobials), and invasive and non-invasive procedures were collected daily. MV duration, time in the ICU and hospital, and outcome at ICU and hospital discharge were recorded prospectively. Clinically suspected nosocomial pneumonia was routinely investigated using cultures of protected distal specimens, protected brushing, or bronchoalveolar lavage, as previously described [2, 18].

Quality of the database

The data-capture software automatically conducted multiple checks for internal consistency of most of the variables at entry into the database. Queries generated by these checks were resolved with the source ICU before incorporation of the new data into the database. At each participating ICU, data quality was controlled by having a senior physician from another participating ICU check a 2% random sample of the study data.

Procedures

Because diagnostic coding has been found unreliable for identifying ALI/ARDS cases [26], we used parameters collected by our data-capture software to select patients with ALI/ARDS (PaO_2/FiO_2<200 or 300). All ICUs followed the same rules for initiating MV. In patients receiving MV, tidal volume was set to maintain a plateau pressure below 30 cm H_2O in most patients and no greater than 35 cm H_2O in all patients. PP (strictly horizontal) was left at the discretion of the attending physician. In all ICUs, PP protocols involved remaining prone for more than 6 hours per day. In both groups, SP consisted in semi-recumbency, unless the patient had refractory shock. Administration of stress ulcer prophylaxis and enteral feeding were at the discretion of the attending physician. None of the study ICUs used selective digestive tract decontamination or continuous aspiration of subglottic secretions.

Statistical Analysis

Results are expressed as median (interquartile range) or n (%) as appropriate. For categorical variables, comparisons were based on chi-square tests for categorical data and Wilcoxon tests for continuous data.

Since the use of PP was not randomly assigned, we developed a PP prediction model to compute a PP propensity score, which we then used to match patients managed with PP to controls managed with SP only. This matching procedure minimized treatment selection bias and potential confounding. The rationale and methods underlying the use of a propensity score for a proposed causal exposure variable have been described elsewhere [19, 27]. The propensity score (probability that each patient would receive PP at any time during the ICU stay) was calculated by multivariate logistic regression using predictive variables collected within 48 hours after ICU admission in the overall population.

Using an algorithm (available at http://www.outcomerea.org/ehtm/matchmacro.pdf), we matched each control to a PP patient on three characteristics (Figure 1): PP propensity score (±10 %), MV duration equal to or greater than MV duration in the PP patient before the first turn prone, and centre. The propensity score was based on risk factors for PP. To take risk factors for VAP into account, we adjusted on imbalances between groups and risk factors for VAP. We then adjusted on the following: at admission, male sex, pneumonia, septic shock, acute respiratory failure, and coma; within 48 hours after ICU admission, vasoactive drugs; and on the day before PP (or the corresponding day in the SP group), antibiotic use, at least one catheter, SOFA score, and PaO2/FiO2 ratio (Table 4).

Assuming a 50% rate of VAP in the PP group, 200 PP patients and 200 matched controls managed with SP only were needed to detect a hazard ratio (HR) of 2 for VAP with greater than 90% power and a type I error risk of 0.05.

Imbalances between groups after matching were tested by conditional logistic regression. Comparisons between matched patients were based on a Cox model. The time of

origin (T0) was defined as the beginning of PP in exposed patients and the equivalent time in matched controls (Figure 1). Only cases of pneumonia occurring between T0 and 48 hours after MV discontinuation were considered. Data were censored at 28 days (starting at T0). Deaths within 28 days after T0 were taken into account. We used Kaplan-Meier plots to evaluate the risk of VAP and death in each group.

Risk factors for VAP and parameters that were not balanced between the PP and SP groups were used to estimate the adjusted HR of VAP using a marginal Cox model for clustered data. This model both takes into account the censored nature of the data and accounts for intra-cluster (intra-pair) dependence using a robust sandwich covariance estimate [28]. Values of $p \leq 0.05$ were considered significant. Analyses were computed using the SAS 9.1 software package (SAS Institute, Cary, NC). Survival curves were drawn using R (R Foundation, Vienna, Austria).

RESULTS

A. Overall population of the database

The study flow chart is shown in Figure 2. Of 2409 included patients, 201 (8%) received PP. Risk factors for VAP, selected based on data in the literature [2] and OUTCOMEREA® database, were male sex, pneumonia diagnosis at admission, chronic respiratory failure, acute respiratory failure at admission, septic shock at admission, use of vasoactive agents within the first 48 hours in the ICU, temperature, heart rate, PaO_2/FiO_2 ratio, and the need for an arterial catheter.

VAP occurred in 414/2208 (19%) SP patients and 90/201 (45%) PP patients. Median duration of PP use was 1 day [1-3]. PP was significantly associated with longer MV duration compared to SP (19 days [8-35] vs. 7 days [4-13], $p<0.0001$), longer time in the ICU (25 days [11-39] vs. 10 days [5-17], $p<0.0001$), and longer time in the hospital (41 [18-68] vs. 24 [12-

43], $p<0.0001$). Mortality was higher in the PP group (95 (47%) vs. 777 (35%) hospital deaths, $p=0.0006$).

Risk factors for PP in the overall population of 2409 patients are listed in Table 1. Predictors of PP at the final step of the multivariate logistic model (Table 2) were male sex, coma, hemorrhagic shock, at least one catheter, core temperature ≥38.2°C, heart rate ≥120/min, prothrombin time ≤65 s, and PaO_2/FiO_2 ratio range within the first 48 hours in the ICU. Matching on propensity score, severity, and centre was successful for 199 PP and 199 SP patients.

B. Case-control analysis

Parameters that were not balanced between the SP and PP groups (Table 3) were as follows: (a) at ICU admission, pneumonia, septic shock, acute respiratory failure, coma, and lowest PaO_2/FiO_2 ratio; (b) during the first 48 hours of MV, use of vasoactive agents and use of at least one catheter; and (c) on the day before PP (or the corresponding day in the SP group), use of antibiotics, use of at least one catheter, lowest PaO_2/FiO_2 ratio, and SOFA score. The median time from ICU admission to PP was 6 days [2-12]. The median time spent in the ICU after T0 was longer in the PP group than in the SP group (14 [6-29] days vs. 3 [1-8] days, $p<0.0001$).

