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ORIGINAL RESEARCH

Influence of Prone Position on the Survival of COVID-19 Patients Undergoing Invasive Mechanical Ventilation: A Propensity Score Matching Study

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Purpose: The role of prone position (PP) in critically ill patients diagnosed with coronavirus disease 2019 (COVID-19) undergoing invasive mechanical ventilation remains unclear. This study aimed to evaluate the potential prognostic benefits of PP.

Patients and methods: This retrospective study included data from 289 critically ill patients with COVID-19 who underwent invasive mechanical ventilation in a multicenter setting. Propensity score matching was used to match 156 patients (78 PP-treated, 78 non-PP-treated) after adjusting for age, sex, underlying disease, and Sequential Organ Failure Assessment score. Between-group comparisons of clinical data, laboratory results, and prognosis were performed. Kaplan–Meier (K–M) survival curve and univariate and multivariate Cox regression analyses were used to explore the relationship between PP and prognosis.

Results: Prone positioning improved oxygenation (oxygenation index in the PP group increased consistently, with the greatest improvement observed on days 12–13 compared with the non-PP group [48 vs 32 mmHg; $P < 0.001$]) and increased hospital survival (80.8% vs 65.4%; $P = 0.047$). K–M survival curve analysis revealed that patients treated with PP had a more favorable prognosis ($P = 0.025$). Multivariate Cox regression revealed that PP was linked to lower risk of death (HR 0.389 [95% CI 0.173–0.878]), while age (HR 1.053 [95% CI 1.012–1.096]), Acute Physiology and Chronic Health Evaluation II score (HR 1.055 [95% CI 1.006–1.107]), and troponin T levels (HR 2.028 [95% CI 1.222–3.367]) were linked to higher risk of death in the overall survival of patients with COVID-19.

Conclusion: PP improved oxygenation and increased the survival rate of critically ill patients with COVID-19 undergoing invasive mechanical ventilation. Adopting PP as much as possible during nursing care may enhance patient survival.

Keywords: COVID-19, prone position, mechanical ventilation, survival, prognosis

Introduction

In December 2022, another coronavirus disease 2019 (COVID-19) outbreak occurred in China, prompting a substantial influx of critically ill patients with COVID-19 into the intensive care unit (ICU) due to acute respiratory distress syndrome (ARDS).[1] Previous research[2–4] has reported that the survival rate during ICU stay among critically ill patients diagnosed with COVID-19 undergoing invasive mechanical ventilation is low, ranging from 33.3% to 47.6%. Therefore, there is a need for comprehensive and effective measures to mitigate mortality rates among this patient population.

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Prone position (PP) enables significant re-expansion of collapsed alveoli and improves oxygenation by optimizing the ventilation-perfusion ratio and promoting alveolar recruitment.[5] Studies have suggested that repeated PP cycles with venovenous extracorporeal membrane oxygenation (ECMO) can reduce in-hospital mortality in patients with COVID-19-related ARDS, particularly in those requiring mechanical ventilation.[6] However, other studies have indicated that PP may lead to nerve damage and plexopathy in patients with COVID-19.[7] Therefore, under suitable conditions, all patients with COVID-19 undergoing invasive mechanical ventilation should receive treatment while prone. However, it is necessary to protect the nerves in such patients to avoid injury.

Studies have shown that factors, such as disease severity, underlying disease(s), and age, may affect the efficacy of PP.[8] However, previous investigations failed to adjust for disease severity, such as the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Therefore, there is an urgent need for more effective methods to evaluate the efficacy of PP.[9] Propensity score matching (PSM) is widely used in retrospective studies and eliminate confounding factors.[10,11] Thus, conducting research using PSM may better reflect the efficacy of PP.

Our study objective is to explore the role of PP in the treatment of patients with COVID-19 receiving mechanical ventilation. To this end, we used PSM to control for potential confounding factors, such as underlying diseases, between PP and non-PP groups. Baseline data tables were used to illustrate the differences in clinical variables before and after PP treatment, to construct a prognostic model using Cox regression analysis, and predict the survival rate of patients with COVID-19 receiving mechanical ventilation using nomograms. Ultimately, this study confirmed the underlying hypothesis that PP confers benefits to patients with COVID-19 receiving mechanical ventilation.

Methods

Study Design

Data from 289 critically ill patients diagnosed with COVID-19, who received invasive mechanical ventilation in the ICUs of three general hospitals in Taizhou City (Zhejiang China) between December 1, 2022, and February 1, 2023, were retrospectively reviewed and analyzed. Among these, 157 were treated with PP and 132 were not. Follow-up began at ICU admission, with endpoints set at patient death or April 28, 2023.

In the PP group, the exclusion criteria were as follows:[12–14] incomplete case records (n = 67); PP duration < 12 h (n = 10); PP treatment initiated before ICU admission (n = 1); and previous ECMO treatment before PP (n = 1). Participants in the matched non-PP group (n = 78) were selected through a 1:1 PSM analysis with the PP group (n = 78) based on age, sex, underlying disease (including preexisting pulmonary disease, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, malignant tumors, hepatitis, and chronic kidney disease), and SOFA score (Figure 1).

