Original Article

Effect of mechanical ventilation and pulmonary rehabilitation in patients with ICU-acquired weakness: a systematic review and meta-analysis

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Background: ICU-acquired weakness (ICU-AW) is characterized by neuromuscular damage such as limb weakness, yet the cause of ICU-AW remains unclear, which significantly increases the time a patient spends on mechanical ventilation (MV)/in ICU and can even affect a patient's survival rate and quality of life after being discharged. Pulmonary rehabilitation (PR)-related measures can effectively improve the ICU-AW situation, but in the specific implementation actions, many obstacles have been produced, and the treatment effect has been controversial, especially in the application process of mechanically ventilated patients. This study aims to confirm the efficacy of using MV alongside PR for patients with ICU-AW.

Methods: We obtained related randomized controlled trials (RCTs) from Chinese and English databases. All RCTs relevant to the use of PR in ICU-AW patients were retrieved from the following databases from their date of inception through January 31th, 2021: PubMed, EMBASE, The Cochrane Central Register of Controlled Trials, CINAHL, Joanna Briggs Institute (JBI), Web of Science, The Wanfang Database, and CNKI. This literature underwent screening, quality evaluation, and index data extraction by two independent researchers. The evaluation data were meta-analyzed with RevMan 5.3 software (Cochrane, London, UK).

Results: In total, we analyzed 15 articles which included 1,710 patients. We found that using PR alongside MV can effectively improve a patient's Medical Research Council (MRC) muscle strength score [mean difference (MD) =4.92, P=0.07], reduce the prevalence of ICU-AW [odds ratio (OR) =0.24, P<0.001], and shorten both MV duration [standardized mean difference (SMD) =−1.50, P<0.001] and ICU stay (SMD =−0.68, P=0.03).

Discussion: Implementing PR alongside MV can effectively reduce ICU-AW in patients. However, our standardized cluster PR study still requires further clarification to confirm how various intervention methods can reduce ICU-AW.

Keywords: Acquired weakness (AW); mechanical ventilation (MV); pulmonary rehabilitation (PR); meta-analysis; ICU

Submitted Jun 29, 2021. Accepted for publication Sep 10, 2021.
doi: 10.21037/apm-21-1928
View this article at: https://dx.doi.org/10.21037/apm-21-1928

Introduction

ICU-acquired weakness (ICU-AW) is characterized by neuromuscular damage such as limb weakness, yet the cause of ICU-AW remains unclear. ICU-AW is a clinical diagnosis, refers to the presence and severity of muscle weakness, common risk factors are drugs (such as neuromuscular blocking drugs, glucocorticoids, steroids), diabetes, long-term ventilation and prolonged immobility lead to axon neurodegenerative disease (1). The incidence rate of ICU-AW is 25–85%, especially in patients undergoing mechanical ventilation (MV). ICU-AW significantly increases the time a patient spends on MV/in ICU and can even affect a patient's survival rate and quality of life after being discharged (2,3). Previous research has found that pulmonary rehabilitation (PR) can help ICU-AW patients with weaning, accelerate discharge time, and improve muscle strength (4,5). In 2013, the American Thoracic Society (ATS) redefined the concept of PR (6). In recent years, scholars around the world have questioned the impact of early intervention methods for ICU-AW patients; however, through our preliminary research, we found that PR measures such as nutritional support, psychological intervention, and muscle stimulation can have a positive impact on ICU-AW (7-9). At present, there is a lack of unified, standardized, and systematic schemes for using MV alongside PR, which has amounted to MV's benefits for ICU-AW remaining unclear. In addition, the implementation of PR can pose many risks, such as activity intolerance, decannulation, etc., which can aggravate the occurrence of ICU-AW and seriously compromise patient safety. We ask a series of scientific questions? Does comprehensive PR work for critically ill patients with MV? Secondly, in what aspects? Finally, is the effect of comprehensive PR training equivalent to that of single rehabilitation training? From our previous research, no meta-analysis of PR has been performed to study its function on ICU-AW. Therefore, this study aims to improve the clinical and theoretical understanding of using MV alongside PR in patients with ICU-AW. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1928).

Methods

Retrieval policy

For this study, relevant data published were retrieved from the following databases from their date of inception through January 31th, 2021 was retrieved from Chinese databases including CNKI, The Wanfang Database, China Science and Technology Journal Database (VIP), and China Biology Medicine Disc (CBM), the China Biomedical Literature Database; and English databases including PubMed, the Cochrane Library, the ATS website, the Joanna Briggs Institute (JBI) Library for Evidence-Based Healthcare (EBHC), EMBASE, CINAHL, the British Thoracic Society (BTS) website, and Web of Science. Our search used the following keywords: "Intensive care unit", "ICU", and "Critical illness"; "Artificial Ventilation" and "Mechanical Ventilation"; "Pulmonary Rehabilitation", "Respiratory Rehabilitation", "Chest physical therapy", and "Chest Physiotherapy"; and "Intensive Care Unit acquired weakness" and "ICU-AW". Our search first assessed systematic reviews from the Cochrane Library and JBI Library, with the titles, abstracts, keywords, and subject words from this search analyzed to confirm we had accurate keywords for our literature search. These subject words and keywords were then searched in the above databases to determine if they met the inclusion criteria. Full texts were then read to confirm their suitability for the study.

