# The effect of early mobilization for critical ill patients requiring mechanical ventilation: a systematic review and meta-analysis

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**Background:** In recent years, there are increasing number of new studies and researches about early mobilization, an update meta-analysis based on high quality studies and focusing on the effectiveness of early mobilization is quite necessary. The purpose of the article is to explore the effect and safety of early mobilization on reducing the length of stay (LOS) and duration of mechanical ventilation in patients undergoing mechanical ventilation in intensive care unit.

**Methods:** The databases PubMed, Scopus, EBSCO and Embase were systematically searched. We designed a search strategy for PubMed that consists of terms related to early mobilization and intensive care unit (ICU). We reported mean difference (MD) and 95% CI for LOS in ICU and hospital, the duration of mechanical ventilation, and reported odds ratio (OR) and 95% CI for mortality at hospital discharge.

**Results:** In total, there were 18 research articles included in the meta-analysis. The early mobilization in intervention group appeared to have positive influence on hospital outcomes with the LOS in ICU (MD =-1.75, 95% CI: -2.70 to -0.79; P=0.0003) and duration of mechanical ventilation (MD =-1.64, 95% CI: -2.41 to -0.87; P<0.0001) significantly decreased. And there was no statistical difference in the analysis of length of hospital stay (MD =-1.58, 95% CI: -4.02 to 0.86; P=0.21) and mortality at hospital charge (OR =1.10, 95% CI: 0.76 to 1.59; P=0.62).

**Conclusions:** Early mobilization in ICU has positive and safe influence on hospital outcomes in mechanical ventilation patients. It confers significant benefit in decreasing the duration of mechanical ventilation and the LOS in ICU. Furthermore, the early mobilization therapy in ICU will not increase mortality at hospital discharge in a research setting.

Keywords: Early mobilization; meta-analysis; critical care; intensive care unit; mechanical ventilation

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## Introduction

With the treatment measures in intensive care unit (ICU), more and more critically ill patients survived and discharged from hospital. The increasing rate of survivors in the ICU brings a new problem: recent studies of recovery after ICU found that many survivors of ICU

suffer long-term poor physical and psychological outcomes associated with the ICU experience (1,2). For critical ill patients undergoing mechanical ventilation (MV) in ICU, it is common to keep complete or nearly complete limb immobilization. The muscle inactivity has been proved to be an important risk factor for intensive care unit-

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Table 1 PubMed search strategy

- 1 Intensive care units [MeSH Terms] or critical care [Title/ Abstract] or critical illness [Title/Abstract] or intensive care [Title/Abstract] or ICU [Title/Abstract] or respiration, artificial [MeSH Terms] or mechanical ventilation [Title/Abstract]
- 2 Early ambulation [MeSH Terms] or rehabilitation [MeSH Terms] or early mobilization [Title/Abstract] or mobility [Title/ Abstract] or exercise therapy [Title/Abstract] or mobilization [Title/Abstract]
- 3 Humans [MeSH Terms] and adult [MeSH Terms] not animals [MeSH Terms]
- 4 Randomized controlled trial [MeSH Terms] or randomized controlled trial [Title/Abstract] or clinical trial [Title/Abstract] or cohort studies [MeSH Terms] or study [Title/Abstract] or comparative study [MeSH Terms] or comparative study [Title/Abstract]
- 5 1 and 2 and 3 and 4

ICU, intensive care unit.

acquired weakness (ICU-AW) (3). And the ICU-AW tends to extend the duration of MV, prolong the length of ICU and hospital stay, increase the risk of mortality at hospital discharge (4,5).

A widely accepted definition of early mobilization is the application of physical activity within the first 2 to 5 days of critical illness or injury (6). The safety consideration used to be a major barrier to generalize the early mobilization in clinical practice (7). But recent systematic reviews and metaanalysis have proved conclusively that early mobilization for ICU patients is safe, with low incidence of adverse events (8,9). The application of early mobilization for patients could maintain the muscle strength and improve physical function (6). For this reason, we can infer that early mobilization could have positive effect on hospital outcomes like increasing the weaning success rate, decreasing the duration of MV, shortening the length of stay (LOS) in ICU and hospital. Previous meta-analysis pointed out the early mobilization appears to have benefit in improving hospital outcomes and quality of life (10,11).

And in recent years, there are increasing number of new studies and researches about early mobilization, an update meta-analysis based on high quality studies and focusing on the effectiveness of early mobilization is quite necessary. Hence, the purpose of this meta-analysis was to explore the effect of early mobilization for critical ill patients on duration of MV, ICU and hospital LOS, patient mortality at hospital discharge.

# Methods

## Inclusion criteria

The studies fulfilled all of the criteria would be included: (I) the patients enrolled should be adults (at least 18 years old), and they were mechanically ventilated in any type of ICU; (II) the study should be the randomized controlled trial (RCT), cohort study or other comparative study with concurrent controls; (III) the intervention should be mobilization, active or passive exercise such as stretching exercises in-bed, bedside sitting training, bed to chair transferring and walking training; (IV) the control group should receive standard medical and nursing therapy. Exclusion criteria: (I) animal studies; (II) the patients are minors (under 18 years of age); (IV) studies haven't reported the concerned outcomes.

# Outcome

Primary outcomes are the ICU and hospital LOS, the duration of MV. Secondary outcome is the mortality at hospital discharge.

# Search strategy

We searched the electronic databases of PubMed, Scopus, EBSCO and Embase from the earliest available date until November 2017. We designed a search strategy for PubMed and the detailed search strategy is included in the *Table 1*. There is no restrictions in language.

# Study selection

Two authors independently conducted the initial search and selection by reading the titles and abstracts. And potential relevant studies were further checked based on the inclusion criteria previously described. All these review authors conducted searches and evaluated the full text of each record independently. Differences in assessment screening were resolved by a third opinion.

# Data extraction

The data extraction was accomplished independently by three authors by using a predesigned data extraction form (*Table 2*). If the data was incomplete or needed further details, review authors would send e-mails to the article author for clarification of results. The primary study end

Study	Desian	Setting	Study Design Setting Patients enrollment C	Group allocation Sample size Male	Sample size		Ade (v)	APACHE II	Interventions
Burtin et al. (12)	RCT	SICU		Intervention	45		56±16	26±6	Using bedside ergometer exercise training and standard physiotherapy session for 20 minutes/day, 5 session/week until ICU discharge
				Control	45	26	57±17	25±4	Daily standardized passive or active motion session of upper and lower limbs
Chang <i>et al.</i> (13)	RCT	SICU	Patients who required mechanical ventilation for at least 72 hours	Intervention	18	10	65.3±13.1	17.3±8.3	Chair-sitting exercises for at least 30 minutes to a maximum of 120 minutes, at least 6 days or discharged from the ICU
				Control	16	<del>.</del>	66.9±17.0	14.6±7.6	Standard nursing care and physical therapy
Chen <i>et al.</i> (14)	RCT	RCC	Receiving MV for >6 hours a day for >21 days, and had previously failed	Intervention	12	~	64.9±21.3	RN	Stretching exercises, muscle strengthening exercises and cardiopulmonary endurance exercise 30–40 minute/session, 4–6 session/week for 10 sessions
			to wean from a mechanical ventilator in the ICU	Control	15	2	66.5±18.7		Standard nursing care and physical therapy
Clark e <i>t al.</i> (15)	Retrospective TBICU cohort study	e TBICU	Critically ill and have injuries resulting from trauma or burns	Intervention	1,132	798	46.6±19.6	NR	Daily physical therapy, active-assisted to active, exercises, mobility training; sitting up in bed, standing and active transfers to chair
				Control	1,044	754	44.1±18.5		Standard nursing care and physical therapy
Denehy <i>et al.</i> (16)	RCT	MICU	Patients in the ICU and Intervention reviewed MV for 5 days or more	Intervention	74	43	61.4±15.9	20.7±7.7	Active functional rehabilitation based upon physiological principles of exercise prescription
				Control	76	52	60.1±15.8	19±6	Standard nursing care and physical therapy
Dong et al. (17)	RCT	ICU	Patients post coronary Intervention artery bypass graft, MV >72 hours	Intervention	53	20	62.6±12.8	16.3±4.2	Head up, transferring from supination to sitting, sitting on the edge of bed, sitting in a chair, transferring from sitting to standing, walking along a bed twice daily
				Control	53	22	60.2±15.1	17.2±4.3	Standard nursing care and physical therapy

Table 2 (continued)