COVID-19 Diagnostic Criteria

COVID-19 was confirmed by real-time reverse transcription polymerase chain reaction tests using nasal and pharyngeal swabs (cycle threshold [Ct] < 35). Clinical diagnosis and typing were performed in accordance with guidelines outlined in the Diagnosis and Treatment Protocol for COVID-19 (Ninth Edition; https://www.gov.cn/zhengce/zhengceku/2022-03/15/content_5679257.htm).

PP Protocol

Based on consensus among medical professionals and nursing staff at the authors' institution, comprehensive protocols for care established a dedicated interdisciplinary team and implemented standardized training procedures that were formulated to ensure the uniformity of PP treatment across patients. The indications for PP were as follows: ARDS with recalcitrant hypoxemia that could not be corrected through conventional mechanical ventilation; severe ARDS with partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio ≤ 100 mmHg; and PaO_2 to FiO_2 ratio < 150 mmHg with positive end-expiratory pressure ≥ 5 cmH_2O and FiO_2 ≥ 0.6. After admission to the ICU, the treatment team assessed the patient's disease condition and preferences, and PP therapy was initiated in accordance with the September 2022 issue of the Shanghai Expert Recommendations on PP Therapy for Patients with COVID-19.

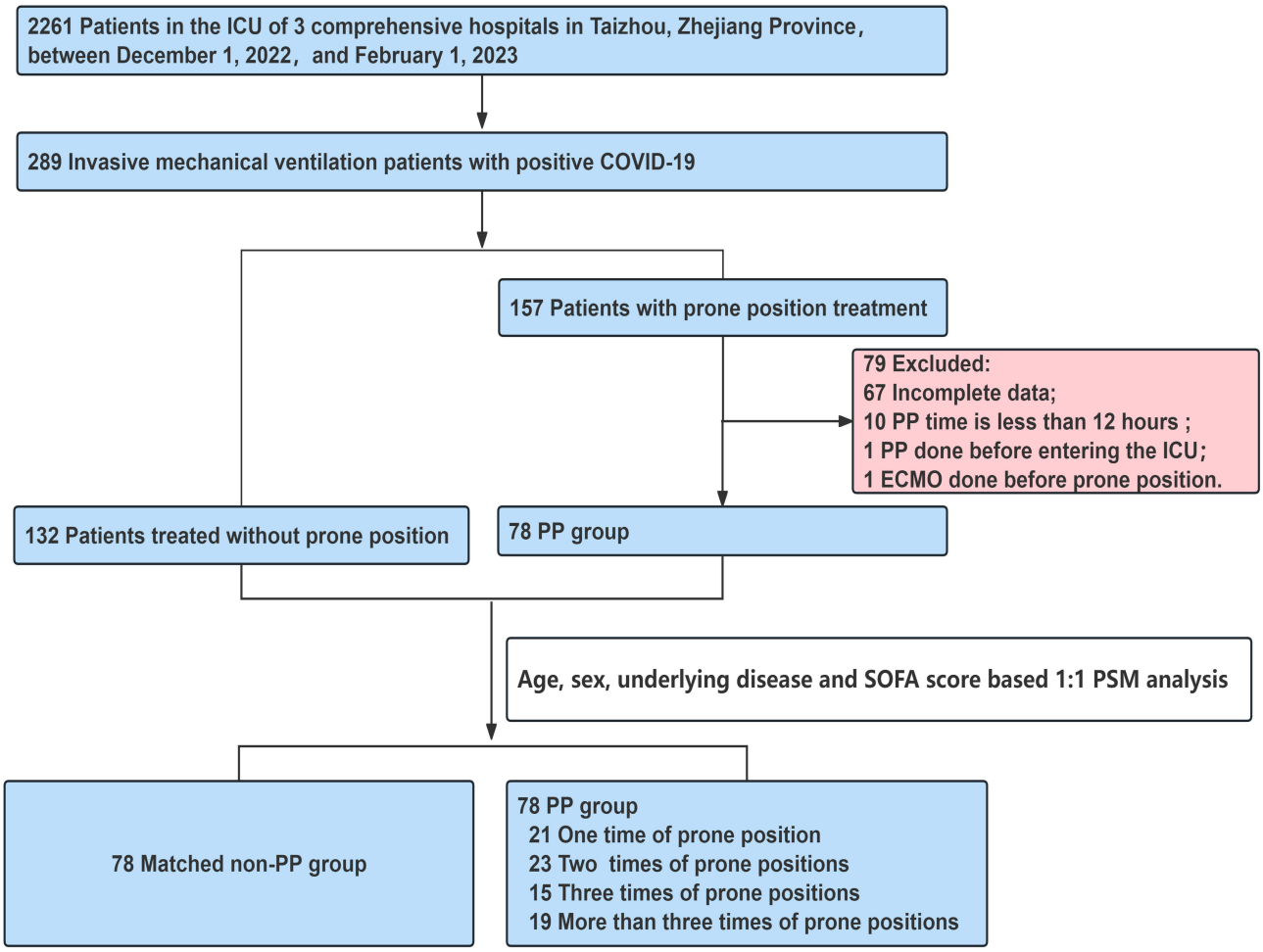

Figure 1 Flow chart of the study.
Abbreviations: ICU, Intensive care unit; COVID-19, Coronavirus disease 2019; PP, Prone position; ECMO, Extracorporeal membrane; SOFA, Sequential organ failure assessment; PSM, Propensity score matching.

