Prone Position Improves Survival rate of Covid-19 Invasive Mechanical Ventilation Patients by Improving Oxygenation Index

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August 16, 2023

Abstract

Background: Invasive mechanical ventilation is a crucial intervention for the management of critical COVID-19 patients. However, the impact of prone position (PP) on patients undergoing invasive mechanical ventilation remains uncertain. This study aims to investigate the potential benefits of PP in terms of improving the oxygenation index and prognosis. **Methods:**A total of 289 critically ill COVID-19 patients were retrospectively gathered from ICU of three general hospitals located in Taizhou, Zhejiang Province from December 1, 2022 to February 1, 2023, all patients were invasive mechanical ventilated. 78 cases of PP group and 78 cases of non-PP group were matched with propensity score matching. The study compared clinical data, laboratory results, and hospitalization survival rate between two groups of patients. Furthermore, we compared the laboratory results, and hospitalization survival across varying numbers of PPs. **Results:**The mean oxygenation index exhibited a greater increase in PP group compared to non-PP group (48 *vs* 32mmHg). Hospital survivors of PP group (63 patients) demonstrated more substantial decrease in their Sequential Organ Failure Assessment scores and C-reactive protein levels compared to non-PP group (51 patients). The initial PP cycle resulted in a significant elevation of the oxygenation index by 30.8 (-16.4,46.9) mmHg; the second PP cycle demonstrated a maximum increase of 56.3 (13.0,92.8) mmHg. A higher frequency of PP yielded a more pronounced improvement in oxygenation and had the potential to enhance the survival rate. Additionally, the eight patients who was improvements in their oxygenation index during the initial three PP cycles and successfully survived had higher lymphocyte counts (0.2-2.4) *vs* (0.1-0.5)$\times 10^{9}$/L and a longer duration of PP (53.0-113.5) *vs* (36.0-98.5)h. **Conclusion:**PP has the potential to enhance the oxygenation index and survival rates among critically ill COVID-19 patients invasive mechanical ventilated. Notably, a positive correlation was observed between the frequency of PP and the improvement of oxygenation. Our investigation further revealed that the efficacy of the PP may be influenced by lymphocyte count and duration of PP.

Introduction

Prone position (PP) has the potential to reexpand collapsed alveoli and improve the oxygenation index significantly[1-3]. However, it is complicated to be operated and has high risk of tissue crush injuries, particularly for the patients invasive mechanical ventilated [4, 5].

In December 2022, COVID-19 lockdown in China, a substantial influx of critically ill patients necessitated admission into the ICU owing to respiratory failure stemming secondary to COVID-19. Nishikimi, M et al. revealed that the 28-day survival rate of COVID-19 patients undergoing invasive mechanical ventilation was merely 37%[6]. Consequently, the implementation of effective measures to mitigate the mortality rate became an urgent necessity.

Previous researches had demonstrated that PP can enhance the oxygenation index in COVID-19 patients mechanical ventilated[7, 8]. Consequently, the Shanghai Expert Group on Clinical Treatment of Novel Coronavirus Pneumonia had developed guidelines for the implementation of PP treatment. And yet, research

on the potential of PP to enhance the survival rate among invasive mechanical ventilated COVID-19 patients was limited. Particularly, the investigation into the therapeutic efficacy of repeated PP cycles remains inconclusive.

The study dynamically compared the changes in laboratory indices, disease severity, and survival rates between PP patients and matched non-PP patients. Additionally, differences in oxygenation index and survival rate were examined across varying numbers of PPs. This study aimed to assess the therapeutic efficacy of PP in critically ill patients with COVID-19 who required invasive mechanical ventilation.

Materials and methods

Study design

This study conducted a retrospective analysis of 289 critically ill COVID-19 patients who received invasive mechanical ventilation in the ICU of three general hospitals in Taizhou City, Zhejiang Province, from December 1, 2022, to February 1, 2023. Among these cases, 157 were treated with PP, while 132 were not.

The exclusion criteria for the PP group included [7-9]: (1) incomplete case records (67 cases); (2) PP duration less than 12 hours (10 cases); (3) PP treatment initiated before admission to the ICU (1 case); (4) prior extracorporeal membrane oxygenator treatment before PP (1 case). The non-PP group (78 cases) was selected through 1:1 propensity score matching (PSM) analysis with the PP group (78 cases) based on age, sex, underlying disease, and Sequential Organ Failure Assessment (SOFA) score(Fig.1).

Among the PP group, 21 cases underwent only one PP cycle, 23 cases underwent two PPcycles, 15 cases underwent three PP cycles, and 19 cases underwent more than three PP cycles. All patients in PP group were diagnosed with COVID-19 and required invasive mechanical ventilation before the first PP. This study specifically examined the initial three instances of PP. The commencement of PP occurred at 2.0 (2.0, 5.0) days after admission to the ICU. Furthermore, each PP lasting for a median duration of 18.0 (16.0, 24.5) hours and an interval between each PP of 8.8 (6.0, 26.9) hours.

None of them developed life-threatening complications during PP (one case exhibited petechiae on both sides of the abdomen, another case presented petechiae on the left wrist, and two cases experienced facial swelling). This study was approved by the Medical Ethics Committee of Taizhou Hospital, Zhejiang Province, China (Approval NO.: K20230116).