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Study	Design	Setting	Patients enrollment	Group allocation	Sample size	Male	Age (y)	APACHE II	Interventions
Hodgson <i>et al.</i> (18)	RCT	MICU	Critically ill adults mechanically ventilated	Intervention	29	17	64±12	<b>19.8±9.8</b>	active functional activities, comprising walking, standing, sitting, and rolling
			for greater than 24 hours	Control	21	13	53±15	15.9±6.9	Standard nursing care and physical therapy
Kayambu <i>et al.</i> (19)	RCT	MICU	Participants ≥18 years who remained mechanically ventilated ≥48 hours	Intervention	26	18	62.5 [30–83]	28±7.6	Individualized early targeted physical rehabilitation program prescribed by the ICU research physiotherapist for 30 min, one to two times daily
				Control	24	14	65.5 [37–85]	27±6.8	standard nursing care and physical therapy
Klein et al. (20)	Prospective comparative Study	NICU	Critically ill patients with primary neurologic injury	Intervention	377	183	61.3±16.7	R	Four progressive mobility milestones from 16 mobility levels according to patients' condition
				Control	260	135	62.7±16.1		standard nursing care and physical therapy
Lai <i>et al.</i> (21)	Retrospective RICU observational study	e RICU	All adults MV patients admitted a medical ICU	Intervention	06	60	65.8±15.7	16.2±5.8	Early mobilization 30 minutes each time, twice daily, 5 days per week
Morris et al. (22)	RCT	RICU	Adult patients admitted Intervention to ICU with acute Control respiratory failure requiring mechanical	Intervention Control	150	66	55±17	RN	Daily therapy until hospital discharge, consisting of passive range of motion, physical therapy, and progressive resistance exercise
			ventilation		150	68	58±14		standard nursing care and physical therapy
Morris <i>et al.</i> (23)	Prospective cohort study	RICU	Within 48 hours of intubation and 72 hours of admission to the	Intervention	165	6	54.0±16.8	23.5±8.8	Sitting in bed/resistance limb training, passive ROM, sitting on bed edge, bed to chair transfer 20–60 minute/sessions daily
			Medical Intensive Care Unit	Control	165	88	55.4±16.8	21.6±8.0	Standard nursing care and physical therapy
Moss et al. (24)	RCT	RICU	Patients who required MV for at least 4 days	Intervention	20	36	56±14	17.9±6.2	Individualized early targeted physical rehabilitation program prescribed by the ICU research physiotherapist for 30 min, one to two times daily until discharge from the ICU
				Control	61	35	49±15	17.4±5.6	Standard nursing care and physical therapy
Table 2 (continued)	ntinued)								

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Study	Design	Setting	Patients enrollment	Group allocation	Sample size	Male	Age (y)	APACHE II	Interventions
Schaller <i>et al.</i> (25)	RCT	SICU	tted	Intervention	104	63	60±17	17±8	Goal-directed sedation with daily awakening trials, early, goal-directed mobilization
			expected to require mechanical ventilation for ≥24 hours	Control	96	64	59±20	17±7	Goal-directed sedation with daily awakening trials
Schweickert RCT <i>et al.</i> (26)	t RCT	RICU	18 years of e ICU who had mechanical n for less than	Intervention	49	20	57.7 [36.3– 69.1]	20.0 [15.8–24.0]	Passive/active ROM; sitting balance activities; activities of daily life; transfer; pregait/walking training 19.2 minute/ session daily in hospital stay
			72 hours	Control	55	32	54.4 [46.5– 66.4]	19.0 [13.3–23.0]	Standard nursing care and physical therapy
Tisworth et al. (27)	Prospective intervention trial	NICU	Patients admitted to the NICU of a tertiary care center	Intervention	63	43	58.4±1.7	NR	Comprehensive mobility initiative utilizing the Progressive Upright Mobility Protocol (PUMP) Plus
				Control	77	37	60.4±2.2		Standard nursing care and physical therapy
Dong <i>et al.</i> (28)	RCT	MICU	r >48 hours but ours, duration of cpected to be ≥1	Intervention	30	21	55.3±16.1	15±4.2	Rehabilitation therapy twice daily, the time and intensity were adjusted according to the condition of the patient
			week	Control	30	20	55.5±16.2	16±4.1	Standard nursing care and physical therapy
y, year; RC burns inten	y, year; RCT, randomized controlled trial; SICU, burns intensive care unit; MICU, medical intensi	sontrolled 11CU, mec	l trial; SICU, surgery inten: dical intensive care unit; N	sive care unit; ICI IICU, neurological	J, intensive care	tre unit; unit; R	RCC, respirat	atory care ce ory intensive	y, year; RCT, randomized controlled trial; SICU, surgery intensive care unit; ICU, intensive care unit; RCC, respiratory care center; NR, not reported; TBICU, trauma and burns intensive care unit; MICU, medical intensive care unit; NICU, neurological intensive care unit; RICU, respiratory intensive care unit; ROM, range of motion.

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points of included studies were the ICU and hospital LOS, the duration of MV. The secondary study end point was the mortality at hospital discharge. Relevant information such as the Acute Physiology and Chronic Health Evaluation (APACHE) II Score, patients enrollment and interventions were abstracted from original articles.

## Quality assessment

The risk of bias for these included studies were independently assessed by two authors. The Physiotherapy Evidence Database (PEDro) scale (29) was used in the quality assessment. We assessed every potential source of bias as "yes" or "no" according to the articles, every "yes" got 1 point and "no" got 0 point. Finally, a score out of 10 was obtained and a higher score showing high quality trials. We also made a "Assessment of quality by the PEDro score" (*Table 3*) to show the quality assessment result.

# Statistical analysis

We used the Review Manager 5.3 to implement the metaanalysis. For the primary outcomes, we reported mean difference (MD) between groups and 95% CI in the article. And the mortality at hospital discharge was reported by odds ratio (OR) and 95% CI. To investigate the potential publication bias, we used the Begg's rank correlation test and the Egger's regression test in the study (31). The I<sup>2</sup> statistic was calculated to evaluate the heterogeneity between studies and we could conclude substantial heterogeneity when I<sup>2</sup> $\geq$ 50% (32). Due to the obvious heterogeneity, we performed subgroup analysis stratified by ethnic group, mean age, mean APACHE II Score, and disease groups to explore the potential contributing factors. In addition, we conducted a sensitivity analysis to find out the influence of one study on the overall risk.

# Results

## Study selection

Our initial search identified 1,253 potentially relevant articles from electronic databases and no further articles were included from other sources, of which 17 studies (12-28) of early mobilization in the ICU were finally included. Within the 17 studies, there are 12 RCTs (12-14,16-19,22,24-26,28) and 5 observational study (15,20,21,23,27). The selection process was presented in the *Figure 1.* These studies were published from 2008 to 2016. Some important characteristics of included articles were showed in *Table 2.* Of the 17 studies, the sample size ranged from 27 to 2,176, and the mean age ranged between 50 and 70 years. The APACHE II score had no statistical difference between the intervention and control group in included studies.

# Risk of bias assessment

The risk of bias assessment was outlined in Table 3. Ten RCTs (14,16-19,22,24-26,28) had good quality and tiny bias with the scores ranged 6 to 8. One historical controlled study (30) had a high risk of bias so we excluded it. Other studies' (12,13,15,20,21,23,27) bias assessment scores ranged 4 to 5. All included studies had eligibility criteria for the included patients, reported between-group difference, measured point estimate and variability. But subject blinding and therapist blinding were impossible to implement for these studies. All the RCTs were random allocated while three trials (17,24,28) didn't reported whether the allocation was concealed. Six RCTs (14,18,19,22,24,26) had assessor blinding and eight RCTs (17-19,22,24-26,28) had measured the key outcomes >85% subjects after allocation. For the observational studies (15,20,21,23,27,30), the scores ranged from 3 to 5. These studies didn't have random or concealed allocation, and the assessor blinding were not mentioned.

# Sensitivity and subgroup analysis

We found substantial heterogeneity among studies of LOS in ICU and hospital. Our sensitivity analyses for included RCTs (*Figure 2*) suggested that one study (17) might contribute to the heterogeneity. The study's participants were patients who had been operated coronary artery bypass surgery. The highly similarities of patients' disease types between the intervention and control group in the study would overestimate the effect of early mobilization and we decided to exclude the study.

We also did the subgroup analyses stratified by ethnic group, mean age, mean APACHE II Score and cause of ICU stay, and the heterogeneity disappeared when we divided the studies into three subgroups by the participants' disease types. Thus, the different kinds of diseases are the source of heterogeneity among included studies. We also compared the difference between the RCTs and observational studies in the effect of early mobilization.