Contraindications to PP were as follows: severe hemodynamic instability in critically ill patients; craniocerebral trauma accompanied by moderate or severe intracranial hypertension; acute bleeding disorders; severe multiple injuries resulting in significant damage to the cervical vertebrae, spine, pelvis, chest wall, and abdomen; severe facial trauma or recent facial surgery; recent orthopedic and abdominal surgeries; ventricular arrhythmias or cardiac pacemakers implanted within 48 h; deep vein thrombosis occurring within 48 h; and pregnancy.

The termination criteria for PP were as follows: intraoperative risk for or occurrence of severe complications; decision to discontinue treatment made by the physician based on disease progression; and voluntary abandonment of treatment by the patient and their family.

Data Collection

Data including age, sex, clinical symptoms, imaging tests, medication history, laboratory indicators, and underlying diseases were obtained from electronic medical records. In this study, indicators with missing data ≥ 60% were excluded.[15,16] Key indicators, such as SOFA score, age, sex, and underlying disease(s), had no missing values. All missing laboratory parameters ultimately included accounted for < 15%, and the median imputation method was implemented.

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Baseline and final laboratory indicators were designated as those obtained within 24 h of admission to the ICU and before discharge from the ICU, respectively. The time point closest to the start or end of the PP (within 24 h) was designated as before or after PP (B-PP or End-PP).

Regarding the PP time points, PP1, PP2, and PP3 were defined as the first, second, and third cycle of PP, respectively. T0 represents 0–6 h before the current PP cycle, T1 represents 0–6 h after the current PP cycle, T2 represents 6–12 h after the current PP cycle, and T3, 0–6 h after the current PP cycle.

Improvement in the PaO_2 to FiO_2 ratio was defined as the mean PaO_2 to FiO_2 ratio at T3 of the current cycle being greater than the mean PaO_2 to FiO_2 ratio at PP1–T0.

Calculation of Scores

The SOFA score[17] was calculated based on the following parameters: PaO_2 to FiO_2 ratio; platelet count; bilirubin level; mean arterial pressure; medication, Glasgow Coma Scale (GCS) score; creatinine level; and urine output. The worst value recorded within 24 h was used to calculate the SOFA score, with higher scores indicating a poorer prognosis.

The APACHE II score[18] comprises the Acute Physiology Score, GCS score, and age. A cumulative score was obtained by summing these 3 components, with higher scores indicating more severe conditions. The most critical value within a 24 h period was selected for the APACHE II evaluation.

Biological Analysis

Arterial blood gas analysis was performed using a laboratory analyzer (RAPID Point 500, Siemens, Erlangen, Germany). EDTA-K2 anticoagulated blood samples were identified using a fully automated blood cell analyzer (BC-6800 Plus, Mindray, Shenzhen, China). Procalcitonin (PCT), troponin T (TnT), and brain natriuretic peptide (BNP) levels were analyzed using an electrochemiluminescence analyzer (E801, Roche Diagnostics, Basel, Switzerland). Sodium citrate plasma samples were centrifuged at 3000 rpm for 10 min, and coagulation parameters were measured using a fully automated hemagglutination analyzer (START MAX, Diagnostica Stago SAS., Asnières-sur-Seine, France).

PSM and Efficiency Verification

PSM was performed using R version 4.2.1 (R Core Team; R Foundation for Statistical Computing, Vienna, Austria). To account for potential influencing factors, clinical variables in the baseline data were analyzed using PSM to control for confounding factors. The parameter settings and effect evaluation of the PSM were as follows:

1. A 1:1 nearest-neighbor matching strategy was implemented, with age, sex, underlying diseases, and SOFA score as the core matching variables.
2. Considering the scarcity and clinical value of the sample in this study, no caliper parameters were set during the matching process to maximize the retention of a valid sample size. Previous studies have also reported that when the sample size was insufficient, the use of calipers may have led to a significant decrease in the test's efficacy.[19] At this point, without using calipers, more samples can be retained, avoiding situations in which excessive screening leads to unreliable results.
3. The matching effect was estimated by generating a propensity score distribution density plot. The results revealed that the overlap of the propensity score distribution curves between the PP and non-PP groups significantly improved after matching (Figure S1A–C). Standardized mean differences were calculated after PSM to assess the balance between the 2 groups. The standardized mean differences of age and SOFA score were 0.184 and 0.289, respectively, and the statistical test results of intergroup comparisons all indicated $P > 0.05$. These findings suggest that the 2 groups achieved a balance in key clinical characteristics, confirming that the PSM method effectively eliminated intergroup selection bias and provided a reliable basis for data analysis in subsequent effect size estimation.

Statistical Analysis

Statistical analysis were performed using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA), and plots were generated using Prism version 9 (GraphPad Inc., San Diego, CA, USA) and R version 4.2.1. Categorical variables are expressed as frequency and percentage to test the balance between the 2 groups and were compared using the chi-squared test. Data from the 2 groups that were normally distributed were compared using the *t*-test, while data that were not normally distributed were compared using the Mann–Whitney *U*-test. Normally distributed data are expressed as mean ± standard deviation, while non-normally distributed data are expressed as median (interquartile range [ie, P_{25}–P_{75}]).

The overall survival rate of patients with COVID-19 was assessed using Kaplan–Meier (K–M) survival curves to examine the influence of PP. When the hazard ratio (HR) > 1, PP was associated with a poorer prognosis, whereas when the HR was < 1, PP was associated with a favorable prognosis. Differences with $P < 0.05$ were considered to be statistically significant.