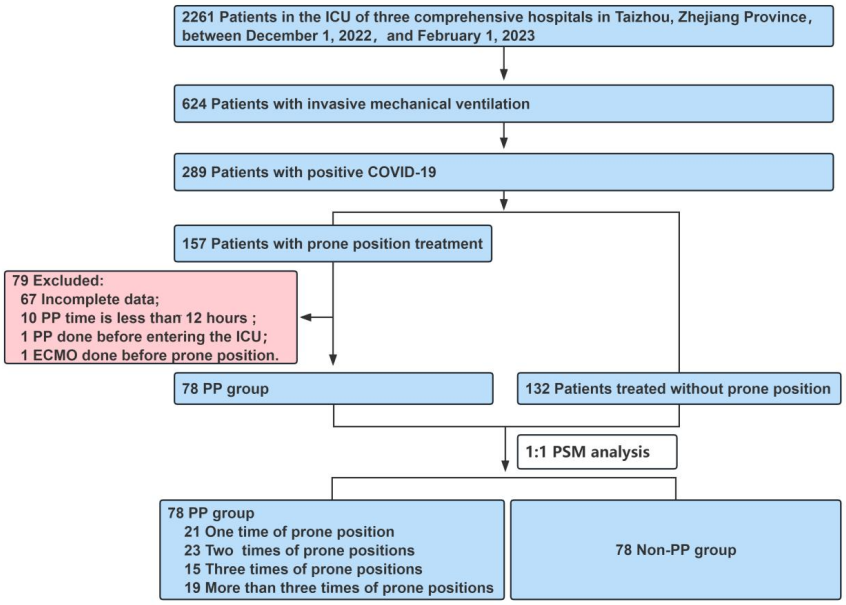

Fig.1 Flow chart of the study. PSM:propensity score matching

COVID-19 diagnostic criteria

COVID-19 were ascertained through the utilization of real-time reverse transcription polymerase chain reaction on nasal and pharyngeal swabs (Ct¡35). Clinical diagnosis and typing were conducted in adherence to the guidelines outlined in the Diagnosis and treatment protocol for COVID-19 (9th edition) [10].

Prone positioning protocol

Guided by the collective agreement among medical professionals and nursing staff within our institution, we have formulated comprehensive protocols for postoperative care, implemented a dedicated interdisciplinary team, and implemented standardized training procedures to ensure the uniformity of PP treatment for patients.

The indications for PP are as follows: When ARDS recalcitrant hypoxemia cannot be corrected by conventional mechanical ventilation; It is strongly recommended for severe ARDS when the oxygenation index is [?]100mmHg; It is recommended for consideration when the oxygenation index is <150mmHg with PEEP [?]5cmH_2O and FiO2 [?]0.6. (After the patient is admitted to the ICU, the treatment team will assess the patient's disease condition and preferences, and initiate PP therapy in accordance with the September 2022 issue of the Shanghai Expert Recommendations on PP Therapy for Patients with COVID-19.)

The contraindications for PP include: 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. Patients with cardiac pacemakers or ventricular arrhythmias implanted within a span of 48 hours; Patients with deep vein thrombosis occurring within a period of 48 hours; Pregnancy.

The termination criteria for PP include: The occurrence of severe complications and potential risks during the operation; The decision to discontinue treatment made by the physician based on the progression of the disease; Voluntary abandonment of treatment by patients and their families.

Data collection

Data was gathered from the electronic medical system including age, gender, underlying disease, clinical symptoms, imaging tests, medication history and laboratory indicators. Indicators with missing data[?]60% were excluded from the statistical analysis. (The comparison of dynamic changes in oxygenation indices between the PP and non-PP groups was limited to the first 13 days of ICU admission.)

The laboratory indicators obtained within 24 hours of the patient's admission to the ICU were designated as the initial laboratory indicators (Entering ICU), while those obtained within 24 hours prior to discharge were designated as the final laboratory indicators (At discharge). The time point closest to the beginning/end of PP (within 24h) was designated as the before/end PP laboratory indicator (B-PP/End-PP).

Detailed information was gathered regarding the PP: encompassing the initiation and conclusion times of each PP; comprehensive respiratory and hemodynamic parameters within the 6-hour pre-PP period, throughout the 12-hour PP duration, and within the 6-hour post-PP period. Additionally, any complications that transpired during the PP were documented.

Definition of PP time point: PP1 refers to the first PP , PP2 refers to the second PP, and PP3 refers to the third PP. T0 represents the time period of 0-6 hours before the current cycle of PP; T1 represents the time period of 0-6 hours in the current cycle of PP; T2 represents the time period of 6-12 hours in the current cycle of PP; and T3 represents the time period of 0-6 hours after the current cycle of PP.

Definition of changes in oxygenation index: Improvement of oxygenation represents that the average oxygenation index in T3 of the current cycle was greater than the average oxygenation index at PP1-T0; No improvement of oxygenation represents that the average oxygenation index in T3 of the current cycle was not greater than the average oxygenation index at PP1-T0.