Study	Eligibility criteria		Random Concealed allocation allocation	Baseline similarity	Subject blinding	Therapist blinding	Assessor blinding	Therapist Assessor Measures of key blinding blinding outcomes >85%	Intention to treatment	Between-group difference reported	Point estimate and variability reported	Total (0–10)
Burtin <i>et al.</i> (12)	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes	4
Chang <i>et al.</i> (13)	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	5
Chen <i>et al.</i> (14)	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes	9
Denehy <i>et al.</i> (16)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	9
Dong <i>et al.</i> (17)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	9
Dong <i>et al.</i> (28)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	9
Hodgson <i>et al.</i> (18)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Kayambu <i>et al.</i> (19)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7
Morris <i>et al.</i> (22)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Moss et al. (24)	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Schaller <i>et al.</i> (25)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Schweickert <i>et al.</i> (26)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	œ
Clark <i>et al.</i> (15)	Yes	No	No	Yes	No	No	No	Yes	No	Yes	Yes	4
Klein <i>et al.</i> (20)	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	5
Lai e <i>t al.</i> (21)	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	5
Malkoc <i>et al.</i> (30)	Yes	No	No	Yes	No	No	No	No	No	Yes	Yes	ю
Morris et al. (23)	Yes	No	No	Yes	No	No	No	Yes	No	Yes	Yes	4
Titsworth et al. (27)	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	5

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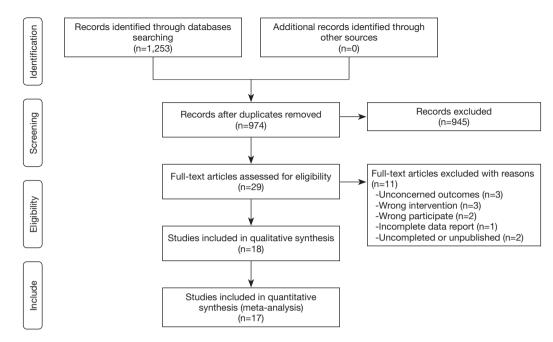


Figure 1 Flow chart of database search and study selection.

## Hospital outcomes

Nine RCTs (12-14,18,22,24-26,28) and four observational studies (15,20,21,23) provided the LOS in ICU and we used a fixed effects model to analyse the data (P=0.43, I<sup>2</sup>=1%). The LOS in ICU had a significant reduction in intervention group MD = -1.75, 95% CI: -2.70 to -0.79; P=0.0003, *Figure S1*). There are four observation studies (15,20,21,23) recorded the LOS in ICU and we used a random model to compare the difference between RCTs and observation (*Figure S2*). We found the decrease in the observational group is more obvious. Through subgroup analysis for included RCTs, the impact of early mobilization for patients in respiratory intensive care unit (RICU) is lower than other groups (*Figure S3*).

Eight RCTs (12-14,18,24-26,28) reported data for the duration of MV measured in number of days with data pooled using a fixed effects model (P=0.46,  $I^2$ =0%). Through analyzing the results we found the duration of MV was significant shortened in intervention group (MD =-1.64, 95%: CI -2.41 to -0.87; P<0.0001, *Figure S1*). Three observation studies (15,21,23) also reported the data and the result (MD =-1.64, 95% CI: -2.59 to -0.68; P=0.008, *Figure S2*) had no statistical difference with the RCTs.

Six RCTs (12,18,22,24-26) and five observational studies (15,20,21,23,27) provided the LOS in hospital data and we used a random effects model to pool the data (P<0.00001,  $I^2$  =82%). By analyzing the data from RCTs, we found there

is no statistical difference in patient's hospital LOS between the intervention and control group (MD =-1.58, 95% CI: -4.02 to 0.86; P=0.21, *Figure S1*). But observation studies discovered the early mobilization could shorten the LOS in hospital (MD =-3.87, 95% CI: -5.23 to -2.51; P<0.00001, *Figure S2*). The subgroup analysis found the early mobilization for the patients in surgery intensive care unit (SICU) or RICU couldn't evidently decrease the LOS in hospital, but medical intensive care unit (MICU) patients' hospital LOS was obviously reduced (*Figure S3*).

Nine RCTs (12,14,16,18,19,22,25,26,28) provided hospital mortality data and we used a fixed effects model to pool the data (P=0.49, I<sup>2</sup>=0%). According to the analytical result (OR =1.10, 95% CI: 0.76 to 1.59; P=0.62, *Figure S1*), there is no statistical difference in mortality risk between the intervention and control group. However, the observation studies (15,20,23) demonstrated that early mobilization could slightly decrease the mortality risk in the intervention group (OR =0.80, 95% CI: 0.65 to 0.99; P=0.04, *Figure S2*). The subgroup analysis found early mobilization might increase the hospital mortality for the patients in SICU (OR =1.98, 95% CI: 1.00 to 3.91; P=0.05, *Figure S3*).

## **Publication bias**

Visual inspection of the Begg's funnel plot did not find

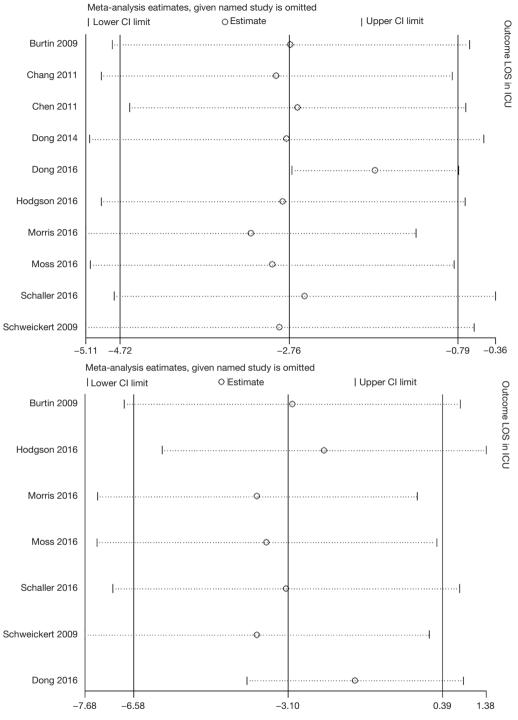


Figure 2 Sensitivity analyses. CI, confidence interval; LOS, length of stay; ICU, intensive care unit.

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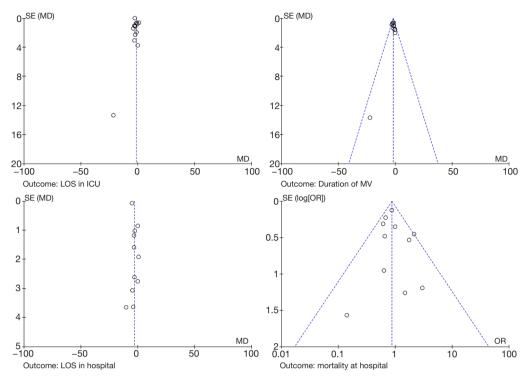


Figure 3 Publication bias assessed by funnel plot. Publication bias was assessed using the effect size of OR of hospital mortality, weighted mean difference of the hospital LOS, ICU, LOS and duration of MV. The results showed that there was no potential publication bias in the present analysis. OR, odds ratio; LOS, length of stay; ICU, intensive care unit; LOS, length of stay.

substantial asymmetry (*Figure 3*). For the LOS in ICU, Egger's test showed 0.776 and Begg's test showed 0.260. For the LOS in hospital, Egger's test showed 0.139 and Begg's test showed 0.537. For the duration of MV, Egger's test showed 0.242 and Begg's test showed 0.951. For the mortality at hospital discharge, Egger's test showed 0.689 and Begg's test showed 0.837. There was no evidence of publication bias among included studies.

## Discussion

This meta-analysis synthesized data from 1,837 intervention group patients and 1,579 control group patients, described an assessment of early mobilization intervention on hospital outcomes. We found that early mobilization therapy for patients receiving MV in ICU had a positive effect on hospital outcomes such as decreasing the LOS in ICU and reducing the duration of MV. And early mobilization therapy in ICU appears to be safe and did not increase mortality at hospital discharge in research settings.

There is a widely accepted consensus that patients undergoing MV in ICU for prolonged periods of time and are likely to have weak muscle strength. The prolonged immobilization and bed ridden take an important part in the ICU-acquired weakness. The early mobilization therapy for critical ill patients could prevent muscle atrophy, enhance muscle force and better muscle coordination. With the benefits of early mobilization therapy, patients could improve functional status with lower MV demands and increase the weaning rate (33). In the meta-analysis, eight RCTs (12-14,18,24-26,28) and three observation studies (15,21,23) compared the duration of MV in intervention group with control group. The duration of MV was consistently shorter in patients receiving early mobilization therapy. These improvements could also possibly shorten the LOS in ICU and hospital. By analyzing the data from included studies (12-14,18,22,24-26,28), for the patients in intervention group, the LOS in ICU had a significant reduction but there was no statistical for the LOS in hospital. And improving muscle function is a long-term process so it might not have instant positive influence on the mortality rate. The comparison of hospital mortality risk between intervention and control group demonstrated that early mobilization had no significant positive or

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negative effect on hospital mortality.

Our subgroup analysis demonstrated that difference disease and ICU types may have potential influence on the outcomes (Figure S3). For the surgical patients in SICU, the hospital mortality in intervention group had distinctly increased. That demonstrated early mobilization therapy should be more careful and adjust the protocol by the patients' wounds and illness, some improper mobilization therapy will lead to adverse events or mortality. For the patients without respiratory system diseases, the impact of reducing the LOS in ICU and hospital is more significant than the RICU patients with respiratory system diseases. And different study design also had effect on the outcomes (Figure S2), the observational studies tend to report overrated results compared with the RCTs. Especially for the hospital mortality, three observation studies (15,20,23) found early mobilization could decrease the mortality rates while the RCTs suggested there was no statistical difference between intervention and control group.