Criteria for inclusion and exclusion

Research design

We analyzed randomized controlled trials (RCTs) of ICU-AW patients who underwent PR with MV.

Subjects included

We selected ICU patients who were over 18 years old and had undergone PR with MV for more than 24 hours. MV patients who had completed the PR program were chosen as the experimental group, while patients who were treated at the same time and who underwent PR without MV were nominated as the control group. In order to clarify the effect of PR intervention, we used one or more of the combined measures aimed at promoting PR and increasing a patient's Medical Research Council (MRC) muscle strength score (6). The following types of studies were excluded: articles regarding single implementation measures; patients who did not undergo MV or were under the age of 18; repetitive publications, conference papers, and review articles; articles with only abstracts, improper data collection, or statistical analysis errors.

Outcome measures

ICU-AW is the most common neuromuscular injury that affects the clinical course and prognosis of ICU patients. Its definitions vary. It is expressed as "Clinically, there is no other reasonable cause of symmetrical disease except critical illness", a syndrome that affects the symptoms of limbs and respiratory muscle strength. The MRC Scale and Grip Strength Test are the gold standard for diagnosis, therefore (10). Main outcome measures: the ICU-AW diagnostic criteria, evaluated by (I) MRC score (10); (II) grip strength; (III) ICU-AW prevalence. Secondary outcome measures: (I) ICU time; (II) mortality; (III) MV duration.

Data extraction

Two raters used a pre-designed data collection form (Microsoft Office Excel 2013) to extract all the data independently. The following information was extracted: First author, publication year, study design, PR type, participant characteristics, sample size, PR approach in the intervention group, PR approach in the control group, outcomes, and the duration of study. This data was cross-checked.

Literature quality evaluation

The authenticity of the included literature was evaluated using the Cochrane risk-of-bias tool for RCTs. The evaluation content included: (I) random sequence generation; (II) allocation concealment; (III) blinding of participant and personnel; (IV) blinding of outcome assessment; (V) incomplete outcome data (VI) selective reporting; (VII) other biases (11). Two researchers evaluated each item separately and categorized them by low bias risk, high bias risk, or unclear risk. If a study fully met the above criteria, it was given the quality grade of A, but if it only partially satisfied the criteria, it was given a B grade, and if it did not meet the criteria at all, it was given a C grade. For any conflicts between the evaluation of the two independent researchers, a third researcher was consulted. Any material found to be of low quality after reading the full text was directly eliminated from the study to guarantee the quality of the literature used.

Statistical methods

Meta-analysis was conducted using RevMan 5.3 software. The same results of the included literature are combined. The odds ratio (OR) and 95% confidence interval (CI) were applied for binary variable evaluation, and the weighted mean difference (WMD), or standardized mean difference (SMD) and 95% CI were applied to evaluate continuous variables. To evaluate quartiles, we used the estimation formula of Hozo *et al.* (12) and estimated it in the online calculator formula (13). Chi-square test was applied to test heterogeneity ($P<0.05$, $I^2>50\%$), and if it was found to exist, sensitivity analysis was applied to find out the cause. A random-effects model was used again if heterogeneity still could not be eliminated. Sensitivity analysis, subgroup analysis, or just descriptive analysis were applied when meeting significant clinical heterogeneity. A fixed-benefit model was used for data with no significant heterogeneity ($P\geq0.05$, $I^2\leq50\%$) (14). Sensitivity analysis will use the method of excluding documents one by one and recording the changes in heterogeneity. If each document is removed one by one, the heterogeneity will not change, indicating that the results are relatively robust. The subgroup analysis will compare the clinical characteristics (countries, intervention methods, literature quality scores) included in all the included literature as sub-sites to see the source of heterogeneity.

Results

Search results

From our preliminary search, 977 Chinese and English articles were obtained, and 343 duplicate articles were removed by EndNote software. After reading through abstracts and full texts, we excluded reviews, non-RCT studies, and studies where patients did not undergo MV. This left us with 15 (4,9,15-27) studies for our analysis (*Figure 1*).

Basic information and methodological quality evaluation of included literature

Of the 15 studies included (4,9,15-27), 4 were in Chinese (24-27) and 11 were in English (4,9,15-23). The literature was selected from six different countries and the years of publication varied between 2009 and 2020, with 80% published in the last 10 years (*Table 1*). RCTs were used in all of the selected literature, intervention methods were described in detail, and outcome indicators were clear. Furthermore, in each study, the baseline data of the trial and control groups were comparable. Regarding literature quality, 3 articles were given an A grade, while the rest were given a B (*Table 2*, *Figures 2,3*).