Calculation of scores

SOFA score: The parameter Include oxygenation index, platelets, bilirubin, mean arterial pressure, medication, Glasgow Coma Scale (GCS) score, creatinine, urine output. The worst value observed within a 24-hour period is utilized for the evaluation of SOFA score within a day It is important to note that a higher SOFA score indicates a poorer prognosis.

APACHE II: The parameter comprises three components, namely the Acute Physiology Score , GCS score, and the Age score. The cumulative score is obtained by summing these three components, with higher scores indicating a more severe condition. The most critical value within a 24-hour period is selected for inclusion in the APACHE II evaluation conducted within a day.

Biological detection

The arterial blood gas analysis was conducted utilizing a Siemens RAPID Point 500. EDTA-K2 anticoagulated blood samples were identified through the utilization of a Mindray BC-6800 Plus fully automated blood cell analyzer. Serum samples were subjected to centrifugation at a speed of 3000 rpm for a duration of 10 minutes, and the detection of CRP was carried out using an AU5831-2 detection module. PCT, TnT, and BNP analyses were performed using a Roche E801 electrochemiluminescence analyzer (Roche Diagnostics, Germany). Sodium citrate plasma samples were centrifuged at 3000 rpm for 10 minutes, and coagulation parameters were collected utilizing a STAR MAX fully automated hemagglutination analyzer (Stago, France).

Statistical analysis

Continuous variables were expressed as (mean±SD) or median (P25, P75), the Mann-Whitney U test was used for comparisons between two groups. Categorical variables were expressed as n (%) and the Chi-square test was utilized to compare rates between two groups. For the comparison of survival rates between groups, Kaplan-Meier survival analysis was employed. Graphs were generated using GraphPad Prism 9 and R (version: 4.2.1). A significance level of $p<0.05$ was considered statistically significant.

Results

Clinical information of study cohorts

This study included 78 PP and 78 non-PP groups, respectively. Among the PP group, 79.5% were male, and the BMI was significantly higher [25.0 (22.7, 27.4) vs 22.5 (20.8, 25.4), p=0.002]. Additionally, the PP group exhibited higher levels of PEEP, Respiratory Rate, and Peak airway pressure [8.5 (6.3, 10.0) *vs* 5.0 (5.0, 7.0);16.0 (15.0, 20.0)*vs* 15.0 (15.0, 15.0);23.0 (18.3, 26.0) *vs* 20.0 (16.0, 24.0), all $p < 0.05$]. In the PP group, 38.5% of patients had Pre-existing pulmonary disease. Furthermore, 84.1% of patients exhibited gross glassy/patchy changes in the lungs. The oxygenation index was found to be lower in the PP group compared to the non-PP group [125.5 (104.3, 169.0) *vs* 212.5 (130.5, 289.5), p<0.001],and the FiO_2 levels were higher [60.0 (45.8, 80.0) *vs* 50.0 (40.0, 61.0), p=0.003]. (Table 1, Fig.S1)

Table 1 Comparison of baseline data between PP group and Non-PP group patients.

	PP group (n=78)	Non-PP group (n=78)	P value
Male (%)	62 (79.5)	61 (78.2)	1.000
Age (year)	77.5 (70.0, 83.0)	76.0 (65.0, 86.0)	0.942
BMI (kg/m^2)	25.0 (22.7, 27.4)	22.5 (20.8, 25.4)	0.002
SOFA score	8.0 (6.0, 9.0)	7.50 (6.0, 9.0)	0.858
APACHE II	22.0 (16.3, 27.0)	22.0 (18.0, 28.0)	0.865
The main reasons for entering the ICU (%)			
Mainly due to COVID-19 infection	35 (44.9)	23 (29.5)	0.076
Chronic disease exacerbation	42 (53.8)	51 (65.4)	
Trauma	1 (1.3)	4 (5.1)	
Intubated (%)	66 (84.6)	70 (89.7)	0.472
Confirmed COVID-19 (%)	60 (76.9)	66 (84.6)	0.310
Infection with sepsis (%)	4 (5.1)	4 (5.1)	1.000
PEEP (cmH_2O)[a]	8.5 (6.3, 10.0)	5.0 (5.0, 7.0)	<0.001
Respiratory Rate (breaths/min)[a]	16.0 (15.0, 20.0)	15.0 (15.0, 15.0)	<0.001
Tidal volume (ml)[a]	456.5 (392.5, 557.3)	452.0 (409.0, 528.0)	0.541
Peak airway pressure (cmH_2O)[a]	23.0 (18.3, 26.0)	20.0 (16.0, 24.0)	0.007
Cydn (ml/cmH2O)[a]	32.6 (23.3, 41.2)	31.5 (25.6, 40.7)	0.892
Underlying disease (%)			
Pre-existing pulmonary disease	30 (38.5)	27 (34.6)	0.739
Hypertension	47 (60.3)	41 (52.6)	0.419
Diabetes	24 (30.8)	22 (28.2)	0.861
Cardiovascular disease	15 (19.2)	14 (17.9)	1.000
Cerebrovascular disease	15 (19.2)	18 (23.1)	0.695
Malignant tumor	19 (24.4)	10 (12.8)	0.100
Hepatitis	6 (7.7)	6 (7.7)	1.000
Chronic kidney disease	11 (14.1)	12 (15.4)	1.000
Chest CT (%)			