Univariate Cox regression analysis was performed on clinical variables, including PP treatment, age, APACHE II score, respiratory rate, BNP, TnT, and aspartate aminotransferase levels, and estimated glomerular filtration rate. Variables with $P < 0.05$ were subsequently incorporated into the multifactorial Cox regression analysis. An independent prognostic factor for patients with COVID-19 was considered when $P < 0.05$. Based on the results of the multivariate analysis, a nomogram was established.

Results

Clinical Information of the Study Cohorts

PSM analysis of 156 patients (n = 78 per group) revealed the following. Pre-PSM, significant intergroup differences in age, SOFA score, and underlying diseases (all $P < 0.05$). These disparities significantly decreased post-PSM, achieving a balance between most confounders (Table 1 and Figure S1C). However, after PSM analysis, the PP group maintained lower median PaO_2 to FiO_2 ratio (125.5 mmHg [IQR 104.3–169.0 mmHg] vs 212.5 mmHg [IQR 130.5–289.5 mmHg]) and higher median FiO_2 (60.0% [IQR 45.8–80.0%] vs 50.0% [IQR 40.0–61.0%]) compared with the matched non-PP group ($P < 0.05$) (Table S1).

Table 1 Relationship Between Clinical Parameters and PP in Patients with COVID-19

	PP Group	Unmatched Non-PP Group	Matched Non-PP Group	P_1 value	P_2 value
	(n=78)	(n=132)	(n=78)		
Sex(male)(%)	62 (79.5)	84 (63.7)	61 (78.2)	0.024	1.000
Age (years)	77.5 (70.0, 83.0)	72.0 (63.8, 82.0)	76.0 (65.0, 86.0)	0.015	0.942
SOFA score[a]	8.0 (6.0, 9.0)	7.0 (5.0, 8.0)	7.50 (6.0, 9.0)	0.002	0.858
APACHE II score[a]	22.0 (16.3, 27.0)	22.0 (17.8, 28.0)	22.0 (18.0, 28.0)	0.458	0.865
Underlying disease (%)					
Pre-existing pulmonary disease	30 (38.5)	29 (22.0)	27 (34.6)	0.016	0.739
Hypertension	47 (60.3)	51 (38.6)	41 (52.6)	0.004	0.419
Diabetes	24 (30.8)	22 (16.7)	22 (28.2)	0.027	0.861
Cardiovascular disease	15 (19.2)	14 (10.6)	14 (17.9)	0.123	1.000
Cerebrovascular disease	15 (19.2)	26 (19.7)	18 (23.1)	1.000	0.695
Malignant tumor	19 (24.4)	14 (10.6)	10 (12.8)	0.014	0.100
Hepatitis	6 (7.7)	6 (4.5)	6 (7.7)	0.521	1.000
Chronic kidney disease	11 (14.1)	12 (9.1)	12 (15.4)	0.371	1.000
Laboratory indicators[a]					
PaO_2 to FiO_2 ratio (mmHg)	125.5 (104.3, 169.0)	200.0 (126.5, 268.5)	212.5 (130.5, 289.5)	<0.001	<0.001
$PaCO_2$ (mmHg)	34.5 (30.3, 40.8)	34.0 (30.0, 41.3)	34.0 (30.0, 39.8)	0.474	0.542
LAC (mmol/L)	2.1 (1.6, 2.8)	2.1 (1.6, 3.4)	2.3 (1.6, 3.2)	0.351	0.433
CRP (mg/L)	65.6 (18.4, 129.5)	64.1 (24.1, 136.7)	64.1 (27.5, 133.9)	0.446	0.414

(*Continued*)

Table 1 (Continued).

	PP Group (n=78)	Unmatched Non-PP Group (n=132)	Matched Non-PP Group (n=78)	P_1 value	P_2 value
WBC (× 10^9/L)	10.1 (7.8, 12.9)	8.9 (6.3, 13.1)	8.9 (6.4, 13.6)	0.320	0.562
LYM (× 10^9/L)	0.5 (0.3, 0.7)	0.6 (0.3, 1.0)	0.5 (0.3, 1.0)	0.027	0.328
BNP (pg/mL)	1537.0 (768.3, 3479.5)	1672.0 (521.0, 6446.0)	1672.0 (472.5, 5370.5)	0.657	0.928
TnT (ng/mL)	0.04 (0.02, 0.10)	0.05 (0.03, 0.12)	0.05 (0.03, 0.12)	0.399	0.103
AST (U/L)	39.0 (27.5, 59.5)	44.0 (27.0, 68.5)	44.0 (27.0, 69.0)	0.394	0.508
eGFR [mL/(min × 1.73m^2)]	60.6 (26.9, 81.9)	48.1 (23.8, 82.8)	50.1 (27.0, 86.3)	0.649	0.976

Notes: Data are presented as n (%) and median (P_{25} and P_{75}). The significance level was set at $P < 0.05$. P_1, Comparison of PP group and Unmatched non-PP group; P_2, Comparison of PP group and matched non-PP group. [a]Data within 24 hours of admission to the ICU.
Abbreviations: SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; Cydn, Dynamic lung compliance; PaO_2, Partial pressure of oxygen; $PaCO_2$, Partial pressure of carbon dioxide; FiO_2, Fractional concentration of oxygen in inspired air; LAC, Lactic acid; CRP, C-reactive protein; WBC, White blood cell; LYM, Lymphocyte; BNP, Brain natriuretic peptide; TnT, TroponinT; AST, Aspartate aminotransferase; eGFR, Estimated Glomerular Filtration Rate.