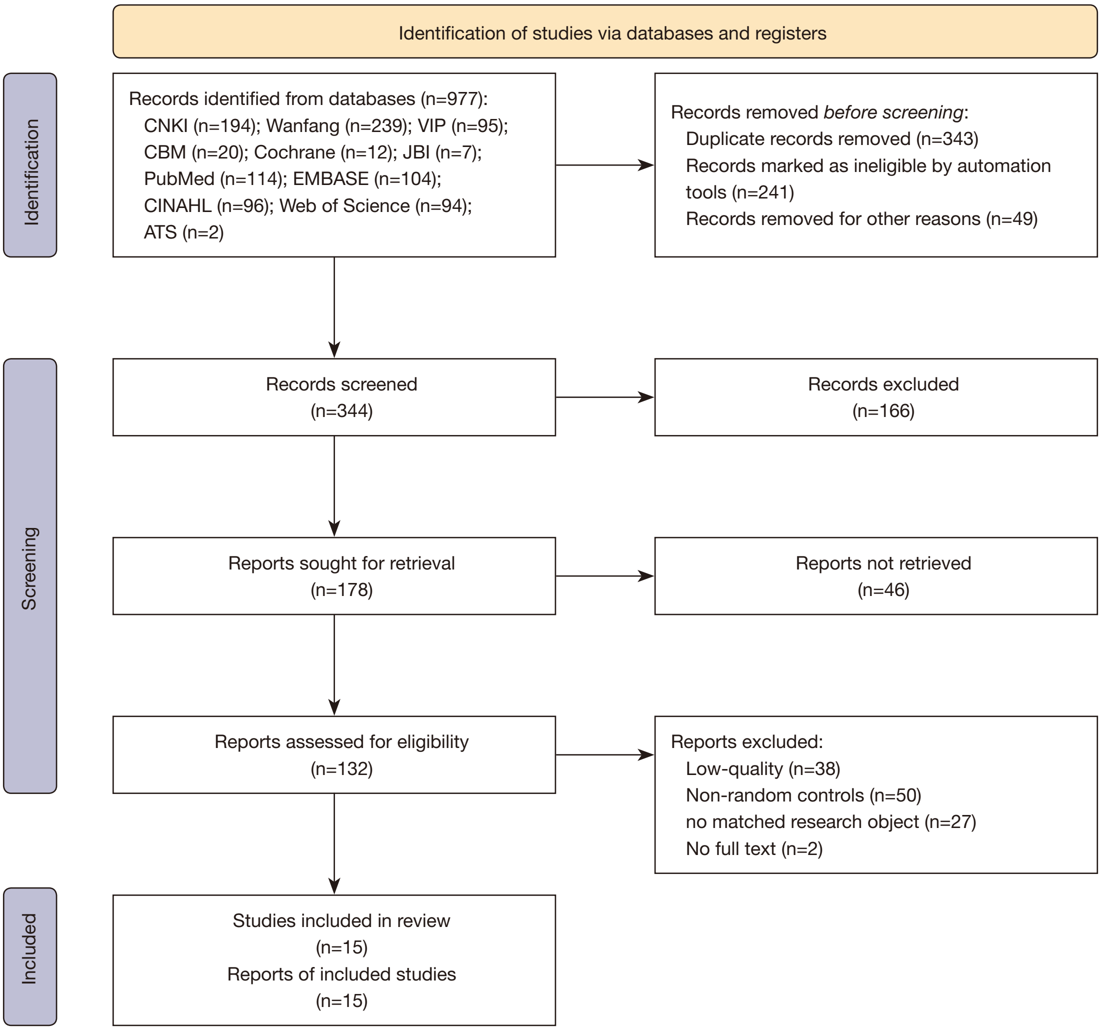

Figure 1 Schematic of literature search and screening. JBI, Joanna Briggs Institute; ATS, American Thoracic Society.

Influence of PR on ICU-AW patients with MV

ICU-AW occurrence was evaluated by an MRC score in 6 articles (17,18,23-26), while muscle strength was used to determine an MRC score in 8 articles (9,15,17,18,20,24,26,27), and grip strength used in 3 articles (4,9,17). The key results of each category were as follows: (I) ICU-AW prevalence: 6 RCT studies (17,18,23-26) reported that PR affected ICU-AW prevalence amongst patients with MV in ICU. The heterogeneity of each study was low ($P<0.001$, $I^2=43\%$), so the analysis was completed via a fixed-benefit model (*Figure 4*). These results show that PR can reduce ICU-AW [OR =0.24, 95% CI: (0.15, 0.38), P<0.001]. (II) MRC score: 8 studies (9,15,17,18,20,24,26,27) reported that PR affects the MRC score of patients with MV in ICU. The heterogeneity of this combined analysis was high ($P<0.001$, $I^2=90.00\%$). Subgroup analysis was conducted according to intervention measures, publication time, and place, and no clinical heterogeneity existed. Therefore, the random-effects model was applied. It showed that PR could effectively strengthen muscles [MD =3.10.0, 95% CI: (–0.272.13, 6.747), P=0.07] (*Figure 5*). (III) Grip strength: 3 studies (4,9,17) reported the grip strength of patients. The heterogeneity of this combined analysis was high ($P<0.001$, $I^2=95.00\%$). This was because the grip strength result reported in the eliminated study was significantly different from the other two. However, these reports show that PR did not influence the grip strength of patients with MV in ICU [SMD =–0.68, 95% CI: (–1.27, 0.08), P=0.03].