Pulmonary plaques or Ground-glass opacity	58 (84.1)	62 (86.1)	0.916
Pulmonary fibrosis	13 (18.8)	19 (26.4)	0.385
Pulmonary consolidation	9 (13.0)	9 (12.5)	1.000
Medication use (%)b			
Antibiotic	76 (97.4)	45 (57.7)	<0.001
Anti COVID-19	39 (50.0)	21 (26.9)	0.005
Immunoglobulin	35 (44.9)	6 (7.7)	<0.001
Dexamethasone	71 (91.0)	58 (74.4)	0.011
Norepinephrine	78 (100.0)	63 (80.8)	<0.001
Blood gas indicators			
PaO_2/FiO_2 ratio (mmHg)	125.5 (104.3, 169.0)	212.5 (130.5, 289.5)	<0.001
FiO_2 (%)	60.0 (45.8, 80.0)	50.0 (40.0, 61.0)	0.003
LAC (mmol/L)	2.1 (1.6, 2.8)	2.3 (1.6, 3.2)	0.433
Inflammation			
CRP (mg/L)	65.6 (18.4, 129.5)	64.1 (27.5, 133.9)	0.414
PCT (ng/ml)	0.4 (0.1, 2.7)	1.1 (0.4, 3.1)	0.036
Blood system			
D-D (mg/L)	2.6 (1.4, 7.4)	2.5 (1.6, 8.3)	0.889
WBC ($\times 10^9$/L)	10.1 (7.8, 12.9)	8.9 (6.4, 13.6)	0.562
LYM ($\times 10^9$/L)	0.5 (0.3, 0.7)	0.5 (0.3, 1.0)	0.328
Hb (g/L)	122.0 (105.3, 138.5)	116.5 (90.3, 130.3)	0.034
PLT (10^9/L)	162.5 (110.8, 199.8)	156.0 (106.5, 216.0)	0.728
Cardiac function			
BNP (pg/ml)	1537.0 (768.3, 3479.5)	1672.0 (472.5, 5370.5)	0.928
TnT (ng/ml)	0.04 (0.02, 0.10)	0.05 (0.03, 0.12)	0.103
LDH (U/L)	516.0 (418.3, 657.0)	386.0 (276.0, 610.0)	0.014
Liver function			
ALT (U/L)	27.0 (16.5, 43.5)	25.5 (16.0, 38.8)	0.725
AST (U/L)	39.0 (27.5, 59.5)	44.0 (27.0, 69.0)	0.508
TBIL (μmol/L)	11.0 (7.3, 17.0)	12.1 (8.5, 14.9)	0.523
Renal function			
Cr (μmol/L)	97.5 (72.3, 201.5)	112.0 (70.5, 186.3)	0.989
Urea (mmol/L)	11.7 (8.0, 19.4)	12.2 (7.9, 18.0)	0.844
eGFR [ml/(min×1.73m^2)]	60.6 (26.9, 81.9)	50.1 (27.0, 86.3)	0.976

Data are n (%) or median (P25,P75).The significance level is 0.05.P values were calculated using Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables.

BMI:Body Mass Index; SOFA:Sequential Organ Failure Assessment; APACHE:Acute Physiology and Chronic Health Evaluation; PEEP:Positive End-Expiratory Pressure; Cydn:Dynamic lung compliance; FiO_2:Fractional concentration of oxygen in inspired air; LAC:Lactic acid; CRP:C-reactive protein; PCT:Procalcitonin; D-D:D-Dimer; WBC:White blood cell; LYM:Lymphocyte; Hb:Hemoglobin; PLT:Platelet; BNP:Brain natriuretic peptide; TnT=TroponinT; LDH:Lactate dehydrogenase; ALT:Alanine aminotransferase; AST:Aspartate aminotransferase; TBIL:Total bilirubin; Cr:Creatinine; eGFR:Estimated Glomerular Filtration Rate.

[a] Data at the beginning of invasive mechanically ventilated.

[b] Medication during ICU treatment.

Dynamics of the oxygenation index in PP group and non-PP group

We conducted a comparative analysis of the changes in oxygenation indices between the PP group and the non-PP group over a 13-day duration. Among the 74 cases in the PP group, their first PP occurred within (3.2±2.8) day on ICU admission, and the termination of PP was observed within (8.0±5.1) day . Notably, the increase in oxygenation index was more pronounced in the PP group compared to the non-PP group (48 *vs* 32 mmHg)(Fig 2).(It is worth mentioning that patient number E28 in the PP group initiated PP on day 25, while E32, E59, and E66 commenced on day 16.)