Similarly, a recent study in pediatric intensive care unit (PICU) found that the early mobilization is safe and beneficial like improving the functional status and decreasing the LOS in PICU (34). Engel *et al.* (35) found that early mobilization could significantly improve the physical and neurocognitive outcomes. Tipping *et al.* (9) proved conclusively that early mobilization for ICU patients is safe. Our study pays specific attention to the effect of early mobilization in ICU with quantitative results and included five up-to-date studies (18,21,22,24,25). And the subgroup analysis demonstrated that difference disease and ICU types may have potential influence on the clinic outcomes. Finally, we reported the differentia between the RCTs evidence and observational studies evidence.

## Study strengths and limitations

The study strengths stem from the clear, targeted inclusion and exclusion criteria, credibility in the data extraction and analysis, comprehensive sensitivity and subgroup analyses. Five of the studies (18,21,22,24,25) included in this study are newly published and have good quality with low risk of bias. Our subgroup analysis found that different disease group may be an influence factor on the outcomes and observational studies might over-rated the effect of early mobilization.

Weakness include there are six (12-14,18,19,28) of the included studies with small sample size (n<100), which may cause small-study effects and tend to report larger

beneficial effects (36). In subgroup analysis, there were only two studies in the minimal subgroup and therefore it might cause some bias. The intensity and amount of early mobilization therapy for the intervention group in different studies were manifold and some specific factual information was unavailable, that limited the subgroup analysis in this meta-analysis.

## Conclusions

The early mobilization for critical ill patients undergoing MV in ICU can improve hospital outcomes like shortening the duration of MV, decreasing the LOS in ICU. The result also suggests the early mobilization therapy is safe and won't increase the mortality at hospital discharge.

Further study should determine the effect of different early mobilization protocol for critical ill patients. More specific studies should be assessed to find out the most effective and safe mobilization protocols.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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## Supplementary

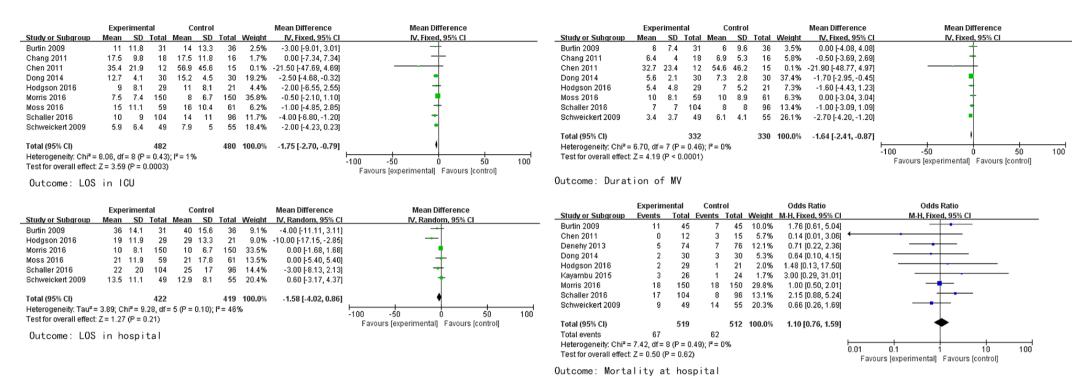


Figure S1 Forest plot for LOS in ICU, the duration of MV, LOS in hospital and mortality at hospital. SD, standard deviation; IV, inverse variance; CI, confidence interval; MV, mechanical ventilation; LOS, length of stay; ICU, intensive care unit.