Table 1 Basic information of included studies

Number	Author and publication date	Country	Sample size	Research objects	Interventions: Experimental group	Interventions: Control group	Outcome measures
1	Abu-Khaber HA, 2013, (15)	Egypt	80	MV time >24 h, respiratory failure, type I, II	Pulmonary function therapy + muscle electrical stimulation + routine nursing	Routine nursing measures	①④
2	Schweickert WD, 2009, (9)	America	104	MV time >27 h, barthel ≥70	Physical therapy + pulmonary function therapy + routine nursing	Routine nursing measures	①③④⑤
3	Dall' Acqua AM, 2017, (16)	Brazil	25	MV time >24 h, respiratory failure, gastrointestinal disease	Electrical stimulation therapy + muscle movement + routine nursing	Routine nursing measures	④⑤⑦
4	Kho ME, 2015, (17)	America	34	MV time >24 h, the length of stay in ICU >48 h	Electrical stimulation therapy + muscle movement + routine nursing	Routine nursing measures	①③⑤
5	Routsi C, 2010, (18)	Greece	52	All patients admitted to ICU (except one patient without MV)	Muscle electrical stimulation + routine nursing	Routine nursing measures	①④⑤⑦
6	Dong ZH, 2014, (19)	China	60	Tracheal intubation or tracheotomy ≥48 h, admitted to ICU	Muscle movement + routine nursing	Routine nursing measures	④⑤⑦
7	Morris PE, 2016, (4)	America	300	Acute respiratory failure patients, with endotracheal tube MV or mask noninvasive ventilation	Muscle movement + routine nursing	Routine nursing measures	③⑤
8	Kayambu G, 2015, (20)	Australia	50	MV time ≥48 h, septicemia	Muscle electrical stimulation + Pulmonary function therapy + routine nursing	Routine nursing measures	①④⑤
9	Patman S, 2001, (21)	Australia	210	Patients with MV after elective or semi emergency cardiac surgery	Respiratory function training + routine nursing	Routine nursing measures	④⑤
10	Zanotti E, 2003, (22)	Italy	24	Chronic hypercapnia caused by COPD, respiratory failure, tracheotomy for MV and severe peripheral muscle atrophy existed	Muscle electrical stimulation + pulmonary function therapy + routine nursing	Routine nursing measures	①⑤
11	Patel BK, 2014, (23)	America	104	MV time ≥72 h, admitted to ICU	Muscle movement + pulmonary function therapy + nutritional support + routine nursing	Routine nursing measures	④⑤
12	Huang HY, 2016, (24)	China	100	Admitted to ICU on the day of MV, and MV time ≥24 h	Muscle movement + pulmonary function therapy + nutritional support + routine nursing	Routine nursing measures	①②④⑤
13	Li YL, 2018, (25)	China	84	MV time ≥24 h， length of stay in ICU ≥24h	Muscle movement + pulmonary function therapy + routine nursing	Routine nursing measures	②④⑤
14	Liang YQ, 2020, (26)	China	85	MV time ≥24 h, length of stay in ICU ≥72 h	Muscle movement + pulmonary function therapy + nutritional support + psychological intervention	Routine nursing measures	①②④⑤
15	Guo T, 2017, (27)	China	398	Length of stay in ICU ≥24 h, MV time ≥24 h	Muscle movement + pulmonary function therapy + routine nursing	Routine nursing measures	①②④⑤

①: muscle strength (MRC score); ②: ICU-AW occurrence rate; ③: grip; ④: MV time; ⑤: hospitalization; ⑥: fatality rate. MV, mechanical ventilation; MRC, Medical Research Council; ICU-AW, ICU-acquired weakness.