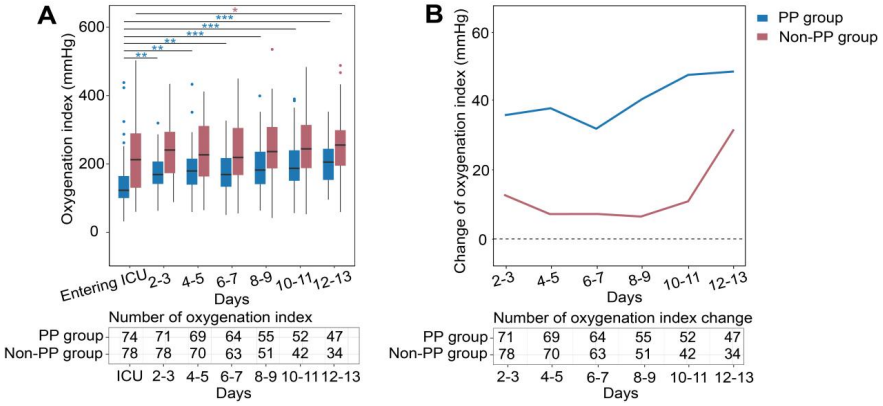

Fig.2 Changes in oxygenation index between patients in PP group and non-PP group.(A) Dynamic monitoring of oxygenation index; Entering ICU:Laboratory indicators within 24 hours of entering the ICU;P values:*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. (B) Dynamic change amplitude of oxygenation index(compared with ICU).

The Relationship between the frequency of PP and oxygenation index

The Improvement of oxygenation in different times of PP showed that PP1 exhibited the highest percentage of oxygenation improvement: PP1 (73.1%,57/78) *vs* PP2 (71.9%,41/57) *vs* PP3 (51.5%,17/33) (Fig 3A).

The more times of PP, the more pronounced of increase in oxygenation index (Fig 3B).

The magnitude of change in oxygenation index was compared among patients who underwent PP at least three times (34 patients), (all compared with the difference in oxygenation index at T0 of the current PP). At the end of the PP (T3), it was observed that PP1 had the highest change: PP1 [30.8 (-16.4,46.9)] *vs* PP2 [7.0 (-11.8,38.0)] *vs* PP3 [1.25 (-28,28)]. Furthermore, during the duration of the PP (T1, T2), PP2 showed the highest change: PP1 [34.5 (17.8,83.4)] *vs* to PP2 [56.3 (13.0,92.8)]*vs* PP3 [40.0 (7.0,67.0)] (Fig 3C).

The oxygenation indices at each point (T0, T1, T2, T3) of PP1 demonstrated a continuous increase after the initiation PP: T0 [115.0 (98.6,147.5)] *vs* T1 [167.0 (133.0,215.0)] *vs* T2 [185.0 (147.5,230.0)]. Furthermore, the oxygenation indices were higher at the end of PP1: T3 [161.3 (116.5,213.4)] *vs* T0 [115.0 (98.6,147.5)] (Fig 3D).

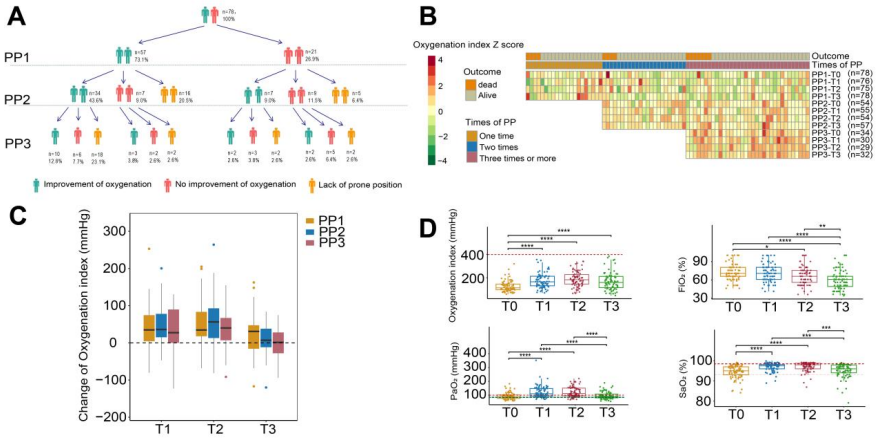

Fig.3 The relationship between the frequency of PP group and the improvement of patient's oxygenation index. (A) Improvement of oxygenation in different times of PP; (B) The oxygenation index from PP1 to PP3; (C) Change amplitude of oxygenation index from PP1 to PP3 with three times or more PP patients (N=34); (D) Arterial blood gas indicators monitoring during PP1.

PP:Prone position;PP1,PP2,PP3:The 1st, 2nd, and 3rd time of PP;T0:0-6 hours before the current PP;T1:Starting from PP for 0-6 hours;T2:Starting from PP for 6-12 hours; T3:0-6 hours after the end of the PP. P values: *p < 0.05; **p < 0.01;***p < 0.001;****p < 0.0001.

The Relationship between PP and survival rate

Within 10 days after the ICUadmission, the PP group exhibited a notably higher survival rate compared to the non-PP group (78.2% *vs*64.1%, p=0.049) (Fig.4A). PP group demonstrated survival rates of 48.7% and 32.1% within 20 and 30 days, respectively (Fig.4B, C). Multiple PP cycles improved hospitalization survival: One time (81.0%, 17/21) *vs* Two times (82.6%, 19/23) *vs* Three times (100.0%, 15/15). Notably, there was no significant disparity in SOFA score based on the frequency of PP (Fig.4D, E).