B1. Risk of VAP

There were 57 episodes of VAP after T0. The incidence of VAP after T0 was not significantly different between the PP and SP groups (24 vs. 13 episodes/1000 patient-days of MV, $p=0.14$). The most common causative microorganisms were *Pseudomonas aeruginosa* (n=20; 35%), Enterobacteriaceae (n=12, 21%), *Escherichia coli* (n=10, 18%), and *Staphylococcus aureus* (n=9, 16%). The rate of multidrug-resistant bacteria was balanced between the two groups.

PP did not influence the VAP risk (HR, 1.33; 95%CI, 0.61-2.92; *p*=0.48). Results (Table 4) were unchanged after adjusting on risk factors for VAP and imbalances between groups (HR, 1.64; 95%CI, 0.70-3.84; *p*=0.25) (Figure 3).

We assessed the impact of PP duration by separately evaluating patients in each quartile of time with PP. Among 109 patients with a single day of PP (with 109 matched SP patients), PP was not associated with VAP (HR, 1.11; 95%CI, 0.39-3.10; *p*=0.85). Neither did the 90 patients with at least 2 days of PP have a lower rate of VAP compared to the 90 matched SP patients (HR, 0.72; 0.32-1.65; *p*=0.44).

B2. Mortality

When we used the marginal Cox model with adjustment on risk factors for hospital death and imbalances between groups, we found that PP significantly delayed hospital mortality (HR, 0.56; 95%CI, 0.39-0.79); *p*=0.001) (Figure 4 and Table 4). However, mortality 28 days after T0 was similar in the PP group (n=73, 36.7%) and in the SP group (n=74, 37.2%). Among patients with a single day of PP (n=109), mortality was not different from that in the matched controls (HR, 0.83; 95%CI, 0.51-1.35; *p*=0.45). In contrast, adjusted mortality in the 90 patients with at least 2 days of PP was significantly lower than in the matched controls (n=27 [30%] in the PP group vs. n=38 [42%] in the controls; HR, 0.30; 95%CI, 0.12-0.74; *p*=0.009).

B3. ARDS patients (PaO_2/FiO_2<200)

When we confined the analysis to patients with PaO_2/FiO_2 ratios less than 200 at admission (i.e., ARDS), we were able to obtain 155 PP-control pairs matched on the PP propensity score, severity, and centre. In this analysis, PP was not associated with the VAP

risk (adjusted HR, 1.03; 95%CI, 0.42-2.56; *p*=0.94) or the risk of death (adjusted HR, 0.90; 95%CI, 0.61-1.32; *p*=0.58).

B4. Subgroup analyses

In the overall population of 398 ALI/ARDS patients (Table 5), 104 patients had PaO_2/FiO_2 ratios less than 120 within 2 days before PP (or the corresponding time in the control group). Among them, 72 received PP and 32 were controls. VAP occurred in 20 (27.8%) PP patients and 2 (6.3%) controls. Of the PP patients, 32 (44.4%) died, compared to 20 (62.5%) controls. After adjustment on imbalances between groups and risk factors for events, PP was associated neither with VAP (HR, 0.69; 95%CI, 0.19-2.52; *p*=0.57) nor with death (HR, 0.56; 95%CI, 0.29-1.09); *p*=0.09).

Among 114 patients with SAPSII score values greater than 50 on the day of the first turn prone (or the corresponding day in controls), 64 received PP and 50 were controls. VAP occurred in 11 (17%) PP patients and 1 (2%) control. Of the PP patients, 41 (64%) died, compared to 39 (78%) of the controls. After adjustment on imbalances between groups and risk factors for events, PP was not associated with VAP (HR, 4.33; 95%CI, 0.70-26.65; *p*=0.11) but was significantly and negatively associated with hospital death (HR, 0.44; 95%CI, 0.29-0.69; *p*=0.0003) (Table5).

DISCUSSION

We found that PP was used in 8% of ALI/ARDS patients with PaO_2/FiO_2 ratio values lower than 300 while receiving MV. In the overall population, PP failed to protect against VAP or death.

Although PP was described more than 30 years ago [29], very few data are available on the rate of PP use outside the setting of physiological studies or randomized controlled trials. In a study describing the management of ARDS over an 8-year period in a single ICU, PP was used in 4% of ARDS patients during the first half of the study period and in 25% during the second half after routine PP use in the sickest patients was incorporated into the standard management protocol [30]. These proportions are consistent with our finding that 8% of patients were turned prone at least once during the ICU stay.

Numerous physiological and clinical studies have shown that PP improves oxygenation [7] by homogenizing the pleural pressure gradient and increasing ventilation to the dorsal areas of the lungs. PP may also reduce lung overdistension [31] and improve alveolar ventilation and lung mechanics, thereby preventing or lessening ventilator-induced lung injury [10]. In addition, PP improves secretion drainage, which is often impaired in intubated patients. These effects would be expected to translate into a decreased risk of VAP [12].

The VAP rate was a secondary evaluation criterion in three randomized controlled trials comparing PP and SP [16, 17, 32]. Only one of these trials found that PP protected against VAP as a secondary endpoint [17]. Another study [32] evaluated the effect of PP on the lung injury score and on the development of VAP as a secondary criterion in 51 comatose patients receiving MV. Patients in the treatment group were turned prone for 4 hours once a day, starting early during the ICU stay. The diagnosis of VAP relied on quantitative cultures from bronchoscopic protected-specimen-brush samples. In this relatively small study, PP was

associated with less deterioration in the lung score, but VAP rates were not significantly different between groups (20% with PP vs. 38% with SP, p=0.14) [32]. In addition, patients kept supine had their head and trunk elevated at 20° instead of being placed in the semi-recumbent position (at least 30° of head-of-bed elevation). The other study that found no effect of PP on the VAP rate was conducted in 136 patients with severe ARDS [16]. PP was started early and used for most of the day. There was no difference in VAP rates between the PP and SP groups. In the largest study (n=791), PP did not affect mortality but decreased the rate of VAP [17]. This study included medical and surgical patients with acute hypoxemic respiratory failure. PP was started early after intubation and used for a mean of 8.6 h/days for a mean of 4.1 days. The diagnosis of VAP was based on quantitative cultures of bronchoalveolar lavage fluid. The VAP rate per 100 patient-days of intubation was 1.66 with PP and 2.14 with SP (p=0.045).