Table 2 Methodological quality evaluation of included literature

Number	Author and publication date	Is it random (selection bias)?	Assign hidden (selection bias)	Blind method (performance bias)	Is the outcome data complete (detection bias)?	Selective report results (attrition bias)	Bias from other sources (reporting bias)
1	Abu-Khaber HA, 2013, (15)	Low risk offset	Unclear	Unclear	Unclear	Low risk offset	Low risk offset
2	Schweickert WD, 2009, (9)	Low risk offset	Low risk offset	Low risk offset	Low risk offset	Low risk offset	Low risk offset
3	Dall' Acqua AM, 2017, (16)	Low risk offset	Low risk offset	Low risk offset	Low risk offset	Low risk offset	Low risk offset
4	Kho ME, 2015, (17)	Low risk offset	Unclear	Unclear	Low risk offset	Unclear	Unclear
5	Routsi C, 2010, (18)	Low risk offset	Unclear	Unclear	Low risk offset	Low risk offset	Unclear
6	Dong ZH, 2014, (19)	Low risk offset	Unclear	Unclear	Unclear	Unclear	Unclear
7	Morris PE, 2016, (4)	Low risk offset	Unclear	Unclear	Low risk offset	Low risk offset	Low risk offset
8	Kayambu G, 2015, (20)	Low risk offset	Low risk offset	Unclear	Unclear	Unclear	Unclear
9	Patman S, 2001, (21)	Low risk offset	Low risk offset	Unclear	Unclear	Unclear	Unclear
10	Zanotti E, 2003, (22)	Unclear	Unclear	Unclear	Low risk offset	Low risk offset	Unclear
11	Patel BK, 2014, (23)	Unclear	Unclear	Unclear	Low risk offset	Low risk offset	Unclear
12	Huang HY, 2016, (24)	Low risk offset	Unclear	Unclear	Low risk offset	Low risk offset	Unclear
13	Li YL, 2018, (25)	Low risk offset	Unclear	Unclear	Unclear	Low risk offset	Unclear
14	Liang YQ, 2020, (26)	Unclear	Unclear	Unclear	Low risk offset	Low risk offset	Unclear
15	Guo T, 2017, (27)	Unclear	Unclear	Unclear	Low risk offset	Low risk offset	Unclear

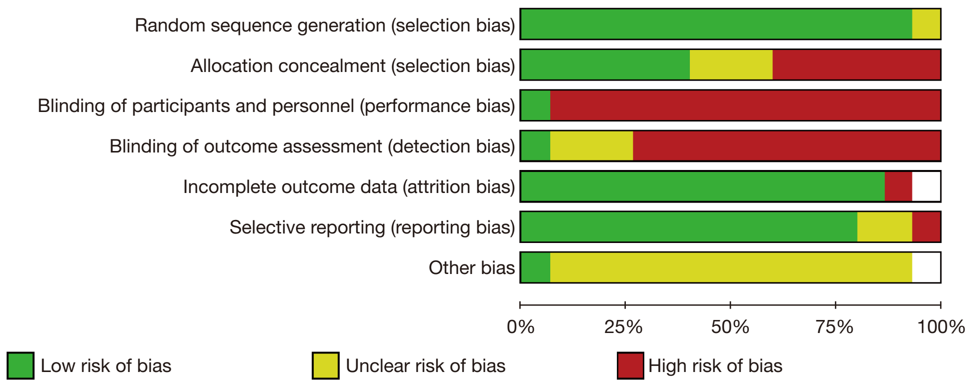

Figure 2 Risk bias diagram.

Figure 3 Risk bias assessment chart.

Effect of PR on MV and ICU time

Fourteen studies (4,9,15,16,18-27) addressed the effect of PR on the amount of time ICU patients spent on MV. Due to the difference in the mean unit of each study, high heterogeneity (P<0.001, I^2=98%) was determined by using SMD combined with effect volume. After excluding the study with largest sample size from analyses, the effects observed in the primary analysis were not changed. Therefore, a random-effects model was used (*Figure 6*). It showed that PR could effectively reduce the amount of time ICU patients spend on MV [SMD =−1.50, 95% CI: (−2.42, −0.57), P=0.002]. Regarding the length of a patient's stay in ICU, 12 Studies (4,9,16,18-22,24-27) reported on the effect PR has on the ICU time of patients with MV. Because the mean units of each study were not unified and the differences were large, high heterogeneity (P<0.001, I^2=96%) was determined by using SMD combined with effect volume. After excluding the study with largest sample size from analyses, the effects observed in the primary analysis were not changed. Therefore, we again applied the random-effects model (*Figure 7*). It showed that PR could effectively reduce the ICU length of stay [SMD =−0.68, 95% CI: (−1.27, −0.08), P=0.03].

Effect of PR on the mortality of ICU patients with MV

Four studies (9,16,19,20) researched the relationship between PR and mortality in ICU patients with MV. We also used the fixed-effects model here as the heterogeneity

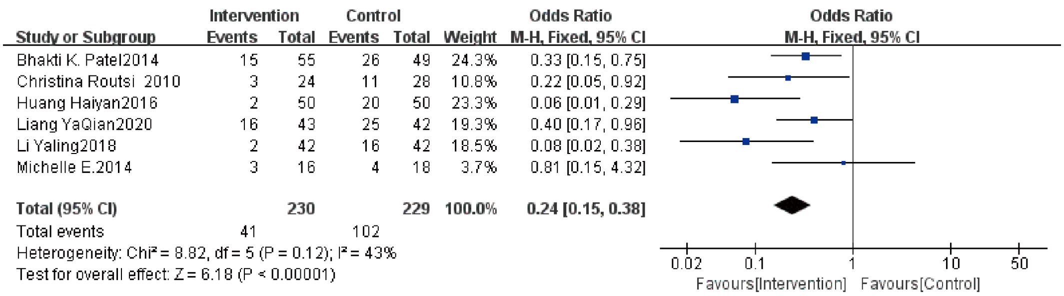

Figure 4 PR effect on ICU-AW. PR, pulmonary rehabilitation; ICU-AW, ICU-acquired weakness; CI, confidence interval.