Study or Subgroup Mean SD Total Mean SD Total Weight	Mean Difference Mean Difference IV, Random, 95% Cl IV, Random, 95% Cl	Experimental Control Mean Difference Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% Cl IV, Fixed, 95% Cl
1.1.1 RCTs           Burtin 2009         11         11.8         31         14         13.3         36         1.5%           Chang 2011         17.5         9.8         18         17.5         11.8         16         1.0%           Cheng 2011         35.4         21.9         12         56.9         45.6         15         0.1%           Dong 2014         12.7         4.1         30         15.2         4.5         30         7.9%           Hodgson 2016         9         8.1         29         11         8.1         21         2.4%           Morris 2016         7.5         7.4         150         8         6.7         150         11.4%           Moss 2016         15         11.1         59         16         10.4         61         3.3%           Schaller 2016         10         9         104         14         11         96         5.5%           Schweickert 2009         5.9         6.4         49         7.9         5         55         7.7%           Subtotal (95% CI)         482         480         40.7%         482         480         40.7%           Heterogeneilty: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 8.0	-3.00 [+9.01, 3.01] 0.00 [-7.34, 7.34] -21.50 [+4.68, -0.32] -2.50 [+4.68, -0.32] -2.00 [-6.55, 2.55] -0.50 [-2.10, 1.10] -1.00 [+8.85, 2.85] -4.00 [-8.80, -1.20] -2.00 [+4.32, 0.23] -1.76 [-2.72, -0.79]	1.2.1 RCTs         Burtin 2009       6       7.4       31       6       9.6       36       2.1%       0.00 [-4.08, 4.08]         Chang 2011       6.4       4       18       6.9       5.3       16       3.5% $-0.50$ [-3.69, 2.69]         Chen 2011       32.7       23.4       12       54.6       46.2       15 $0.0\%$ $-21.90$ [-48.77, 4.97]         Dong 2014       5.6       2.1       30       7.3       2.8       30       22.7% $-1.70$ [-2.95, $-0.45$ ]         Hodgson 2016       5.4       4.8       29       7       5.2       21       4.5% $-1.60$ [-4.43, 1.23]         Moss 2016       10       8.1       59       10       8.9       6       8.2% $-1.00$ [-3.09, 1.09]         Schaller 2016       7       7       104       8       8       96       8.2% $-1.00$ [-3.09, 1.09]       9         Schweickert 2009       3.4       3.7       49       6.1       4.1       55       15.9% $-2.70$ [-4.20, -1.20]       9         Subtocat (95% Ct)       332       330       60.8% $-1.64$ [-2.41, -0.87]       9       9         Heterogeneity: ChP = 6.70, df = 7 (P =
I.1.2 Observational studies           Clark 2013         10.4         14         1132         11         16.2         1044         14.0%           Klein 2015         4.75         0.64         377         7.37         0.68         260         23.4%           Lai 2016         6.9         3.5         90         9.9         7.6         63         8.8%           Morris 2008         5.5         5.2         145         6.9         6.5         135         13.1%           Subtotal (95% CI)         1744         1502         59.3%         Heterogeneity: Tau <sup>2</sup> = 0.91; Chi <sup>2</sup> = 12.60, df = 3 (P = 0.006); I <sup>2</sup> = 76%           Test for overall effect: Z = 3.33 (P = 0.0009)         Total (95% CI)         2226         1982         100.0%		1.2.2 Observational Studies         Clark 2013       7.8       13.4       1132       8.9       17.4       1044       20.7%       -1.10 [-2.41, 0.21]         Lai 2016       4.7       2.3       90       7.5       7       63       11.1%       -2.80 [-4.59, -1.01]         Morris 2008       8.8       9.1       145       10.2       9.6       136       7.4%       -1.40 [-3.59, 0.79]         Subtotal (95% Cl)       1367       1242       39.2%       -1.64 [-2.59, -0.68]       146         Heterogeneity: Chi <sup>2</sup> = 2.30, df = 2 (P = 0.32); P = 13%       Test for overall effect: Z = 3.37 (P = 0.0008)       1572       100.0%       -1.64 [-2.24, -1.04]       100       -50       50       100         Heterogeneity: Chi <sup>2</sup> = 9.01, df = 10 (P = 0.53); P = 0%       1572       100.0%       -1.64 [-2.24, -1.04]       100       -50       50       100         Tost (95% Cl)       1699       1572       100.0%       -1.64 [-2.24, -1.04]       -100       -50       50       100         Heterogeneity: Chi <sup>2</sup> = 9.01, df = 10 (P = 0.53); P = 0%       50       100       -50       50       100       -50       50       100
Heterogeneity: Tau <sup>2</sup> = 0.62; Chi <sup>2</sup> = 23.68, df = 12 (P = 0.02); l <sup>2</sup> = 49% Test for overall effect: Z = 5.00 (P < 0.00001) Test for subaroup differences: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.84), l <sup>2</sup> = 0% Outcome : LOS in ICU	-100 -50 0 50 100 Favours [experimental] Favours [control]	Test for subarrous differences: ChP = 0.00. df = 1 (P = 1.00). P = 0% Outcome: Duration of MV
Experimental Control	Mean Difference Mean Difference	Experimental Control Odds Ratio Odds Ratio
Study or Subgroup Mean SD Total Mean SD Total Weight 1.3.1 RCT	IV, Random, 95% Cl IV, Random, 95% Cl	Study or Subgroup Events Total Events Total Weight M.H. Fixed, 95% Cl M.H. Fixed, 95% Cl
Burtin 2009 36 14.1 31 40 15.6 36 4.4%		1.4.1 RCT Burtin 2009 11 45 7 45 2.1% 1.76 (0.61, 5.04)
Burtin 2009 36 14.1 31 40 15.6 36 4.4% Hodgson 2016 19 11.9 29 29 13.3 21 4.4%	-10.00 [-17.15, -2.85]	Burtin 2009 11 45 7 45 2.1% 1.76 [0.61, 5.04]
Burtin 2009 36 14.1 31 40 15.6 36 4.4% Hodgson 2016 19 11.9 29 29 13.3 21 4.4% Morris 2016 10 8.1 150 10 6.7 150 13.3%	-10.00 [-17.15, -2.85]	Burtin 2009 11 45 7 45 2.1% 1.76 [0.61, 5.04] Chen 2011 0 12 3 15 1.2% 0.14 [0.01, 3.06] ↓ Denehy 2013 5 74 7 76 2.6% 0.71 [0.22, 2.36]
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         15.0         13.3%           Mors 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%	-10.00 [-17.15, -2.85] 0.00 [-1.88, 1.68] 0.00 [-5.40, 5.40] -3.00 [-8.13, 2.13]	Burtin 2009     11     45     7     45     2.1%     1.76 [0.61, 5.04]       Chen 2011     0     12     3     15     1.2%     0.14 [0.01, 3.06]       Denehy 2013     5     74     7     76     2.6%     0.71 [0.22, 2.36]       Dong 2014     2     30     3     30     1.1%     0.64 [0.10, 4.15]       Hodgson 2016     2     29     1     21     0.4%     1.48 [0.13, 17.50]
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Moss 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%	-10.00 [-17.15, -2.85] 0.00 [-1.88, 1.68] 0.00 [-5.40, 5.40] -3.00 [-8.13, 2.13] 0.60 [-8.17, 4.37]	Burtin 2009       11       45       7       45       2.1%       1.76 [0.61, 5.04]         Chen 2011       0       12       3       15       1.2%       0.14 [0.01, 3.06]         Denehy 2013       5       74       7       76       2.6%       0.71 [0.22, 2.36]         Dong 2014       2       30       3       01.1%       0.64 [0.10, 4.15]
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Morss 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         15.5         11.1         49         12.9         8.1         55         9.0%           Stubtotal (95% CI)         422         419         44.3%	-10.00 [-17.15, -2.85] 0.00 [-1.88, 1.68] 0.00 [-5.40, 5.40] -3.00 [-8.13, 2.13]	Burtin 2009       11       45       7       45       2.1%       1.76 [0.61, 5.04]         Chen 2011       0       12       3       15       1.2%       0.14 [0.01, 3.06]         Denehy 2013       5       74       7       76       2.6%       0.71 [0.22, 2.36]         Dong 2014       2       30       3       0       1.1%       0.64 [0.10, 4.15]         Hodgson 2016       2       29       1       21       0.4%       1.48 [0.13, 17.50]         Kayambu 2015       3       26       1       24       0.4%       1.00 [0.50, 2.01]
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Moss 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%	-10.00 [-17.15, -2.85] 0.00 [-1.88, 1.68] 0.00 [-5.40, 5.40] -3.00 [-8.13, 2.13] 0.60 [-8.17, 4.37]	Burtin 2009       11       45       7       45       2.1%       1.76 [0.61, 5.04]         Chen 2011       0       12       3       15       1.2%       0.14 [0.01, 3.06]         Denehy 2013       5       74       7       76       2.6%       0.71 [0.22, 2.36]         Dong 2014       2       30       3       01.1%       0.64 [0.10, 4.15]