The 21% VAP rate in our cohort of 2409 patients is consistent with previous data [2]. The VAP incidence rate of 24/1000 MV days in our PP group is only slightly higher than the rate in PP patients in the largest randomized controlled study [17], and crude mortality rates are similar (31% and 36%, respectively). However, the prevalence of VAP in our study was lower than hypothesized, which decreased the power of the study.

PP duration in our study was considerably shorter, than in previous studies probably because no uniform PP protocol was used. However, our data shed light on outcomes in everyday practice. We identified several risk factors for PP: admission diagnosis of ARDS or pneumonia, shock at admission, vasoactive drug use, low PaO_2/FiO_2 ratio, and prolonged MV.

PP is widely believed to improve bronchial secretion drainage, thereby limiting colonization of the distal lung, an effect expected to decrease the risk of VAP. However, other effects of PP may increase the risk for VAP. Once patients are turned prone, they are in the

horizontal position, which may be associated with a higher risk of aspiration than the semi-recumbent supine position [33], particularly in patients receiving enteral feeding [34]. PP has also been associated with greater residual gastric volumes and poorer tolerance of enteral nutrition, which in turn are associated with a higher risk of VAP [35]. Data from a *P. aeruginosa* unilateral pneumonia mouse model suggest that PP may promote the dissemination of localized infection to the contralateral lung [36]. Finally, the influence of PP on the VAP risk may vary with the timing of PP relative to MV initiation. When PP is started more than 3 days after MV initiation, the distal airways may already be colonized [37, 38] and, therefore, potential benefits from improved secretion drainage may be lost.

Although PP dramatically increased oxygenation in severely hypoxemic patients [15-17, 37, 39-41], no effect on mortality was found in randomized controlled trials. Similarly, our results do not support the routine use of PP in patients on MV whose PaO_2/FiO_2 ratio is less than 300. Furthermore, they suggest that a longer time spent prone does not increase the incidence of VAP. That PP does not affect mortality may be ascribable to the major contribution of sepsis and multiorgan failure to mortality in ARDS patients, as opposed to respiratory disease [42] the use of unproven rescue treatments (inhaled nitric oxide or prone position) may be use as a rescue therapy in patients with refractory hypoxemia [15, 39, 42].

Interestingly, post hoc subgroup analyses done by Gattinoni et al [15] identified a subgroup in which PP was associated with a significant decrease in 10 day mortality. This subgroup was defined by $PaO_2/FiO_2 \leq 88$ mm Hg, SAPS II >49, and tidal volume of 12 ml/kg. In our study, PP for more than 2 days was associated with significantly lower hospital mortality in patients with SAPS II >50 on the first day of PP. There was also a trend toward a decreased mortality in with PaO_2/FiO_2 <120 mm Hg (Table 5) corresponding to the quartile of patients with the lowest values in the initial study group (table 3). We did not study tidal volume because high volumes such as those reported by Gattinoni et al [15] have not been

used in our ICUs for over 10 years. Altogether, these data suggest that PP may be helpful in patients whose acute illness is very severe. Furthermore, they are consistent with a recently published meta-analysis showing that beyond the increase of PaO_2/FiO_2 PP may improve survival in patients with greater severity of the acute illness [43] may be through other mechanisms. Furthermore the fact that PP decreased mortality in this group may also suggest that we should use it for a longer period of time independently on the effect of its beneficial effect on gas exchange.

Our study has several limitations. The presence of absence of radiographic pulmonary infiltrates was not specifically recorded in the database. However, we performed a survey of all the 12 participating centers to insure that they all use this specific classic characteristics of ALI/ARDS. There is no consensus regarding the criteria for using PP or the optimal duration of PP. In addition, a possible centre effect was taken into account by including the centre in the propensity score.

In conclusion, our prospective multicenter cohort study suggests that the use of PP is not superior to SP to prevent VAP. However, PP may improve survival in longer PP use and in the sickest patients (SAPS II >50).

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Table 1. Risk factors for prone positioning in 2409 patients who received endotracheal mechanical ventilation within 48 h after ICU admission, for at least 2 days, and who had PaO_2/FiO_2 ratios less than 300 during the first 48 h on mechanical ventilation

Variables	Supine (n=2208)	Prone (n=201)	*p* value
Age	66 [54 - 76]	65 [50 - 75]	0.04
Male sex	1411 (63.9)	150 (74.6)	0.002
Transfer from ward	1055 (47.8)	112 (55.7)	0.03
Severity scores at admission			
SAPS II	52 [40 - 64]	51 [40 - 65]	0.85
APACHE II score	20 [15 - 25]	20 [15 - 25]	0.64
SOFA score	7 [5 - 10]	7 [5 - 11]	0.79
Immunosuppression			
Chemotherapy	138 (6.3)	10 (5)	0.47
Steroid therapy >1 month or >2 mg/kg	82 (3.7)	11 (5.5)	0.22
AIDS	45 (2)	2 (1)	0.31
Bone marrow aplasia	33 (1.5)	4 (2)	0.59
Diagnosis at admission			
Pneumonia	450 (20.4)	63 (31.3)	0.0003
Septic shock	249 (11.3)	31 (15.4)	0.08
Cardiac arrest	181 (8.2)	4 (2)	0.002
Acute respiratory failure	130 (5.9)	24 (11.9)	0.001
Stroke	124 (5.6)	7 (3.5)	0.20
Acute renal failure	94 (4.3)	3 (1.5)	0.06
COPD exacerbation	78 (3.5)	5 (2.5)	0.44
Cardiogenic pulmonary oedema	66 (3)	5 (2.5)	0.69
Multiple organ failure	34 (1.5)	7 (3.5)	0.04
Admission category (missing for 8 pts)			
Medical	1562 (71)	135 (67.5)	
Emergency surgery	406 (18.4)	36 (18)	0.23
Scheduled surgery	233 (10.6)	29 (14.5)	
Previous health status (McCabe)			
Not fatal	1267 (57.4)	118 (58.7)	
Fatal within 5 years	730 (33.1)	69 (34.3)	0.48
Fatal within 1 year	211 (9.6)	14 (7)	
Co-morbidities			
Immunosuppression	274 (12.4)	29 (14.4)	0.41
Respiratory failure	383 (17.3)	42 (20.9)	0.21
Cardiovascular failure	344 (15.6)	26 (12.9)	0.32
Cirrhosis	143 (6.5)	21 (10.4)	0.03
Renal failure	103 (4.7)	9 (4.5)	0.90
At least one chronic disease	962 (43.6)	99 (49.3)	0.12
Main symptom at admission			
Acute respiratory failure	623 (28.2)	71 (35.3)	0.03
Coma	520 (23.6)	17 (8.5)	<0.0001
Septic shock	407 (18.4)	40 (19.9)	0.61
Multiple organ failure	73 (3.3)	11 (5.5)	0.11
Cardiogenic shock	101 (4.6)	6 (3)	0.30
Haemorrhagic shock	89 (4)	20 (10)	0.0001
Monitoring and scheduled surgery	202 (9.1)	15 (7.5)	0.42
COPD exacerbation	53 (2.4)	8 (4)	0.17
Acute renal failure	34 (1.5)	6 (3)	0.12
Trauma	21 (1)	3 (1.5)	0.46