Treatment with PP Enhanced the PaO_2 to FiO_2 Ratio

Within 13 days of ICU admission, the PaO_2 to FiO_2 ratio in the PP group was consistently higher than that in the non-PP group, peaking on days 12–13 (48 vs 32 mmHg). In addition, PP initiation times varied among the patients: 74 patients underwent PP on the day of ICU admission; 3 (patients E32, E59, and E66) on day 16; and 1 (patient E28) on day 25 (Figure 2A and B).

The frequency of PP exhibited a positive correlation with the PaO_2 to FiO_2 ratio (Figure S2). Among the subgroups, PP1 yielded the highest improvement rate (73.1% [57/78]), followed by PP2 (71.9% [41/57]), and PP3 (52.9% [18/34]) (Figure 2C).

Changes in PaO_2 to FiO_2 ratio were compared in 34 patients who underwent PP ≥ 3 times. During PP (T1, T2), PP2 yielded the highest change (56.3 mmHg [IQR 13.0–92.8 mmHg]), followed by PP1 (34.5 mmHg [IQR 17.8–83.4 mmHg]) and PP3 [40.0 (7.0, 67.0) mmHg]. After the PP cycle (T3), PP1 yielded the highest change

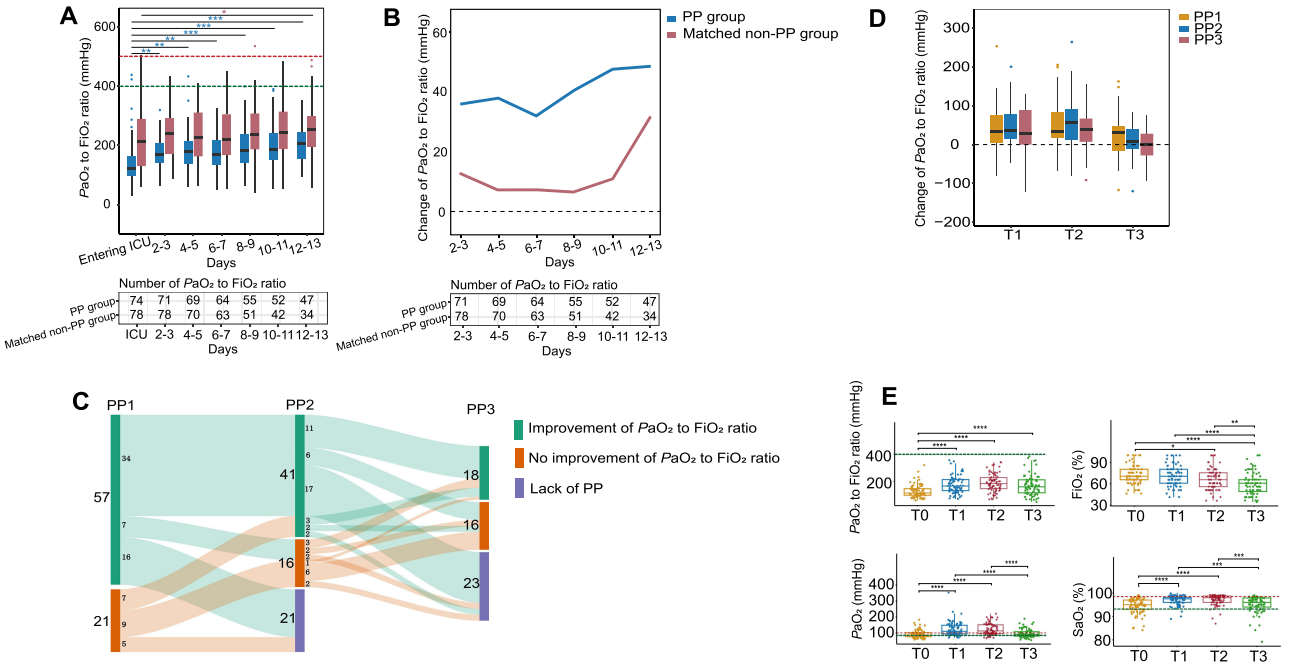

Figure 2 The relationship between the frequency of PP and the improvement of the PaO_2 to FiO_2 ratio. (**A**) Dynamic monitoring of PaO_2 to FiO_2 ratio. (**B**) Dynamic change amplitude of PaO_2 to FiO_2 ratio (compared with entering ICU). (**C**) Improvement of PaO_2 to FiO_2 ratios at different times of PP; (**D**) Change amplitude of the PaO_2 to FiO_2 ratio from PP1 to PP3 in patients who underwent PP three or more times (N=34); (**E**) Arterial blood gas indicators monitoring during PP1.
Notes: The black dashed line denotes the change level of 0. The red dashed line denotes the upper boundary of the reference range for the index, while the green dashed line signifies the lower boundary (PaO_2 to FiO_2 ratio: 400–500mmHg; PaO_2: 80–100mmHg; SaO_2: 93–99%). Entering ICU: Laboratory indicators within 24 hours of entering the ICU. PP1, PP2, PP3; the 1st, 2nd, and 3rd time of PP; T0: 0–6 hours before the current PP; T1: 0–6 h following the start of PP; T2: 6–12 h following the start of PP; T3: 0–6 hours after the end of PP. *P < 0.05; **P < 0.01;***P < 0.001;****P < 0.0001.
Abbreviations: PP, prone position; PaO_2, Partial pressure of oxygen; FiO_2, Fractional concentration of oxygen in inspired air; SaO_2, Saturation of arterial oxygen.