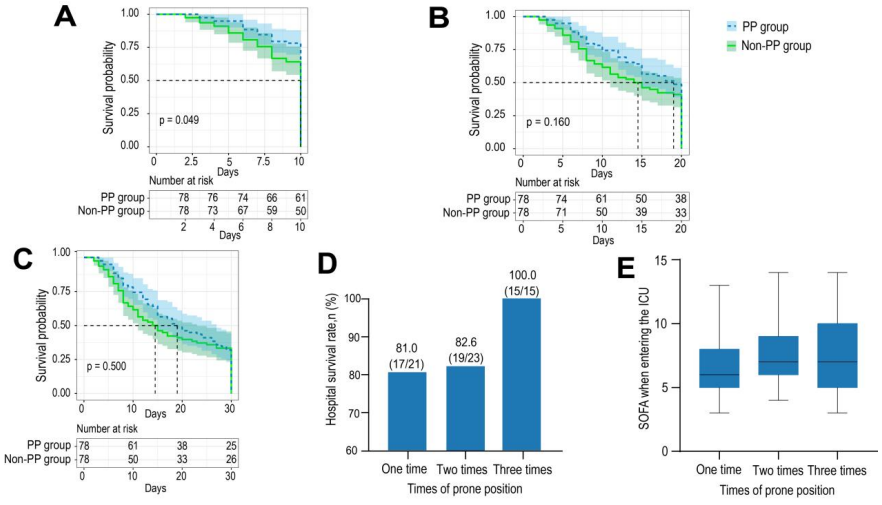

Fig.4 The relationship between prone position and its frequency with hospital survival rate. (A) 10-day survival analysis; (B) 20-day survival analysis; (C) 30-day survival analysis; (D) The hospital survival rate

of patients with different prone position frequencies; (E) SOFA of patients with different prone position frequencies.

Comparison of oxygenation index, SOFA score and CRP between PP group and non-PP group ofhospital survivors

The **hospital survivors** of PP group(n=63) exhibited a higher BMI [25.0 (22.5, 27.5) *vs* . 22.2 (20.2, 24.9), p=0.003] and a greater prevalence of malignancies (27.0% *vs* . 9.8%, p=0.038) compared to the non-PP group (n=51). Furthermore, the PP group demonstrated a higher incidence of bacterial (92.1% *vs* . 66.7%, p=0.001) and mycotic (71.4% *vs* . 49.0%, p=0.024)infection during ICU. Additionally, they had a lower oxygenation index [127.0 (101.5, 164.5) *vs* 228.0 (138.0, 314.0), p<0.001] (See table S1).

The oxygenation index after PP treatment is higher than before [168.0 (135.5,195.5) *vs* 111.0 (93.0,132.0)],while SOFA score, CRP decreased [8.0 (6.0,9.0) *vs* 9.0 (7.0,10.0)]; [59.7 (24.9, 121.0) *vs* 90.6 (52.1,137.0)] (Fig 5).

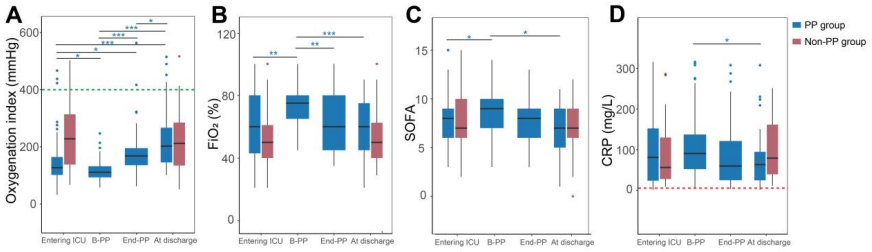

Fig.5 Comparison of laboratory indicators of surviving patients between PP and non-PP group. (A-D) Dynamic monitoring of oxygenation index,FiO2,SOFA and CRP.

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. P values: *p < 0.05; **p < 0.01; ***p < 0.001.

Comparison of baseline data between patients of oxygenation improvement and without improvement in the initital three PP cycles

Eight hospital survivors who experienced enhanced oxygenation in the initial three PP cycles exhibited that their lymphocyte counts were ranging from 0.2 to 2.4 ($\times 10^9$/L), WBC were ranging from 3.3 to 16.2 ($\times 10^9$/L), and cumulative duration of PP were 53.0 to 113.5 (h). Additionally, five patients a lymphocyte count exceeding 0.5 ($\times 10^9$/L).

Patients who did not experience any improvement in oxygenation exhibited that lymphocyte counts ranging from 0.1 to 0.5 ($\times 10^9$/L), white WBC ranging from 2.3 to 11.4 ($\times$109/L), and a total duration of the first three PP periods ranging from 36.0 to 98.6 hours. Among these patients, four individuals had a total duration of the first three PP periods of less than 46 hours (Fig 6).