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Morss 2016         21         11.9         59         21         17.8         61         6.3%           Schalter 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Stubtotal (95% CI)         422         20         104         25         17         96         6.7%           Schubted (95% CI)         422         419         44.3%         44.3%           Heterogeneity: Tau <sup>2</sup> = 3.89; Chi <sup>2</sup> = 9.28, df = 5 (P = 0.10); I <sup>2</sup> = 46%         Test for overall effect: Z = 1.27 (P = 0.21)	-10.00 [-17.15, -2.85] 0.00 [-1.88, 1.68] 0.00 [-5.40, 5.40] -3.00 [-8.13, 2.13] 0.60 [-8.17, 4.37]	Burtin 2009       11       45       7       45       2.1%       1.76 [0.61, 5.04]         Chen 2011       0       12       3       15       1.2%       0.14 [0.01, 3.06]         Denehy 2013       5       74       7       76       2.6%       0.71 [0.22, 2.36]         Dong 2014       2       30       3       30       1.1%       0.64 [0.10, 4.15]         Hodgson 2016       2       29       1       21       0.4%       3.00 [0.29, 31.01]         Kayambu 2015       3       26       1       24       0.4%       3.00 [0.29, 31.01]         Morris 2016       18       150       18       150       6.3%       1.00 [0.50, 2.01]         Schwiecker 2009       9       49       14       55       4.3%       0.66 [0.26, 1.69]         Subtotal (95% CI)       519       512       21.2%       1.10 [0.76, 1.59]       4.18       4.18
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Mors 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Subtotal (95% CI)         422         419         44.3%           Heterogeneity: Tau <sup>2</sup> = 3.89; Chi <sup>2</sup> = 9.28, df = 5 (P = 0.10); I <sup>2</sup> = 46%         Test for overall effect: Z = 1.27 (P = 0.21)           1.3.2 Non-RCT         1.3.2 Non-RCT         1.3.2 Non-RCT         1.3.1 Non-RCT	-10.00 [-17.15, -2.85] 0.00 [-1.68, 1.68] 0.00 [-5.40, 5.40] -3.00 [-8.13, 2.13] 0.60 [-3.17, 4.37] -1.58 [-4.02, 0.86]	Burtin 2009       11       45       7       45       2.1%       1.76 [0.61, 5.04]         Chen 2011       0       12       3       15       1.2%       0.14 [0.01, 3.06]         Denehy 2013       5       74       7       76       2.6%       0.71 [0.22, 2.36]         Dong 2014       2       30       3       30       1.1%       0.64 [0.10, 4.15]         Hodgson 2016       2       29       1       21       0.4%       3.00 [0.29, 31.01]         Kayambu 2015       3       26       1       24       0.4%       3.00 [0.29, 31.01]         Morris 2016       18       150       6.3%       1.00 [0.50, 2.01]
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Morss 2016         21         11.9         59         21         17.8         61         6.3%           Schalter 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Stubtotal (95% CI)         422         20         104         25         17         96         6.7%           Schubted (95% CI)         422         419         44.3%         44.3%           Heterogeneity: Tau <sup>2</sup> = 3.89; Chi <sup>2</sup> = 9.28, df = 5 (P = 0.10); I <sup>2</sup> = 46%         Test for overall effect: Z = 1.27 (P = 0.21)	-10.00 [-17.15, -2.85] 0.00 [-1.88, 1.68] 0.00 [-5.40, 5.40] -3.00 [-8.13, 2.13] 0.60 [-8.17, 4.37]	Burtin 2009       11       45       7       45       2.1%       1.76 [0.61, 5.04]         Chen 2011       0       12       3       15       1.2%       0.14 [0.01, 3.06]         Denehy 2013       5       74       7       76       2.6%       0.71 [0.22, 2.36]         Dong 2014       2       30       3       30       1.1%       0.64 [0.10, 4.15]         Hodgson 2016       2       29       1       21       0.4%       3.00 [0.29, 31.01]         Kayambu 2015       3       26       1       24       0.4%       3.00 [0.29, 31.01]         Morris 2016       18       150       18       150       6.3%       1.00 [0.50, 2.01]         Schwiecker 2009       9       49       2.28       2.15 [0.88, 5.24]         Subtotal (95% CI)       519       512       21.2%       1.10 [0.76, 1.59]
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Mors 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Subtotal (95% CI)         422         419         44.3%           Heterogeneity: Tau <sup>2</sup> = 3.89; Chi <sup>2</sup> = 9.28, df = 5 (P = 0.10); I <sup>2</sup> = 46%         Test for overall effect: Z = 1.27 (P = 0.21)           1.3.2 Non-RCT         Clark 2013         16.8         18.4         1132         19.2         28.2         1044         12.7%           Klein2015         10.21         1.0.4         377         15.16         0.96         260         15.1%           Lai 2016         19.2         15.2         90         24         20.7	-10.00 [-17.15, -2.85] 0.00 [-18.8, 16.8] 0.00 [-5.40, 5.40] -3.00 [-8.13, 2.13] 0.60 [-3.17, 4.37] -1.58 [-4.02, 0.86] -2.40 [-4.42, -0.38] -4.95 [-5.11, -4.79] -4.80 [-10.80, 1.20]	Burtin 2009 11 45 7 45 2.1% 1.76 [0.61, 5.04] Chen 2011 0 12 3 15 1.2% 0.14 [0.01, 3.06] Denehy 2013 5 74 7 76 2.6% 0.71 [0.22, 2.36] Dong 2014 2 30 3 30 1.1% 0.64 [0.10, 4.15] Hodgson 2016 2 29 1 21 0.4% 1.48 [0.13, 17.50] Kayambu 2015 3 26 1 24 0.4% 3.00 [0.29, 31.01] Morris 2016 18 150 6.3% 1.00 [0.50, 2.01] Schaller 2016 17 104 8 96 2.8% 2.15 [0.88, 5.24] Schweickert 2009 9 49 14 55 4.3% 0.66 [0.26, 1.69] Subtotal (95% Cl) 519 512 21.2% 1.10 [0.76, 1.59] Total events 67 62 Heterogeneity: Chi <sup>p</sup> = 7.42, df = 8 (P = 0.49); P = 0% Test for overall effect: Z = 0.50 (P = 0.62)
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Mors 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Subtotal (95% CI)         422         419         44.3%           Heterogeneity: Tau <sup>2</sup> = 3.89; Chi <sup>2</sup> = 9.28, df = 5 (P = 0.10); I <sup>2</sup> = 46%         Test for overall effect: Z = 1.27 (P = 0.21)           1.3.2 Non-RCT         Clark 2013         16.8         18.4         1132         19.2         28.2         1044         12.7%           Kiein2015         10.21         1.04         377         15.16         0.96         260         15.1%           Lai 2016         19.2         2.5         90         24         20.7	-10.00 [-17.15, -2.85] 0.00 [-5.80, 5.40] -3.00 [-8.13, 2.13] 0.60 [-3.17, 4.37] -1.58 [-4.02, 0.86] -2.40 [-4.42, -0.38] -4.95 [-5.11, -4.79] -4.80 [-10.80, 1.20] -3.30 [-5.62, -0.98]	Burtin 2009 11 45 7 45 2.1% 1.76 [0.61, 5.04] Chen 2011 0 12 3 15 1.2% 0.14 [0.01, 3.06] Denehy 2013 5 74 7 76 2.6% 0.71 [0.22, 2.36] Dong 2014 2 30 3 30 1.1% 0.64 [0.10, 4.15] Hodgson 2016 2 29 1 21 0.4% 1.48 [0.13, 17.50] Kayambu 2015 3 26 1 24 0.4% 3.00 [0.29, 31.01] Morris 2016 18 150 18 150 6.3% 1.00 [0.50, 2.01] Schaller 2016 17 104 8 96 2.8% 2.15 [0.88, 5.24] Schweicker 2009 9 49 14 55 4.3% 0.66 [0.26, 1.69] Subtotal (95% CI) 519 512 21.2% 1.10 [0.76, 1.59] Total events 67 62 Heterogeneity: Chi <sup>2</sup> = 7.42, df = 8 (P = 0.49); I <sup>2</sup> = 0% Test for overall effect: Z = 0.50 (P = 0.62) 1.4.2 Non-RCT
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Mors 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Subtotal (95% CI)         422         419         44.3%           Heterogeneity: Tau <sup>2</sup> = 3.89; Chi <sup>2</sup> = 9.28, df = 5 (P = 0.10); P = 46%         Test for overall effect: Z = 1.27 (P = 0.21)           1.3.2 Non-RCT         Clark 2013         16.8         18.4         1132         19.2         28.2         1044         12.7%           Klein2015         10.21         1.04         377         15.16         0.96         260         15.1%           Lai 2016         19.2         15.2         90         24         20.7	-10.00 [-17.15, -2.85] 0.00 [-1.88, 1.68] 0.00 [-5.81, 2.13] 0.60 [-3.17, 4.37] -1.58 [-4.02, 0.86] -2.40 [-4.42, -0.38] -4.95 [-5.11, -4.79] -3.30 [-5.62, -0.98] -3.40 [-6.53, -0.27]	Burtin 2009 11 45 7 45 2.1% 1.76 [0.61, 5.04] Chen 2011 0 12 3 15 1.2% 0.14 [0.01, 3.06] Denehy 2013 5 74 7 76 2.6% 0.71 [0.22, 2.36] Dong 2014 2 30 3 30 1.1% 0.64 [0.10, 4.15] Hodgson 2016 2 29 1 21 0.4% 1.48 [0.13, 17.50] Kayambu 2015 3 2.6 1 24 0.4% 3.00 [0.29, 31.01] Morris 2016 18 150 18 150 6.3% 1.00 [0.50, 2.01] Schaller 2016 17 104 8 96 2.8% 2.15 [0.88, 5.24] Schweickert 2009 9 49 14 55 4.3% 0.66 [0.26, 1.69] Subtotal (95% CI) 519 512 21.2% 1.10 [0.76, 1.59] Total events 67 62 Heterogeneity: Chi <sup>P</sup> = 7.42, df = 8 (P = 0.49); P = 0% Test for overall effect: Z = 0.50 (P = 0.62) 1.4.2 Non-RCT Clark 2013 134 1132 138 1044 50.5% 0.88 [0.68, 1.14]