(30.8 mmHg [IQR −16.4 to 46.9 mmHg]), followed by PP2 (7.0 mmHg [IQR −11.8 to 38.0 mmHg]) and PP3 (1.25 mmHg [IQR −28 to 28 mmHg]) (Figure 2D). During PP1 cycles, median PaO_2 to FiO_2 ratios exhibited a continuous increase at each time point (T0, 115.0 mmHg [IQR 98.6–147.5 mmHg] vs T1, 167.0 mmHg [IQR 133.0–215.0 mmHg] vs T2, 185.0 mmHg [IQR 147.5–230.0 mmHg]) (Figure 2E).

Among 8 surviving patients with improved PaO_2 to FiO_2 ratios after 3 PP cycles, lymphocytes (LYM; 0.2–2.4 × 10^9/L [with 5 cases > 0.5 × 10^9/L]), white blood cells (WBC; 3.3–16.2 × 10^9/L), and cumulative PP duration 53.0–113.5 h exhibited a tendency to be higher than those in 5 non-improved patients (LYM 0.1–0.5 × 10^9/L; WBC 2.3–11.4 × 10^9/L; duration 36.0–98.6 h [with 4 cases < 46 h PP]), although the differences were not statistically significant (Figure S3).

Treatment with PP Improved Survival Rate

Survivors in the PP group (n = 63) exhibited a higher malignant tumor rate (27.0% vs 9.8%), but lower PaO_2 to FiO_2 ratio (127.0 mmHg vs 228.0 mmHg) than matched non-PP group survivors (n = 51) (Table S2). At the End-PP, the survivors' PaO_2 to FiO_2 ratio was significantly higher than B-PP (168.0 mmHg vs 111.0 mmHg) (all P < 0.05) (Figure 3A–D).