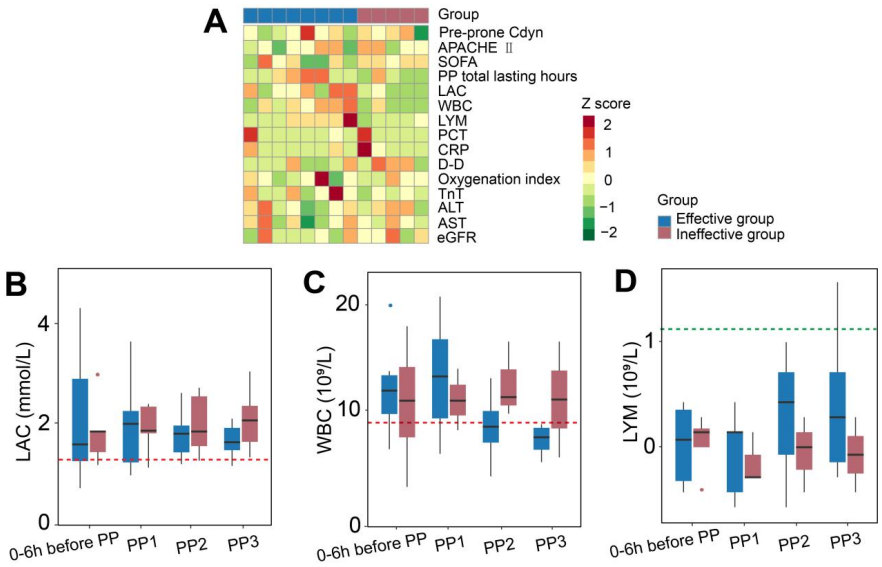

Fig.6 Comparison of baseline data and dynamic laboratory indicators between Patients who experienced improved or no improvement in the oxygenation index from PP1 to PP3. (A) Comparison of Baseline data; (B-D) Dynamic monitoring of LAC, WBC and LYM. The data in the box plot is based on the average level of each patient at the corresponding stage.

PP1,PP2,PP3:The 1st, 2nd, and 3rd time of prone position.

Discussion

This study aimed to examine the impact of the PP on critically ill COVID-19 patients receiving invasive mechanical ventilation. We employed a matching technique to establish comparable groups. The findings revealed that PP has the potential to enhance the oxygenation levels and All-cause survival rate. Furthermore, a positive correlation was observed between the frequency of PP and the extent of oxygenation improvement. The potential mechanism underlying the effect of the PP may be associated with variations in lymphocyte count and the duration of PP.

According to our data, the utilization of PP appeared to enhance oxygenation and improve short-term survival rate in COVID-19 patients who are invasive mechanical ventilated. Within 10 days after ICU admission,, the survival rate of individuals in the PP group was notably higher compared to those in the non-PP group, 94.9% of patients received PP treatment. However, no significant disparity in survival rate was observed between the two groups at the 20-day and 30-day. 29.5% and 6.4% of patients in the PP group have undergone PP treatment for 10-20 days and 20-30 days, respectively. Notably, patients who underwent PP three times exhibited a 100.0% survival rate during their hospitalization period.

The survival rate during ICU stay was observed to be lower in patients with critical COVID-19 infection, ranging from 33.3% to 47.6% [11-13]. In a retrospective analysis conducted by Douglas, I.S et al [14], a total of 61 critically ill patients receiving invasive mechanical ventilation for COVID-19 were examined, revealing a hospital survival rate of 68.9% in the PP group. However, the study lacked a control group to ascertain whether the PP intervention influenced the survival rate. Similarly, Engerstrom, L et al [15] investigated 1714 patients on mechanical ventilation in the ICU with neocoronary, and determined that the PP did not have a significant impact on the 30-day survival rate. Hence, it can be inferred that the implementation of PP yields enhanced short-term survival rates, and the adoption of multiple PPs contributes to improved survival rates during hospitalization; however, their impact on long-term survival appears to be comparatively limited.

The data presented in our study indicates a positive correlation between the frequency of PP and the extent

of improvement in oxygenation. Specifically, the oxygenation index continued to rise for a duration of 6 hours following the conclusion of the initial PP, with the most significant increase observed during the second PP. Among the 14 patients, the second PP resulted in the highest increase in oxygenation index (ranging from 109 mmHg to 373 mmHg), and 4 patients achieved normal levels of oxygenation index.

Previous research has established[16, 17] the efficacy of PP in enhancing the oxygenation index among patients. In a retrospective analysis conducted by Tyler T. Weiss et al [7], involving 42 COVID-19 patients receiving invasive mechanical ventilation, it was observed that repeated PP yielded a more significant improvement in oxygenation. However, the impact of varying frequencies of PP on oxygenation alteration remained inconclusive. Our study, on the other hand, determined that PP1 exhibited the longest duration of oxygenation, while PP2 demonstrated the most substantial increase in oxygenation levels for the majority of patients.

The current study provides evidence that PP can effectively mitigate the severity of COVID-19 in critically ill patients who require invasive mechanical ventilation. Previous research has demonstrated the utility of the SOFA score in evaluating disease severity among mechanically ventilated patients. In this study, approximately half of the patients experienced a decrease in their SOFA score following treatment with PP. Notably, nearly one-third of the patients exhibited a reduction in SOFA score exceeding 20%, while another one-third did not demonstrate any improvement in their SOFA score.