Table 1 (continued)

Variables	Supine (n=2208)	Prone (n=201)	*p* value
Treatment during the first 48 hours			
Vasoactive drugs	1413 (64)	156 (77.6)	0.0001
Steroids	680 (30.8)	76 (37.8)	0.04
Antibiotics	1753 (79.4)	169 (84.1)	0.11
Enteral nutrition	566 (25.6)	35 (17.4)	0.01
Parenteral nutrition	385 (17.4)	45 (22.4)	0.08
Procedures during the first 48 hours			
Arterial catheter	1119 (50.7)	126 (62.7)	0.001
Central catheter	1403 (63.5)	162 (80.6)	$<10^{-4}$
Swan catheter	107 (4.8)	20 (10)	0.002
At least one catheter	1482 (67.1)	170 (84.6)	<0.0001[4]
Laboratory variables in the first 48 hours			
Temperature, maximum (°C)	38.2 [37.7 - 38.9]	38.6 [38 - 39.2]	<0.0001
Heart rate, maximum (bpm)	116 [100 - 135]	126 [108 - 144]	<0.0001
Prothrombin rate, maximum (%)	69 [55 - 80]	61 [49 - 74]	<0.0001
Lowest PaO_2/FiO_2 ratio	165.5 [112 - 220]	129 [85 - 193]	<0.0001
Laboratory variables in the first 48 hours, in categories			
Temperature ≥38.2°C	1146 (51.9)	144 (71.6)	<0.0001
Heart rate ≥120 bpm	1027 (46.5)	128 (63.7)	<0.0001
Prothrombin rate ≤65%	917 (41.5)	117 (58.2)	<0.0001
PaO_2/FiO_2 ratio			
<100	436 (19.7)	73 (36.3)	<0.0001
100-159	600 (27.2)	57 (28.4)	
160-219	614 (27.8)	39 (19.4)	
220-299	558 (25.3)	32 (15.9)	

SAPSII, Simplified Acute Physiology Score II; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease.

[a] Evaluated using the APACHE II score (Knaus criteria)

Variables within the first 48 hours in the ICU were obtained as follows:

- In patients who received PP on the first ICU day, we only used the worst data collected on Day 0;
- In patients who received MV on the second ICU day (Day 1), we used the worst data collected on Day 1; and
- In patients who received MV on the first ICU day (Day 0), we used the worst data collected between Day 0 and Day 1.

Table 2: Predictors of prone positioning (PP) at the final step of the multivariate logistic model

Intercept	Estimator	Odds Ratio
Male	0.4377	1.55 [1.10 - 2.18]
Coma	-0.8015	0.45 [0.27 - 0.76]
Haemorrhagic shock	0.9845	2.68 [1.56 - 4.60]
Variables collected within the 48 first hours*		
At least one catheter	0.6325	1.88 [1.25 - 2.84]
Temperature ≥38.2°C	0.8655	2.38 [1.70 - 3.31]
Heart rate ≥120 bpm	0.4157	1.52 [1.11 - 2.08]
Prothrombin rate ≤65%	0.4966	1.64 [1.21 - 2.24]
PaO_2/FiO_2 ratio*		
<100	0.8611	2.37 [1.51 - 3.71]
100-159	0.3551	1.43 [0.90 - 2.26]
160-219	-0.0767	0.93 [0.57 - 1.52]
220-299	-	-

*: Variables collected within the first 48 hours after ICU admission

Variables within the first 48 hours in the ICU were obtained as follows:

- In patients who received PP on the first ICU day, we only used the worst data collected on Day 0;
- In patients who received MV on the second ICU day (Day 1), we used the worst data on Day 1; and
- In patients who received MV on the first ICU day (Day 0), we used the worst data collected between Day 0 and Day 1.

The Hosmer-Lemeshow of 3.7 (P=0.89) indicated good fit of the data, and discrimination was good (area under the receiver-operating characteristics curve, 0.74).

We performed stepwise logistic regression with a 5% threshold on all risk factors for prone positioning identified in the univariate analyses: male sex; transfer from ward; admission diagnosis of pneumonia; admission diagnosis of acute respiratory failure; chronic cirrhosis; acute respiratory failure at admission; coma at admission; haemorrhagic shock at admission; use of vasoactive drugs, steroids, or enteral nutrition within 48 hours after ICU admission; at least one catheter within 48 hours after ICU admission; and categories of temperature, heart rate, prothrombin time, and PaO_2/FiO_2 ratio within 48 hours after ICU admission.

To calculate the predicted risk for prone positioning in an individual patient:

- compute the logit: logit = sum (‘Beta estimate’ multiplied by value of corresponding parameter); then
- compute the probability, using the logit: p =(exp (logit)) divided by (1+exp(logit))

Table 3: Comparison of 199 patients treated with prone positioning and 199 individually matched patients kept in the supine position