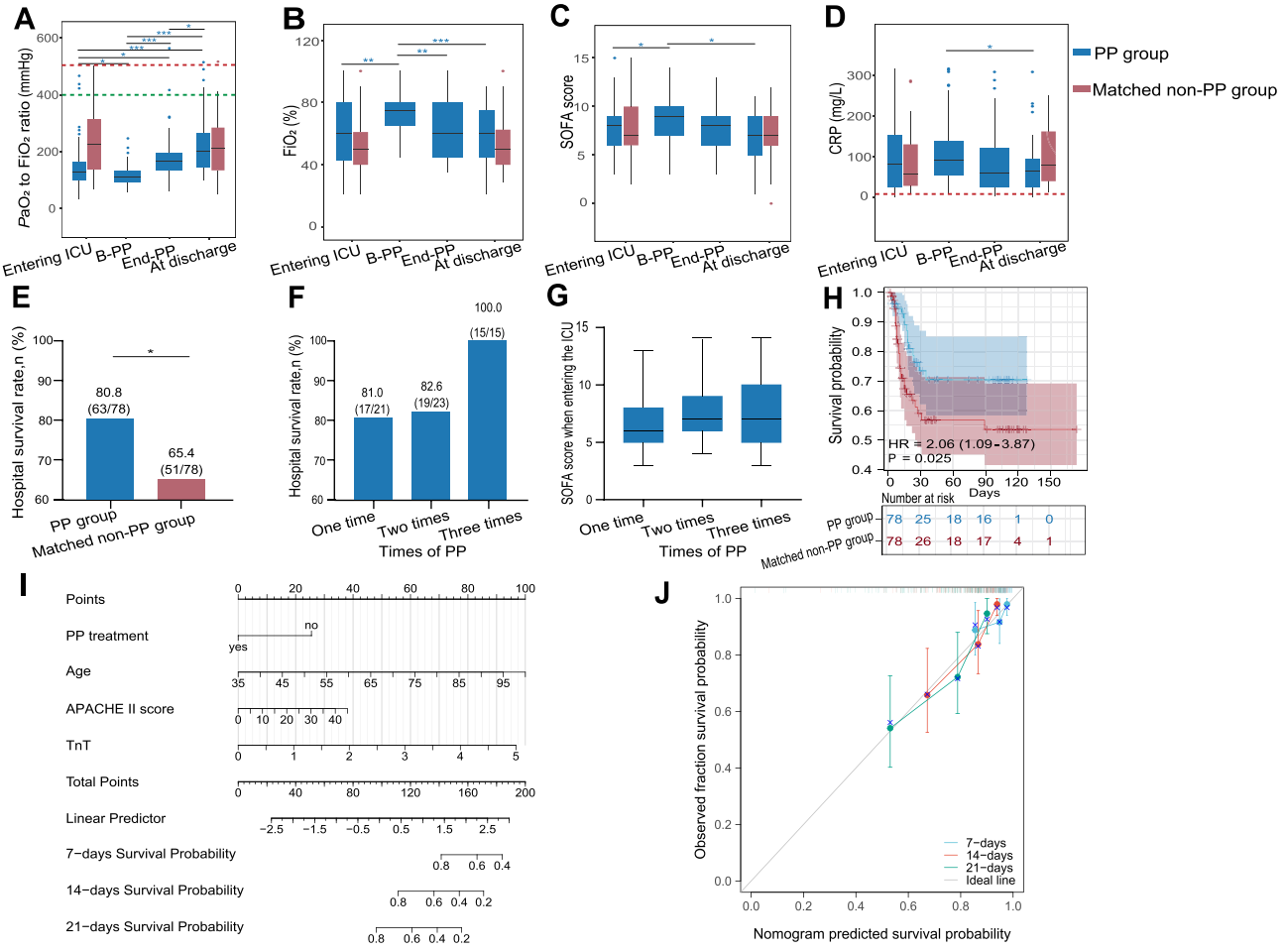

Figure 3 The relationship of PP and survival rate. (**A–D**) Dynamic monitoring of PaO_2 to FiO_2 ratio, FiO_2, SOFA and CRP of surviving patients; (**E**) The hospital survival rate of patients with PP group and matched non-PP group; (**F**) The hospital survival rate of patients with different PP frequencies; (**G**) SOFA score of patients with different PP frequencies; (**H**) Kaplan-Meier survival curves in two groups; (**I**) Nomograms for predicting 7, 14, and 21-year OS. (**J**) The calibration curves for predicting OS at A 7, 14, and 21-year overall survival in COVID-19 Patients with invasive mechanical ventilation.

Notes: The red dashed line denotes the upper boundary of the reference range for the index, while the green dashed line signifies the lower boundary (PaO_2 to FiO_2 ratio: 400–500mmHg; CRP: 0–6.0mg/L). Entering ICU, Laboratory indicators within 24 hours of entering the ICU; B-PP, Laboratory indicators closest to the start of prone position (Less than 24 hours); End-PP, Laboratory indicators closest to the end time of prone position (Less than 24 hours); At discharge, Laboratory indicators within 24 hours before discharge. The significance level was set at P < 0.05. *P < 0.05; **P < 0.01; ***P < 0.001.

Abbreviations: PP, prone position; PaO_2, Partial pressure of oxygen; FiO_2, Fractional concentration of oxygen in inspired air; SOFA, Sequential Organ Failure Assessment; CRP, C-reactive protein; APACHE, Acute Physiology and Chronic Health Evaluation; TnT, TroponinT.

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Table 2 Multivariate Analysis of Overall Survival in the in COVID-19 Patients with Invasive Mechanical Ventilation

Characteristics	Total (N)	Univariate Analysis		Multivariate Analysis	
		Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
PP treatment	156				
Yes	78	0.488 (0.260–0.919)	0.026	0.389 (0.173–0.878)	0.023
No	78	Reference		Reference	
Age (years)	156	1.042 (1.011–1.074)	0.007	1.053 (1.012–1.096)	0.010
APACHE II score	156	1.041 (1.008–1.074)	0.014	1.055 (1.006–1.107)	0.028
TnT (ng/mL)	147	1.716 (1.249–2.358)	0.001	2.028 (1.222–3.367)	0.006
Respiratory Rate (breaths/min)	155	0.845 (0.719–0.992)	0.040	0.794 (0.617–1.020)	0.071
BNP (pg/mL)	137	1.000 (1.000–1.000)	0.011	1.000 (1.000–1.000)	0.242
AST (U/L)	152	1.007 (1.002–1.012)	0.005	1.006 (1.000–1.012)	0.069
eGFR [mL/(min × 1.73m^2)]	156	0.989 (0.980–0.999)	0.025	0.994 (0.980–1.008)	0.410

Abbreviations: PP, prone position; APACHE, Acute Physiology and Chronic Health Evaluation; TnT, TroponinT; BNP, Brain natriuretic peptide; AST, Aspartate aminotransferase; eGFR, Estimated Glomerular Filtration Rate.

The PP group experienced a higher hospital survival rate than the matched non-PP group (80.8% vs 65.4%; P = 0.047) (Figure 3E). Multiple PP cycles improved survival (1 cycle, 81.0% [17/21]; 2 cycles, 82.6% [19/23]; 3 cycles, 100.0% [15/15]) and SOFA scores did not differ according to PP frequency (Figure 3F and G). The K–M curve showed that the mortality rate of the matched non-PP group was 2.06 times that of the PP group (HR 2.06, P = 0.025) (Figure 3H).

Cox regression analysis revealed that age (HR 1.053 [95% CI 1.012–1.096]; P = 0.010), APACHE II score (HR 1.055 [95% CI 1.006–1.107]; P = 0.028), and TnT level (HR 2.028 [95% CI 1.222–3.367]; P = 0.006) were independent risk factors for mortality, whereas PP treatment (HR 0.389 [95% CI 0.173–0.878]; P = 0.023) acted as a protective factor (Table 2).

The nomogram predicted survival in patients with COVID-19 receiving invasive mechanical ventilation, indicating that PP treatment, younger age, lower APACHE II score, and lower TnT levels were associated with higher 7-, 14-, and 21-day survival rates. Calibration curves exhibited good agreement between the predicted and observed survival probabilities (Figure 3I and J).