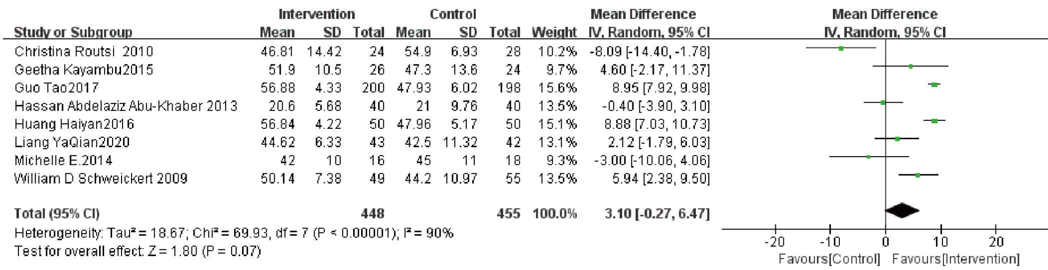

Figure 5 PR effect on MRC score. PR, pulmonary rehabilitation; MRC, Medical Research Council; CI, confidence interval.

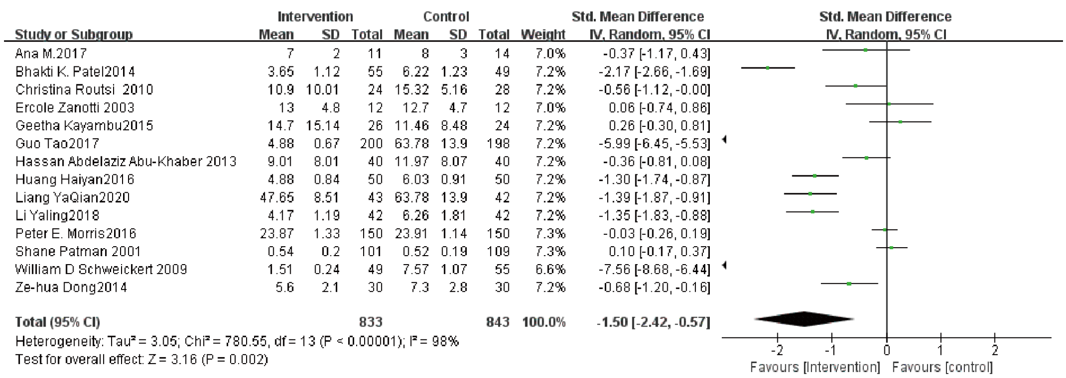

Figure 6 PR effect on MV time. PR, pulmonary rehabilitation; MV, mechanical ventilation; CI, confidence interval.

of each study was low (P=0.42, I^2=0%). From this, we found PR had no influence on the mortality of ICU patients with MV [OR =0.74, 95% CI: (0.36, 1.52), P=0.42].

Sensitivity and publication bias analysis

All literature with a large heterogeneity were eliminated one by one, leaving us with a smaller amount of research to conduct our meta-analysis to analyze the cause of heterogeneity. The results showed no significant change, indicating that the merged results were relatively stable. More than 10 results of studies were combined, and a funnel plot was drawn from these results. It showed that the results of PR on the combined results of MV time and ICU time of

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ana M.2017	10	4	11	16	9	14	7.6%	-0.80 [-1.62, 0.03]
Christina Routsi 2010	19.12	14.9	24	28.18	22.37	28	8.2%	-0.46 [-1.02, 0.09]
Ercole Zanotti 2003	42.7	42.4	12	36.7	26.8	12	7.6%	0.16 [-0.64, 0.97]
Geetha Kayambu2015	15.22	10.35	26	11.46	8.48	24	8.2%	0.39 [-0.17, 0.95]
Guo Tao2017	7.53	2.08	200	13.32	2.59	198	8.7%	-2.46 [-2.72, -2.20]
Huang Haiyan2016	7.53	4.1	50	11.32	1.59	50	8.5%	-1.21 [-1.64, -0.78]
Liang YaQian2020	130.49	10.39	43	157.69	15.11	42	8.3%	-2.08 [-2.62, -1.55]
Li Yaling2018	8.4	1.93	42	11.7	5.81	42	8.5%	-0.76 [-1.20, -0.31]
Peter E. Morris2016	7.62	1.89	150	8.04	1.71	150	8.8%	-0.23 [-0.46, -0.01]
Shane Patman 2001	1.77	1.77	101	1.52	1.12	109	8.7%	0.17 [-0.10, 0.44]
William D Schweickert 2009	5.9	13.2	49	7.6	6.1	55	8.6%	-0.17 [-0.55, 0.22]
Ze-hua Dong2014	12.7	4.1	30	15.2	4.5	30	8.3%	-0.57 [-1.09, -0.06]
Total (95% CI)			**738**			**754**	**100.0%**	**-0.68 [-1.27, -0.08]**