Variables	Supine (n=199)	Prone (n=199)	*p* value
Age	66 [54 - 76]	65 [50 - 75]	0.24
Male sex	133 (66.8)	149 (74.9)	0.08
Transfer from ward	95 (47.7)	110 (55.3)	0.12
Severity scores at admission			
SAPS II	52 [37 - 64]	51 [40 - 66]	0.79
APACHE II score	20 [16 - 25]	19 [15 - 25]	0.59
SOFA score	7 [5 - 10]	7 [5 - 11]	0.65
Immunosuppression			
Chemotherapy	11 (5.5)	9 (4.5)	0.64
Steroid therapy >1 month or >2 mg/kg	9 (4.5)	11 (5.5)	0.66
AIDS	7 (3.5)	2 (1)	0.12
Bone marrow aplasia	5 (2.5)	3 (1.5)	0.43
Diagnosis at admission			
Pneumonia	39 (19.6)	63 (31.7)	0.006
Septic shock	16 (8)	30 (15.1)	0.02
Acute respiratory failure	13 (6.5)	24 (12.1)	0.08
Stroke	9 (4.5)	7 (3.5)	0.62
Acute renal failure	9 (4.5)	3 (1.5)	0.10
COPD exacerbation	9 (4.5)	5 (2.5)	0.29
Cardiogenic pulmonary oedema	7 (3.5)	5 (2.5)	0.57
Multiple organ failure	7 (3.5)	7 (3.5)	1.00
Admission category (missing for 2 pts)			
Medical	138 (69.7)	134 (67.7)	
Emergency surgery	36 (18.2)	35 (17.7)	0.75
Scheduled surgery	24 (12.1)	29 (14.6)	
Previous health status (McCabe)			
Not fatal	108 (54.3)	117 (58.8)	
Fatal within 5 years	64 (32.2)	68 (34.2)	0.14
Fatal within 1 years	27 (13.6)	14 (7)	
Co-morbidities *			
Immunosuppression	26 (13.1)	28 (14.1)	0.74
Respiratory failure	36 (18.1)	42 (21.1)	0.42
Cardiovascular failure	36 (18.1)	26 (13.1)	0.18
Cirrhosis	17 (8.5)	21 (10.6)	0.51
Renal failure	6 (3)	9 (4.5)	0.44
At least one chronic disease	94 (47.2)	98 (49.2)	0.68
Main symptom at admission			
Acute respiratory failure	42 (21.1)	71 (35.7)	0.002
Coma	58 (29.1)	17 (8.5)	<0.0001
Septic shock	32 (16.1)	39 (19.6)	0.36
Multiple organ failure	11 (5.5)	11 (5.5)	1.00
Cardiogenic shock	6 (3)	6 (3)	1.00
Haemorrhagic shock	15 (7.5)	19 (9.5)	0.47
Monitoring and scheduled surgery	22 (11.1)	15 (7.5)	0.23
COPD exacerbation	5 (2.5)	8 (4)	0.41
Acute renal failure	0	6 (3)	0.99
Trauma	3 (1.5)	3 (1.5)	1.00
Lowest PaO_2/FiO_2 ratio within 48 hours after ICU admission	154 [96 - 220]	130 [85 - 194]	0.006

Table 3 (continued

Treatment during the first 48 hours			
Vasoactive drugs	124 (62.3)	154 (77.4)	0.0009
Steroids	68 (34.2)	75 (37.7)	0.44
Antibiotics	152 (76.4)	168 (84.4)	0.05
Enteral nutrition	46 (23.1)	35 (17.6)	0.17
Parenteral nutrition	43 (21.6)	44 (22.1)	0.90
Procedures during the first 48 hours			
Arterial catheter	98 (49.2)	124 (62.3)	0.004
Central catheter	116 (58.3)	160 (80.4)	<0.0001
Swan catheter	13 (6.5)	20 (10.1)	0.23
At least one catheter	125 (62.8)	168 (84.4)	<0.0001
Variables collected on the day before PP			
Antibiotics	128 (64.3)	163 (81.9)	0.0001
At least one catheter	113 (56.8)	162 (81.4)	<0.0001
PaO_2/FiO_2 ratio	254 [185 - 337]	193 [121 - 296]	<0.0001
SOFA	5 [4 - 9]	7 [5 - 10]	0.005

COPD, chronic obstructive pulmonary disease; SAPSII, Simplified Acute Physiology Score II; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; AIDS, acquired immunodeficiency syndrome

* Evaluated using the APACHE II score (Knaus criteria).

Values of *p* were obtained by conditional logistic regression.

Table 4: Risk of ventilator-associated pneumonia and death associated with prone positioning (Cox model)

	Event	Hazard ratio	95%CI	*p* value
After adjustment for confounding variables: imbalanced variables and VAP risk factors*	Pneumonia	1.64	[0.70 ; 3.84]	0.25
After adjustment for confounding variables: imbalanced variables and hospital risk factors‡	Death	0.56	[0.39 ; 0.79]	0.001

VAP, ventilator-associated pneumonia; 95%CI, 95% confidence interval

*Adjusted on the following: at admission, male sex, pneumonia, septic shock, acute respiratory failure, and coma; within 48 hours after ICU admission, vasoactive drugs; and on the day before prone positioning (or the corresponding day in the control group), antibiotic use, at least one catheter, SOFA score, and PaO_2/FiO_2 ratio.

‡ Adjusted on the following: at admission, SAPS II, at least one chronic disease, pneumonia, septic shock, cardiac arrest, acute respiratory failure, and coma; within 48 hours after ICU admission, vasoactive drugs; and on the first day of prone positioning, antibiotic use, enteral or parenteral nutrition, catheter, SOFA score, and PaO_2/FiO_2 ratio.

Table 5. Post hoc analyses of the effects of prone positioning on the occurrence of ventilator-associated pneumonia
The marginal Cox model was used to compute the hazard ratio adjusted on imbalances between groups and risk factors for events.

Effects of prone positioning (PP) on risk of ventilator-associated pneumonia (VAP)

	Sample size		VAP			
Population	**Supine**	**Prone**	**Supine**	**Prone**	**HR**	***p* value**
All	199	199	8 (4%)	49 (24.6%)	1.64 [0.70-3.84]	0.25
Single day of PP	109	109	7 (6.4%)	12 (11%)	1.11 [0.39-3.10]	0.85
At least two days of PP (time-dependent covariate)	90	90	1 (1.1%)	37 (41.1%)	0.72 [0.32-1.65]	0.44
Minimum PF ratio <120 within 2 days before PP	32	72	2 (6.3%)	20 (27.8%)	0.69 [0.19-2.52]	0.57
SAPS >50 on the first day of PP	50	64	1 (2%)	11 (17.2%)	4.33 [0.70-26.65]	0.11
Only patients with PF ratio <200 at admission	153	153	7 (4.6%)	40 (26.1%)	1.03 [0.42-2.56]	0.94