Discussion

To the best of our knowledge, the present study is among the first to investigate the clinical effects of PP by applying a matching technique to establish comparable groups. Our findings indicated that PP improved the PaO_2 to FiO_2 ratio and survival in critically ill patients with COVID-19 undergoing invasive ventilation. Patients who did not receive PP, were older, or had high APACHE II score and TnT levels showed lower survival rates.

Notably, we observed that the duration of PP was significantly longer in patients who demonstrated improvement in the initial 3 PP cycles than in those who did not. The effect of PP on PaO_2 to FiO_2 improvement persisted up to six hours after repositioning. Previous studies have emphasized the efficacy of PP in enhancing the PaO_2 to FiO_2 ratio.[20]

Additionally, we found that a more frequent application of PP was associated with more significant improvement(s) in the oxygenation index. Weiss et al suggested that repeated PPs may improve PaO_2 the FiO_2 ratios in patients with COVID-19 undergoing invasive mechanical ventilation.[12] However, the inherent association between the frequency of PP and PaO_2 to FiO_2 ratios improvement was not reported. In contrast, our findings showed that PP1 had the longest duration of PaO_2 to FiO_2 ratio improvement, and PP2 demonstrated the most substantial increase in PaO_2 to FiO_2 ratios

in most patients. These findings suggest that multiple PP sessions may optimize oxygenation parameters and support the potential benefit of increasing PP frequency in critically ill patients with COVID-19 undergoing invasive ventilation.

Our findings indicate that the hospital survival rate was higher in the PP group (80.8% vs 65.4%). Notably, patients who underwent PP ≥ 3 times exhibited a 100.0% survival rate. Douglas et al[21] reported a hospital survival rate of 68.9% in the PP group among critically ill patients with COVID-19 receiving invasive mechanical ventilation. However, they did not include a control group to confirm whether the PP intervention influenced the survival rate. Our data showed that PP implementation improved survival rate, as demonstrated by the PSM analysis comparing the PP and non-PP groups. Furthermore, our findings indicate that multiple cycles of PP during hospitalization may further enhance its effect during hospitalization.

In our study, SOFA scores decreased in approximately half of the patients who received PP. Nearly one-third of patients who exhibited a SOFA score reduction exceeding 20% with baseline SOFA scores <8. Some researchers believe that PP therapy may reduce SOFA scores in patients with COVID-19, thereby improving their condition.[22,23] Lower baseline SOFA scores (≤ 11) predicted more significant oxygenation improvement with PP, suggesting its potential utility in forecasting treatment efficacy.[24]

Patients whose SOFA scores did not improve had significantly longer delays before PP initiation (3 days vs 1 day), and shorter PP duration (15.5 h vs 22.0 h) than those in whom SOFA scores improved. Previous studies[25,26] have shown that early and prolonged implementation of PP may enhance PaO_2 the FiO ratios in individuals with COVID-19-induced lung infections. Therefore, PP should be implemented as early as possible.

The exploratory nature of our data revealed that survivors who showed PaO_2 to FiO_2 ratios improvement during the first three PP sessions exhibited a higher tendency toward higher LYM levels than those who did not. This indicated that LYM levels may be a valuable predictive indicator of PP efficacy. Previous studies have demonstrated that LYM are a reliable biomarker for the severity of COVID-19 and a critical dynamic indicator for predicting the prognosis of patients undergoing treatment involving PP.[27–29]

Severe COVID-19 impairs cellular immune function and reduces LYM levels by directly invading immune cells or triggering over-reactive immune responses. Thus, LYM monitoring is essential to ensure the efficacy of PP therapy. Given the exploratory nature of this study (with no formal statistical analysis performed due to the sample size), these findings require verification in future large-sample studies.

Limitations of the present study include its small sample size, residual confounding from unmatched variables (eg, no calipers in PSM), biases inherent to retrospective study designs, and limited generalizability. Moreover, the enrolled patients may have exhibited more severe and complex medical conditions. Nonetheless, we collected complete data from 3 general hospitals, and all patients who underwent treatment involving PP were included as much as possible to comprehensively analyze the universality of PP. Additionally, we used 1:1 PSM and Cox regression analyses to ensure between-group comparability and, thus, reduce the effect of confounding factors.

Conclusion

This multicenter retrospective cohort study used PSM and Cox regression analysis to reduce confounding factors. PSM was used to perform a real-world evaluation of the efficacy of therapy delivered with patients positioned prone. PP may serve as an effective intervention to improve the oxygenation index and enhance the survival rate of critically ill patients with COVID-19 undergoing invasive mechanical ventilation. Specifically, the frequency of PP was associated with the degree of improvement in the PaO_2 to FiO_2 ratio; the potential increase in the survival rate may also be closely related to PP. Monitoring of LYM and the SOFA score may assist in identifying appropriate patients. Therefore, we recommend the implementation of PP in suitable patients receiving invasive mechanical ventilation.

Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of Taizhou Hospital, Zhejiang Province, China (Approval NO.: K20230116). All procedures followed were in accordance with the Declaration of Helsinki and its subsequent amendments. Informed consent was waived by our institutional review board due to the retrospective nature of our study, and data were anonymized and kept confidential.

Consent for Publication

Written informed consent for publication was obtained from all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests.

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