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Mors 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Stubtotal (95% CI)         422         419         44.3%           Heterogeneity: Tau <sup>2</sup> = 3.89; Chi <sup>2</sup> = 9.28, df = 5 (P = 0.10); I <sup>2</sup> = 46%         Test for overall effect: Z = 1.27 (P = 0.21)           1.3.2 Non-RCT         Clark 2013         16.8         18.4         1132         19.2         28.2         1044         12.7%           Kiein2015         10.21         1.04         377         15.16         0.96         260         15.1%           Lai 2016         19.2         2.5         90         24         20.7	-10.00 [-17.15, -2.85] 0.00 [-5.80, 5.40] -3.00 [-8.13, 2.13] 0.60 [-3.17, 4.37] -1.58 [-4.02, 0.86] -2.40 [-4.42, -0.38] -4.95 [-5.11, -4.79] -4.80 [-10.80, 1.20] -3.30 [-5.62, -0.98]	Burtin 2009 11 45 7 45 2.1% 1.76 [0.61, 5.04] Chen 2011 0 12 3 15 1.2% 0.14 [0.01, 3.06] Denehy 2013 5 74 7 76 2.6% 0.71 [0.22, 2.36] Dong 2014 2 30 3 30 1.1% 0.64 [0.10, 4.15] Hodgson 2016 2 29 1 21 0.4% 1.48 [0.13, 17.50] Kayambu 2015 3 26 1 24 0.4% 3.00 [0.29, 31.01] Morris 2016 18 150 18 150 6.3% 1.00 [0.50, 2.01] Schaller 2016 17 104 8 96 2.8% 2.15 [0.88, 5.24] Schweicker 2009 9 49 14 55 4.3% 0.66 [0.26, 1.69] Subtotal (95% CI) 519 512 21.2% 1.10 [0.76, 1.59] Total events 67 62 Heterogeneity: Chi <sup>2</sup> = 7.42, df = 8 (P = 0.49); I <sup>2</sup> = 0% Test for overall effect: Z = 0.50 (P = 0.62) 1.4.2 Non-RCT
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Mors 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Subtotal (95% CI)         422         419         44.3%           Heterogeneity: Tau <sup>2</sup> = 3.89; Chi <sup>2</sup> = 9.28, df = 5 (P = 0.10); I <sup>2</sup> = 46%         Test for overall effect: Z = 1.27 (P = 0.21)           1.3.2 Non-RCT         Clark 2013         16.8         18.4         1132         19.2         28.2         1044         12.7%           Klein2015         10.21         1.04         377         15.16         0.96         260         15.1%           Lai 2016         19.2         15.2         90         24         20.7	-10.00 [-17.15, -2.85] 0.00 [-1.88, 1.68] 0.00 [-5.81, 2.13] 0.60 [-3.17, 4.37] -1.58 [-4.02, 0.86] -2.40 [-4.42, -0.38] -4.95 [-5.11, -4.79] -3.30 [-5.62, -0.98] -3.40 [-6.53, -0.27]	Burtin 2009 11 45 7 45 2.1% 1.76 [0.61, 5.04] Chen 2011 0 12 3 15 1.2% 0.14 [0.01, 3.06] Denehy 2013 5 74 7 76 2.6% 0.71 [0.22, 2.36] Dong 2014 2 30 3 30 1.1% 0.64 [0.10, 4.15] Hodgson 2016 2 29 1 21 0.4% 1.48 [0.13, 17.50] Kayambu 2015 3 26 1 24 0.4% 3.00 [0.29, 31.01] Morris 2016 18 150 18 150 6.3% 1.00 [0.50, 2.01] Schaller 2016 17 104 8 96 2.8% 2.15 [0.88, 5.24] Schweickert 2009 9 49 14 55 4.3% 0.66 [0.26, 1.69] Subtotal (95% CI) 519 512 21.2% 1.10 [0.76, 1.59] Total events 67 62 Heterogeneity: Chi <sup>p</sup> = 7.42, df = 8 (P = 0.49); i <sup>p</sup> = 0% Test for overall effect: Z = 0.50 (P = 0.82) 1.4.2 Non-RCT Clark 2013 134 1132 138 1044 50.5% 0.88 [0.88, 1.14] Klein2015 45 377 43 260 17.9% 0.68 [0.24, 1.07] Morris 2008 20 165 30 165 10.5% 0.62 [0.34, 1.15]
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Mors 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Subtotal (95% CI)         422         419         44.3%         Heterogeneity: Tau <sup>2</sup> = 3.89; Chi <sup>2</sup> = 9.28, df = 5 (P = 0.10); P = 46%         Test for overall effect: Z = 1.27 (P = 0.21)         13.2         Non-RCT         Clark 2013         16.8         18.4         1132         19.2         28.2         10.44         12.7%           Kiein2015         10.21         1.04         377         15.16         0.96         260         15.1%           Lai 2016         19.2         2         2         0.4         2.5         16.6%	-10.00 [-17.15, -2.85] 0.00 [-5.40, 5.40] -3.00 [-8.13, 2.13] 0.60 [-3.17, 4.37] -1.58 [-4.02, 0.86] -2.40 [-4.42, -0.38] -4.95 [-5.11, -4.79] -3.30 [-5.62, -0.98] -3.40 [-5.53, -0.27] -3.87 [-5.23, -2.51] -2.83 [-4.62, -1.05] -100 -50 0 50 100	Burtin 2009 11 45 7 45 2.1% 1.76 [0.61, 5.04] Chen 2011 0 12 3 15 1.2% 0.14 [0.01, 3.06] Denehy 2013 5 74 7 76 2.6% 0.71 [0.22, 2.36] Dong 2014 2 30 3 30 1.1% 0.64 [0.10, 4.15] Hodgson 2016 2 29 1 21 0.4% 1.48 [0.13, 17.50] Kayambu 2015 3 26 1 24 0.4% 3.00 [0.29, 31.01] Morris 2016 18 150 18 150 6.3% 1.00 [0.50, 2.01] Schaller 2016 17 104 8 96 2.8% 2.15 [0.88, 5.24] Schweicket 2009 9 49 14 55 4.3% 0.66 [0.26, 1.69] Subtoal (95% CI) 519 512 21.2% 1.10 [0.76, 1.59] Total events 67 62 Heterogeneity: Chi <sup>p</sup> = 7.42, df = 8 (P = 0.49); P = 0% Test for overall effect: Z = 0.50 (P = 0.62) 1.4.2 Non-RCT Clark 2013 134 1132 138 1044 50.5% 0.88 [0.88, 1.14] Klein2015 45 377 43 260 17.9% 0.68 [0.44, 1.07] Morris 2008 20 165 10.5% 0.62 [0.24, 1.15]
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Mors 2016         21         11.9         59         21         17.8         61         6.3%           Schaller 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Subtotal (95% CI)         422         419         44.3%           Heterogeneity: Tau*= 3.89; Chi*= 9.28, df = 5 (P = 0.10); P = 46%         Test for overall effect: Z = 1.27 (P = 0.21)           1.3.2 Non-RCT         Clark 2013         16.8         18.4         1132         19.2         28.2         1044         12.7%           Klein2015         10.21         1.04         377         15.16         0.96         260         15.1%           Lai 2016         19.2         15.2         90         24         20.7         63	-10.00 [-17.15, -2.85] 0.00 [-18.8, 16.8] 0.00 [-5.8, 16.8] 0.00 [-5.40] -3.00 [-8.13, 2.13] 0.60 [-3.17, 4.37] -1.58 [-4.02, 0.86] -2.40 [-4.42, -0.38] -4.95 [-5.11, -4.79] -4.95 [-5.11, -4.79] -3.30 [-5.62, -0.98] -3.40 [-6.53, -0.27] -3.47 [-5.23, -2.51] -2.83 [-4.62, -1.05]	Burtin 2009 11 45 7 45 2.1% 1.76 [0.61, 5.04] Chen 2011 0 12 3 15 1.2% 0.14 [0.01, 3.06] Denehy 2013 5 74 7 76 2.6% 0.71 [0.22, 2.36] Dong 2014 2 30 3 30 1.1% 0.64 [0.10, 4.15] Hodgson 2016 2 29 1 21 0.4% 1.48 [0.13, 17.50] Kayambu 2015 3 26 1 24 0.4% 3.00 [0.29, 31.01] Morris 2016 18 150 6.3% 1.00 [0.50, 2.01] Schaller 2016 17 104 8 96 2.8% 2.15 [0.88, 5.24] Schweickert 2009 9 49 14 55 4.3% 0.66 [0.26, 1.69] Subtotal (95% Cl) 519 512 21.2% 1.10 [0.76, 1.59] Total events 67 62 Heterogeneity: ChiP = 7.42, df = 8 (P = 0.49); P = 0% Test for overall effect: Z = 0.50 (P = 0.62) 1.4.2 Non-RCT Clark 2013 134 1132 138 1044 50.5% 0.88 [0.68, 1.14] Klein2015 45 377 43 260 17.9% 0.68 [0.44, 1.07] Morris 2008 20 165 30 165 10.5% 0.88 [0.68, 1.14] Klein2015 45 377 43 260 17.9% 0.68 [0.44, 1.07] Morris 2008 20 165 30 165 10.5% 0.88 [0.65, 0.99] Total events 199 211 Heterogeneity: ChiP = 1.68, df = 2 (P = 0.43); P = 0%
Burtin 2009         36         14.1         31         40         15.6         36         4.4%           Hodgson 2016         19         11.9         29         29         13.3         21         4.4%           Morris 2016         10         8.1         150         10         6.7         150         13.3%           Morsis 2016         21         11.9         59         21         17.8         61         6.3%           Schalter 2016         22         20         104         25         17         96         6.7%           Schweickert 2009         13.5         11.1         49         12.9         8.1         55         9.0%           Subtotal (95% CI)         422         419         44.3%           Heterogeneity: Tau <sup>2</sup> = 3.89; Chi <sup>2</sup> = 9.28, df = 5 (P = 0.10); I <sup>2</sup> = 46%         Test for overall effect: Z = 1.27 (P = 0.21)           1.3.2 Non-RCT         Clark 2013         16.8         18.4         1132         19.2         28.2         1044         12.7%           Klein2015         10.21         1.04         377         15.16         0.96         260         15.1%           Lai 2016         19.2         15.2         90         24         20.7	-10.00 [-17.15, -2.85] 0.00 [-5.40, 5.40] -3.00 [-8.13, 2.13] 0.60 [-3.17, 4.37] -1.58 [-4.02, 0.86] -2.40 [-4.42, -0.38] -4.95 [-5.11, -4.79] -3.30 [-5.62, -0.98] -3.40 [-5.53, -0.27] -3.87 [-5.23, -2.51] -2.83 [-4.62, -1.05] -100 -50 0 50 100	Butin 2009 11 45 7 45 2.1% 1.76 [0.61, 5.04] Chen 2011 0 12 3 15 1.2% 0.14 [0.01, 3.06] Denehy 2013 5 74 7 76 2.6% 0.71 [0.22, 2.36] Dong 2014 2 30 3 30 1.1% 0.64 [0.10, 4.15] Hodgson 2016 2 29 1 21 0.4% 1.48 [0.13, 17.50] Kayambu 2015 3 26 1 24 0.4% 3.00 [0.29, 31.01] Morris 2016 18 150 18 150 6.3% 1.00 [0.50, 2.01] Schaller 2016 17 104 8 96 2.8% 2.15 [0.88, 5.24] Schweicket 2009 9 49 14 55 4.3% 0.66 [0.26, 1.69] Total events 67 62 Heterogeneity: Chi <sup>P</sup> = 7.42, df = 8 (P = 0.49); P = 0% Test for overall effect: $Z = 0.50$ (P = 0.49); P = 0% Total events 199 211 Heterogeneity: Chi <sup>P</sup> = 1.68, df = 2 (P = 0.43); P = 0% Total events 199 211 Heterogeneity: Chi <sup>P</sup> = 1.68, df = 2 (P = 0.43); P = 0% Test for overall effect: $Z = 2.08$ (P = 0.43); P = 0% Total events 199 211 Heterogeneity: Chi <sup>P</sup> = 1.68, df = 2 (P = 0.43); P = 0% Test for overall effect: $Z = 2.08$ (P = 0.04)