Effects of PP on risk of death

	Sample size		Death			
Population	**Supine**	**Prone**	**Supine**	**Prone**	**HR**	***p* value**
All	199	199	74 (37.2%)	73 (36.7%)	0.56 [0.39-0.79]	0.001
Single day of PP	109	109	31 (33%)	46 (42.2%)	0.83 [0.51-1.35]	0.45
At least two days of PP (time-dependent covariate)	90	90	38 (42.2%)	27 (30%)	0.30 [0.12-0.74]	0.009
Minimum PF ratio <120 within 2 days before PP	32	72	20 (62.5%)	32 (44.4%)	0.56 [0.29-1.09]	0.09
SAPS >50 on the first day of PP	50	64	39 (78%)	41 (64.1%)	0.44 [0.29-0.69]	0.0003
Only patients with PF ratio <200 at admission	153	153	53 (34.6%)	61 (39.9%)	0.90 [0.61-1.32]	0.58

Abbreviations

ALI/ARDS:	acute lung injury/acute respiratory distress syndrome
APACHE II score:	Acute Physiologic and Chronic Health Evaluation II score
COPD:	chronic obstructive pulmonary disease
ICU:	intensive care unit
MV:	mechanical ventilation
PaO_2/FIO_2 ratio:	ratio of arterial partial oxygen pressure over fraction of inspired oxygen
PP:	prone positioning
SAPS II:	Simplified Acute Physiology Score, version II
SOFA Score	Sepsis-related Organ Failure Assessment score
SP:	supine position
VAP:	ventilator-associated pneumonia

Figure legends

Figure 1: Diagram of the matching process. Matching criteria are in grey (propensity score ±10% calculated over the first 48 hours after ICU admission, centre, and mechanical ventilation (MV) duration before prone positioning (PP) in the PP group or on the corresponding day (Day 0) in the supine positioning (SP) group). We calculated the number of patients with ventilator-associated pneumonia after Day 0.

Figure 2. Flow chart of patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) and matching procedure

MV, endotracheal mechanical ventilation; T0, time of the first turn prone; VAP, ventilator-associated pneumonia; P/F, ratio of arterial oxygen partial pressure over fraction of inspired oxygen. There was no significant difference in VAP occurrence after T0 between the groups with and without prone positioning (24 vs. 13 VAP episodes/100 patient-days of MV, respectively).

Figure 3. Kaplan-Meier estimates of the occurrence over time of ventilator-associated pneumonia (VAP) in the group kept in the supine position (solid line) and in the group treated with prone positioning (dotted line).

Figure 4. Kaplan-Meier estimates of 28-day hospital survival in the group kept in the supine position (solid line) and in the group treated with prone positioning (dotted line).

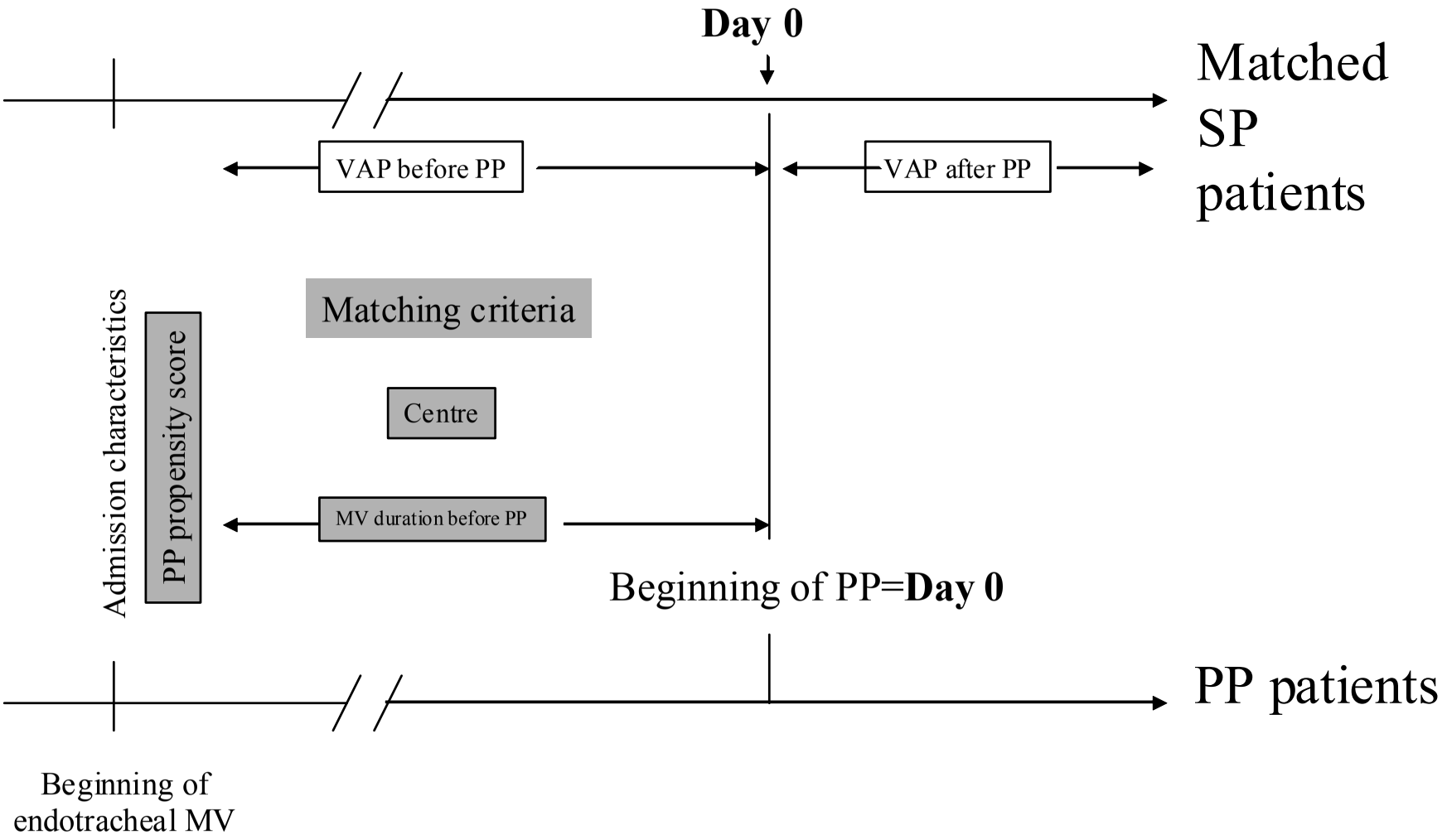
Day 0
Matched SP patients
VAP before PP
VAP after PP
Matching criteria
Admission characteristics
PP propensity score
Centre
MV duration before PP
Beginning of PP=Day 0
PP patients
Beginning of endotracheal MV