Patients who did not experience any improvement in SOFA score exhibited a significantly longer average duration between their admission to ICU and the commencement of PP (3day *vs* 1day). Additionally, these patients had a shorter average duration of each PP (15.5h *vs*22.0h). Previous research studies[20, 21] have demonstrated that PP enhances oxygenation in patients, yet it remains uncertain whether PP effectively reduces the severity of the disease. We hypothesize that the alteration in disease severity among patients may be associated with the start time and duration of PP interventions.

Furthermore, a comparison was conducted between patients who exhibited improvement and survival in the initial three PP oxygenation indices and those who did not. The findings revealed that the duration of PP was significantly longer in patients who demonstrated improvement in the initial three PP oxygenation indices. Previous studies [22, 23] have also reported that early and prolonged implementation of PP may yield enhanced oxygenation outcomes in individuals afflicted with COVID-19-induced lung infections.

Okin et al. [24] conducted a study involving 157 patients with neocoronary who were subjected to invasive mechanical ventilation. Their analysis revealed that extended durations of PP ([?]24h) led to notable enhancements in respiratory compliance, oxygenation indices, as well as 30-day and 90-day survival rates. The researchers concluded that recurrent supine positioning could potentially exacerbate atelectasis injury and ventilator-induced lung injury. Consequently, they suggest that initiating and prolonging PP may offer greater benefits in terms of improving oxygenation.

In the present study, it was observed that lymphocyte counts could potentially serve as a useful indicator for assessing the efficacy of PP. The collected data revealed that patients who demonstrated improvement and survival after undergoing the initial three sessions of PP with oxygenation exhibited higher WBC and lymphocyte counts upon admission to the ICU compared to those who did not experience any enhancement in oxygenation. Furthermore, it was observed that the lymphocyte counts of patients who failed to exhibit any improvement in oxygenation were consistently [?]0.5×109/L. Previous studies [25, 26] have demonstrated that lymphocyte count serves as a valuable and dependable measure for assessing the severity of COVID-19. Patients with severe COVID-19 exhibit compromised cellular immune function, resulting in a diminished lymphocyte count.

However, the current body of academic literature exhibits a dearth of information pertaining to the correlation between lymphocyte counts and PP. In a prospective study undertaken by Coppo et al. [27], it was discovered that an active inflammatory response was linked to a more advantageous PP oxygenation index. Our contention is that PP might exhibit diminished efficacy in patients with diminished lymphocyte counts and compromised immune systems.

This study is a retrospective investigation conducted on a limited sample size. The participants of this study consisted of critically ill patients diagnosed with COVID-19, who were receiving invasive mechanical ventilation in ICU. These patients exhibited more severe and intricate medical conditions, as well as a higher number of influencing factors. However, we conducted the study in which we included PPs from three general hospitals simultaneously.The relevant information and inspection data was complete. Additionally, we employed a 1:1 PSM analysis to ensure comparability between the PP group and non-PP group, thereby minimizing differences in objective factors. We then dynamically compared the oxygenation index, disease severity, and survival rate between the two groups throughout their hospitalization, thus presenting the impact of PP in a comprehensive and multi-faceted manner across multiple centers.

Conclusions

The PP has been found to enhance the oxygenation index and increase the 10-day survival rate of critically ill COVID-19 patients receiving invasive mechanical ventilation in ICU. The frequency of PP correlates with a more significant improvement in the oxygenation index. However, it is worth noting that the effectiveness of PP may be reduced in patients with lower absolute lymphocyte values, while earlier and longer PP may yield better outcomes. Despite the challenges associated with implementing PP in patients on invasive mechanical ventilation, it is recommended to be performed whenever feasible, provided there are no clear contraindications to invasive mechanical ventilation.

Abbreviations

PP: Prone position; SOFA: Sequential Organ Failure Assessment; APACHE:Acute Physiology and Chronic Health Evaluation; BMI:Body Mass Index; PEEP:Positive End-Expiratory Pressure; Cydn:Dynamic lung compliance; FiO_2:Fractional concentration of oxygen in inspired air; LAC:Lactic acid; CRP:C-reactive protein; WBC:White blood cell; LYM:Lymphocyte.

Acknowledgements

We would like to thank the nurses in three general hospitals located in Taizhou, Zhejiang Province for sampling specimens, and thank the patients for being enrolled in this study.

Author contributions

Yuwei Zheng takes responsibility for the content of the manuscript, including the data and analysisand wrote the manuscript. Bo Shen,Yinghe Xu contributed to the conception and design of the study, analysis, and interpretation of the data , Xiaojie Bi,Chaochao Chen contributed to the conception and design of the study, collection, analysis, and interpretation of the data, and revised the manuscript, Jing Wang and Yufen Zheng contributed to the collection, analysis, and interpretation of the data and revised the manuscript. Jun Li, Shiyong Chen, Hongguo Zhu , and Jiaqin Xu contributed to the collection of the data and revised the manuscript. Qiaofei Zheng, Yuan Yuan,Yafei Wang,Wenyuan Zhang,and Yongpo Jiang contributed to the conception of the study.interpretation of the data, and revised the manuscript. All authors read and approved the final manuscript.

Funding

Support was provided solely from institutional and/or departmental sources.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Taizhou Hospital, Zhejiang Province, China (Approval NO.: K20230116).

Consent for publication

None.

Competing interests

The authors declare no competing interests.

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