Heterogeneity: $Tau^2 = 1.03$; $Chi^2 = 288.90$, df = 11 ($P < 0.00001$); $I^2 = 96\%$

Test for overall effect: Z = 2.24 (P = 0.03)

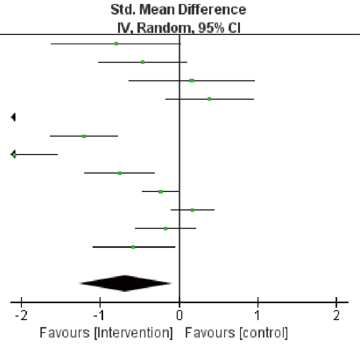

Figure 7 Effect of PR on length of stay in ICU. PR, pulmonary rehabilitation; CI, confidence interval.

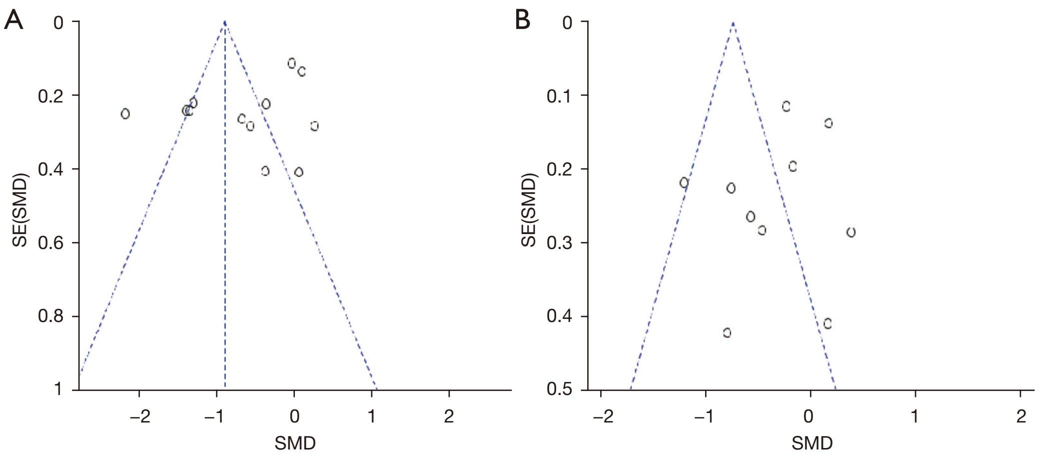

Figure 8 Funnel plot of MV time (A) and ICU time (B). MV, mechanical ventilation; SMD, standardized mean difference.

patients were biased. As a result, we should be careful about concluding the meta-analysis results of our study's index, as shown in *Figure 8A,8B*.

Discussion

PR can increase patients' muscle strength with MV to a certain extent, but it is not enough to significantly improve the grip strength

As the results of our study show, when compared with the control group, the experimental group that underwent PR with MV can be seen to have improved muscle strength, thus reducing ICU-AW prevalence and improving their MRC scores. This was consistent with other systematic reviews (28,29). However, among the 8 included studies that gave MRC scores, one double-blind, single-center RCT (17) presented no difference in MRC scores between an MV and non-MV group. The reason may be that the trial was terminated before reaching the specified sample size (n=34) of the study due to insufficient capital investment, so the real difference could not be detected. The other 7 studies (9,15,18,20,24,26,27) showed that PR could effectively improve a MV patient's MRC score through electrical muscle stimulation (9,15,18,20), exercise training (9,20,24,27), psychological intervention (24,27), respiratory function training (9,15,24,27), nutritional support (24,27), and body position management (9,20,24,27). The reason may be that most of the above interventions are physical therapies, which effectively improve the microcirculation of local and systemic skeletal muscles. In addition, inspiratory muscle training and inspiratory resistance training were included in PR, which was helpful to avoid diaphragmatic dysfunction (DD). From another perspective, DD and ICU-AW can be considered two sides of the same coin, with infection/inflammation and MV, considered the pathophysiological cause of DD (30,31). This is because infection led to cytokine release, inducing mitochondrial free radical survival, thus reducing muscle endurance and strength. In its pathology, muscle fiber injury and muscle strength injury are included in considering DD. Furthermore, relevant studies have found that using MV within 38–40 hours can lead to atrophy of patients' diaphragm muscle fiber, edema, and airway damage (32), which is similar to the pathological characteristics of ICU-AW. Therefore, PR can exercise the muscle strength of limbs and improve lung condition and reduce difficulty during ventilator extubation.