Figure 1

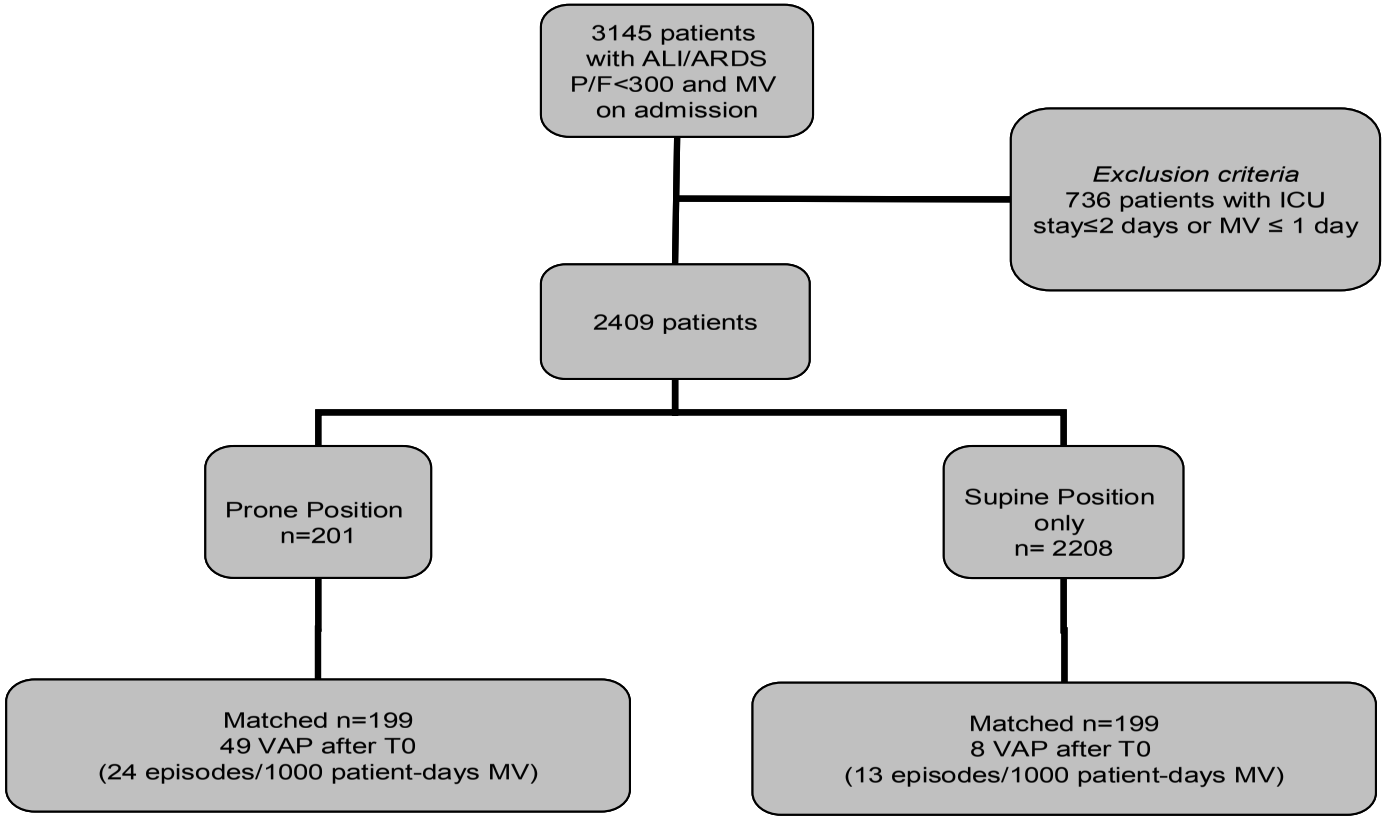
3145 patients with ALI/ARDS P/F<300 and MV on admission
Exclusion criteria
736 patients with ICU stay≤2 days or MV ≤ 1 day
2409 patients
Prone Position n=201
Supine Position only n= 2208
Matched n=199
49 VAP after T0
(24 episodes/1000 patient-days MV)
Matched n=199
8 VAP after T0
(13 episodes/1000 patient-days MV)