Figure S2 Subgroup analysis comparing the result of RCTs and observational studies. RCTs, randomized controlled trial; SD, standard deviation; IV, inverse variance; CI, confidence interval; MV, mechanical ventilation; LOS, length of stay; ICU, intensive care unit.

Experimental Control Study or Subgroup Mean SD Total Mean SD Total Weig	Mean Difference ht IV, Fixed, 95% Cl	Mean Difference IV, Fixed, 95% Cl	Experimental Control Mean Difference Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% Cl IV, Fixed, 95% Cl
1.1.1 SICU           Burtin 2009         11         11.8         31         14         13.3         36         2.4           Chang 2011         17.5         9.8         18         17.5         11.8         16         1.7           Schaller 2016         10         9         104         14         11         96         11.7           Subtotal (95% CI)         153         148         15.7           Heterogeneity: Chi² = 1.02, df = 2 (P = 0.60); l² = 0%         Test for overall effect: Z = 2.79 (P = 0.005)	% 0.00 [-7.34, 7.34] % -4.00 [-6.80, -1.20]	*	1.2.1 SICU         Burtin 2009       6       7.4       31       6       9.6       36       3.5%       0.00 [-4.08, 4.08]         Chang 2011       6.4       4       18       6.9       5.3       16       5.8%       -0.50 [-3.69, 2.69]         Schaller 2016       7       7       104       8       96       13.4%       -1.00 [-3.09, 1.09]         Subtotal (95% Cl)       153       148       22.7%       -0.72 [-2.32, 0.89]       Image: Close Cl
1.1.2 RICU           Chen 2011         35.4         21.9         12         56.9         45.6         15         0.1           Morris 2016         7.5         7.4         150         8         6.7         150         35.4           Moss 2016         15         11.1         59         16         10.4         61         6.1           Schweickert 2009         5.9         6.4         49         7.9         5         51         18.4           Subtotal (95% Cl)         270         281         60.4         16         16.1         15.1         16.1         16.1         15.1         16	% -1.00 [-4.85, 2.85] % -2.00 [-4.23, 0.23]		<b>1.2.2 RICU</b> Chen 2011 $32.7$ $23.4$ $12$ $54.6$ $46.2$ $15$ $0.1\%$ $-21.90$ $[+48.77, 4.97]$ Moss 2016       10       8.1 $59$ 10 $8.9$ $61$ $6.3\%$ $0.00$ $[-3.04, 3.04]$ Schweickert 2009 $3.4$ $3.7$ $49$ $6.1$ $4.5$ $26.70$ $-2.20, -1.20]$ Subtotal (95% Cl)       120       131 $32.5\%$ $-2.22$ $-3.57, -0.88]$ Heterogeneity: Chi² = 4.50, df = 2 (P = 0.11); P = 56%       Test for overall effect: Z = $3.24$ (P = 0.001) $-4.22$ $-3.24$ $-4.22$ $-3.24$ $-4.22$ $-3.24$ $-4.22$ $-3.24$ $-2.22$ $-3.57, -0.88$ $-4.22$ $-4.22$ $-4.22$ $-3.24$ $-4.22$ $-4.22$ $-3.24$ $-4.22$ $-4.22$ $-4.22$ $-3.24$ $-4.22$
1.1.3 MICU           Dong 2014         12.7         4.1         30         15.2         4.5         30         19.2           Hodgson 2016         9         8.1         29         11         8.1         21         4.4           Subtotal (95% Cl)         59         51         23.4           Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0%         Test for overall effect: Z = 2.40 (P = 0.02)         10	% -2.00 [-6.55, 2.55]	•	<b>1.2.3 MICU</b> Dong 2014       5.6       2.1       30       7.3       2.8       30       37.4%       -1.70 [-2.95, -0.45]         Hodgson 2016       5.4       4.8       29       7       5.2       21 $7.3\%$ -1.60 [-4.43, 1.23]         Subtotal (95% Cl)       59       51       44.7%       -1.68 [-2.83, -0.54]         Heterogeneity: Chi <sup>2</sup> = 0.00, df = 1 (P = 0.95); P = 0%       Test for overall effect: Z = 2.88 (P = 0.004)
Total (95% Cl)         482         480         100.4           Heterogeneity: Chi <sup>2</sup> = 8.06, df = 8 (P = 0.43);   <sup>2</sup> = 1 %         Test for overall effect: Z = 3.59 (P = 0.0003)         Test for subaroup differences: Chi <sup>2</sup> = 3.51. df = 2 (P = 0.17).   <sup>2</sup> = 43.1%           Outcome : LOS in ICU         <	-100 -5	0 0 50 100 xperimental] Favours [control]	Total (95% CI)       332       330       100.0%       -1.64 [-2.41, -0.87]         Heterogeneity:       Chi² = 6.70, df = 7 (P = 0.46); I² = 0%       -100       -50       0       50       100         Test for overall effect:       Z = 4.19 (P < 0.0001)
Experimental Control	Mean Difference	Mean Difference	Experimental Control Odds Ratio Odds Ratio
Study or Subgroup Mean SD Total Mean SD Total Weig 1.3.1 SICU		IV, Random, 95% Cl	Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl 1.4.1 SICU
Burtin 2009         36         14.1         31         40         15.6         36         10.1           Schaller 2016         22         20         104         25         17         96         13.5           Subtotal (95% Cl)         135         132         24.           Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.05, df = 1 (P = 0.82); i <sup>2</sup> = 0%         Test for overall effect: Z = 1.57 (P = 0.12)	% -3.00 [-8.13, 2.13]	  •	Burtin 2009       11       45       7       45       10.0%       1.76 [0.61, 5.04]         Schaller 2016       17       104       8       96       13.1%       2.15 [0.88, 5.24]         Subtotal (95% CI)       149       141       23.1%       1.98 [1.00, 3.91]         Total events       28       15         Heterogeneity: Chiã= 0.08, df = 1 (P = 0.77); i² = 0%         Test for overall effect: Z = 1.97 (P = 0.05)
1.3.2 RICU         Morris 2016       10       8.1       150       10       6.7       150       18.2         Moss 2016       21       11.9       59       21       17.8       61       13.2         Schweickert 2009       13.5       11.1       49       12.9       8.1       55       15.1         Subtotal (95% CI)       258       266       46.         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.08, df = 2 (P = 0.96); i <sup>2</sup> = 0%       Test for overall effect: Z = 0.12 (P = 0.90)         1.3.3 MICU       1.3.3 MICU       1.3.3 MICU       1.3.4 MICU	% 0.00 [-5.40, 5.40] % 0.60 [-3.17, 4.37]		<b>1.4.2 RICU</b> Chen 2011       0       12       3       15       5.7%       0.14 [0.01, 3.06]         Morris 2016       18       150       18       150       29.8%       1.00 [0.50, 2.01]         Schweickert 2009       9       49       14       55       20.3%       0.66 [0.26, 1.69]         Subtotal (95% Cl)       211       220       55.8%       0.79 [0.46, 1.36]         Total events       27       35         Heterogeneity: Chil# = 1.78, dff = 2 (P = 0.41);  F = 0%         Test for overall effect Z = 0.86 (P = 0.39)
Dong 2014         22         3.8         53         29.1         4.6         53         18.3           Hodgson 2016         19         11.9         29         29         13.3         21         10.0           Subtotal (95% Cl)         82         74         28.3           Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); i² = 0.%         Test for overall effect: Z = 9.05 (P < 0.00001)	% -10.00 [-17.15, -2.85]	-	1.4.3 MICU         Denehy 2013       5       74       7       76       12.1%       0.71       [0.22, 2.36]
Total (95% Cl)         475         472         100.           Heterogeneity:         Tau² = 16.59; Chi² = 45.23, df = 6 (P < 0.00001); I² = 87	% -100 -: Eavours (	50 0 50 100 experimental) Favours (control)	Kayambu 2015       3       26       1       24       1.7%       3.00 [0.29, 31.01]         Subtotal (95% CI)       159       151       21.2%       0.96 [0.42, 2.21]         Total events       12       12         Heterogeneity: Chi <sup>a</sup> = 1.44, df = 3 (P = 0.70); I <sup>a</sup> = 0%         Test for overall effect: Z = 0.10 (P = 0.92)
Outcome:LOS in hospital			Total (95% CI)       519       512       100.0%       1.10 [0.76, 1.59]         Total events       67       62         Heterogeneity: Chi <sup>2</sup> = 7.42, df = 8 (P = 0.49); I <sup>2</sup> = 0%       0.01       0.1       1       10         Test for overall effect: Z = 0.50 (P = 0.62)       0.01       0.1       1       10       100         Test for suboroup differences: Chi <sup>2</sup> = 4.43, df = 2 (P = 0.11), I <sup>2</sup> = 54.8%       Favours [experimental]       Favours [control]         Outcome: Mortality at hospital       Image: Additional control in the state

Figure S3 Subgroup analysis comparing the result of different ICU type. SD, standard deviation; IV, inverse variance; CI, confidence interval; MV, mechanical ventilation; LOS, length of stay; ICU, intensive care unit; SICU, surgery intensive care unit; RICU, respiratory intensive care unit; MICU, medical intensive care unit.