Compared with the routine nursing of the control group, PR failed to increase the grip strength of patients. This is exemplified by 2 of the included studies (4,17) (P>0.05). The reason may be that the current concept of intensive care is being strengthened by "routine care" over time and that the concept of "early rehabilitation training" is now included in routine nursing plans, thus reducing the difference in the effects of control intervention. Secondly, the patients did not get the rehabilitation course according to the safety standard of intervention screening, and the best rehabilitation time was not defined, resulting in the difference not being enough to affect the increase of handgrip strength. Therefore, it is suggested that different grading schemes should be added to intervention measures to improve the knowledge of how different schemes should be implemented at different age groups (5).

PR can improve lung function, shorten MV and ICU time, but it cannot reduce mortality

We found that PR can shorten MV and ICU time when compared with the routine nursing control group. This is consistent with the results of other meta-analyses (33,34). Fourteen studies (4,9,15,16,18-27) included here described the difference of MV time between an experimental and control group; however, no obvious difference was found in the MV time of 5 studies (4,16,20-22) (P>0.05). The reason may be that although patients with severe diseases included in 2 of the studies (16,20) were diagnosed with chronic obstructive pulmonary disease (COPD) in acute exacerbation, and they also partly had sepsis. Excessive protein catabolism in the muscles of sepsis patients can lead to the loss of respiratory muscle volume, multiple organ dysfunction syndromes, and the use of sedatives (35), which ultimately leads to the MV time not changing significantly. Therefore, it is suggested that a further subgroup analysis should be carried out in the screening of patients to distinguish whether the difference exists due to other factors such as sepsis and multiple organ failure. For 3 of the included studies (4,21,22), the sample size was small, and the inclusion criteria were not strictly reviewed, which led to an increase in confounding factors. However, we also found that sedation, narcotic drugs, and other diseases had a certain impact on respiratory muscles, yet resulted in no statistical significance in the test results (P>0.05).

Ultimately, PR could not reduce the mortality of patients with MV. Four studies (9,16,19,20) reported the mortality outcomes of MV, and 3 of them (16,19,20) showed there was no significant relationship between mortality and PR (P>0.05). This is consistent with the study of Dres *et al.* (3). The reason may be that the long-term independent risk factors of ICU-AW are long-term MV and the effects of drugs such as norepinephrine and fentanyl. ICU-AW was not an independent risk factor of mortality, and its influencing factors spoke more to its ability to change the original disease. Although the occurrence of ICU-AW can aggravate a patients' death process and make it easier for limb muscle damage to cause hemorrhagic shock, we need to further explain its pathological role through the differences of chemokines and oxidative stress-free radicals in animal models. Moreover, these results may also relate to the small sample sizes of the included studies, thereby failing to provide strong data to show the difference in mortality among patients with MV.

Limitations and prospects of this study

Before concluding, it is important to address the limitations of our study. Firstly, in the research literature included in our analysis, the intervention methods were not strictly unified. This was the main reason for high heterogeneity, which can impact our data analysis results. Another factor impacting our analysis is the small sample sizes and a small number of outcome indicators included in some studies. Secondly, single intervention rehabilitation measures were not compared with comprehensive rehabilitation measures, and the correlation between ICU-AW and muscle metabolism, nutrition, psychological intervention, and DD was also not further analyzed and explained. Although there is high heterogeneity in the results of the meta-analysis, this may be due to the different countries included, leading to positional bias. When we processed the meta-analysis results, we also conducted a subgroup analysis and found that different countries have affected the research results to a certain extent, although this is not enough to fully explain the reasons for the high heterogeneity.

We reviewed the therapeutic effects of PR on ICU-AW, and noticed that muscle training, exercise therapy, electrical stimulation therapy, and nutritional therapy were used as the most commonly used treatment items in the PR program. Most of these projects have been bundled treatment. However, the role played by each of these items alone is not explained. We suggest that the intervention scheme of using MV alongside PR should be further clarified for future research. This could include carrying out a series of cluster non-drug interventions in terms of respiratory function exercises, early activities, nutritional support, psychological intervention, and so on. This evaluation should also be based on the best-standardized treatment period, appropriate intervention intensity and duration, and long-term observations should be carried out by using core outcome indicators, such as muscle strength, muscle thickness, and self-care ability (36).

Conclusions

In ICU patients with MV, PR can effectively reduce ICU-AW prevalence, strengthen muscles, and shorten MV and ICU duration. However, whether it can increase muscle strength and reduce mortality still requires further verification. At present, there is no standardized PR program for ICU-AW patients, although it has been suggested that a series of cluster PR programs be formed in the future. To conclude, we also feel it is necessary to clarify further the roles and tasks of various intervention methods in comprehensive PR and clarify their relationship with ICU-AW.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1928

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/APM-21-1928). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editors: J. Goetz and J. Chapnick)

Cite this article as: Huang D, Zhao W, Chen Y, Shen B, Wang Y, Guan H, Luo W. Effect of mechanical ventilation and pulmonary rehabilitation in patients with ICU-acquired weakness: a systematic review and meta-analysis. Ann Palliat Med 2021;10(9):9594-9606. doi: 10.21037/apm-21-1928