Figure 2

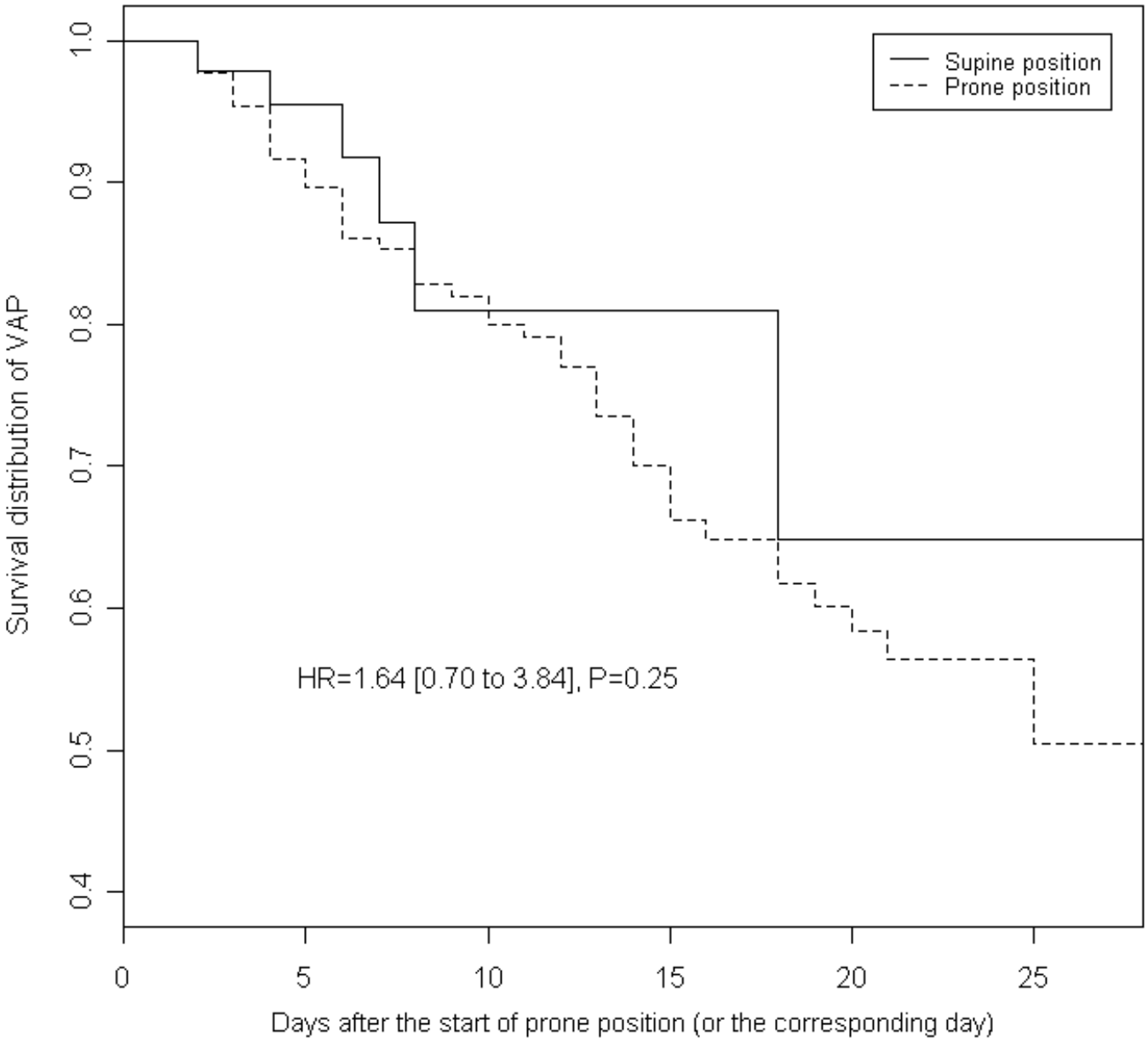
Supine position
Prone position
Survival distribution of VAP
1.0
0.9
0.8
0.7
0.6
0.5
0.4
HR=1.64 [0.70 to 3.84], P=0.25
0
5
10
15
20
25
Days after the start of prone position (or the corresponding day)

Figure 3

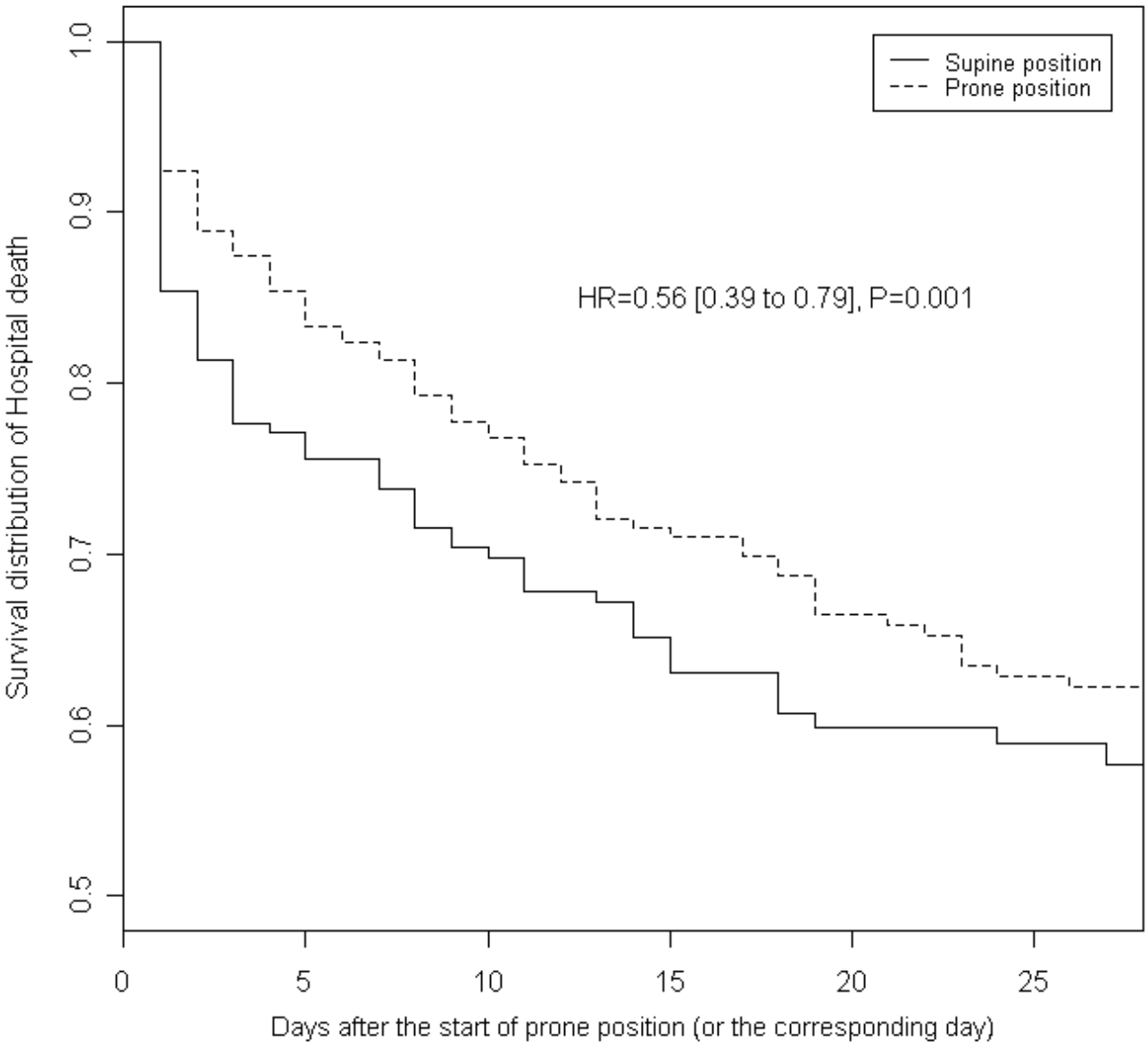
Supine position
Prone position
HR=0.56 [0.39 to 0.79], P=0.001
Survival distribution of Hospital death
1.0
0.9
0.8
0.7
0.6
0.5
0
5
10
15
20
25
Days after the start of prone position (or the corresponding day)

Figure 4

APPENDIX

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