OPEN

Effectiveness of Bundle Interventions on ICU Delirium: A Meta-Analysis*

Shan Zhang, PhD[1]

Yuan Han, MD[1]

Qian Xiao, PhD[1]

Haibin Li, PhD[2]

Ying Wu, PhD, RN, ACNP, ANP, NFESC[1]

OBJECTIVE: To evaluate the impact of bundle interventions on ICU delirium prevalence, duration, and other patients' adverse outcomes.

DATA SOURCES: The Cochrane Library, PubMed, CINAHL, EMBASE, PsychINFO, and MEDLINE from January 2000 to July 2020. The protocol of the study was registered in International prospective register of systematic reviews (CRD42020163147).

STUDY SELECTION: Randomized clinical trials or cohort studies that examined the following outcomes were included in the current study: ICU delirium prevalence and duration, proportion of patient-days with coma, ventilator-free days, mechanical ventilation days, ICU or hospital length of stay, and ICU or inhospital or 28-day mortality.

DATA EXTRACTION: Using a standardized data-collection form, two authors screened the studies and extracted the data independently, and assessed the studies' quality using the Modified Jadad Score Scale for randomized clinical trials and the Newcastle-Ottawa Scale for cohort studies.

DATA SYNTHESIS: Eleven studies with a total of 26,384 adult participants were included in the meta-analysis. Five studies (three randomized clinical trials and two cohort studies) involving 18,638 patients demonstrated that ICU delirium prevalence was not reduced (risk ratio = 0.92; 95% CI, 0.68–1.24). Meta-analysis showed that the use of bundle interventions was not associated with shortening the duration of ICU delirium (mean difference = −1.42 d; 95% CI, −3.06 to 0.22; two randomized clinical trials and one cohort study), increasing ventilator-free days (mean difference = 1.56 d; 95% CI, −1.56 to 4.68; three randomized clinical trials), decreasing mechanical ventilation days (mean difference = −0.83 d; 95% CI, −1.80 to 0.14; four randomized clinical trials and two cohort studies), ICU length of stay (mean difference = −1.08 d; 95% CI, −2.16 to 0.00; seven randomized clinical trials and two cohort studies), and inhospital mortality (risk ratio = 0.86; 95% CI, 0.70–1.06; five randomized clinical trials and four cohort studies). However, bundle interventions are effective in reducing the proportion of patient-days experiencing coma (risk ratio = 0.47; 95% CI, 0.39–0.57; two cohort studies), hospital length of stay (mean difference = −1.47 d; 95% CI, −2.80 to −0.15; four randomized clinical trials and one cohort study), and 28-day mortality by 18% (risk ratio = 0.82; 95% CI, 0.69–0.99; three randomized clinical trials).

CONCLUSIONS: This meta-analysis fails to support that bundle interventions are effective in reducing ICU delirium prevalence and duration, but supports that bundle interventions are effective in reducing the proportion of patient-days with coma, hospital length of stay, and 28-day mortality. Larger randomized clinical trials are needed to evaluate the impact of bundle interventions on ICU delirium and other clinical outcomes.

***See also p. 380.**

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KEY WORDS: bundle interventions; delirium; intensive care unit; meta-analysis

Delirium is a common but mostly preventable complication among patients in the ICUs, with the incidence ranged as high as 70–87% (1, 2). ICU patients complicated with delirium have been identified with prolonged mechanical ventilation (MV), longer hospital stay, and increased mortality (2, 3). The severity of adverse outcomes was also associated with delirium duration, the longer the duration, and the worse the adverse outcomes (3, 4). Therefore, prevention of delirium from its happening or early management to reverse ICU delirium is critical to minimize the adverse effects on clinical outcomes associated with ICU delirium among identified patients (5–7).

Although the pathogenesis of ICU delirium is not completely clear, it is proposed that multiple risk factors collectively contributed to the onset and persistence of ICU delirium (7, 8). Therefore, clinical guidelines, including the pain, agitation, delirium, immobility, and sleep (PADIS) guidelines, have recommended to use a bundle approach, such as the "ABCDEF bundle" to target on eliminating multiple modifiable risk factors of ICU delirium to reduce the chances of or shorten the duration of delirium to be occurred in critically ill adults (6, 9). Among the different components of the ABCDEF bundle, A stands for Assess, prevent, and manage pain, which is a major risk factor of ICU delirium; B represents Both spontaneous awakening trials (SATs) for sedative patients and spontaneous breathing trials (SBTs) if patients were on mechanical ventilators; C refers to the Choice of analgesics and sedatives, as the use of analgesics and sedatives is a major risk factor of ICU delirium; D denotes for Delirium monitoring or management, which includes reorientation, improving sleep and wakefulness, as well as reducing hearing and/or visual impairment, etc; E implies Early exercise/mobility as immobility is a major risk factor of ICU delirium; and F refers to Family engagement and empowerment (restrictive ICU visit is a major risk factor of ICU delirium) (9). Not every ICU patient has all the above-mentioned risk factors; therefore, the appropriate subset of interventions from the ABCDEF bundle should be tailored to patients' specific risk factors.

It has been proposed that the ABCDEF bundle maybe more effective than any single-component strategy in preventing and managing ICU delirium with its evidence largely driven from before-after studies (10–13) or pilot studies (14, 15). After the PADIS Guidelines were released, a number of well-designed robust randomized clinical trials (RCTs) (16–18) have been conducted to evaluate the bundle interventions in minimizing modifiable risk factors related to ICU delirium, therefore reducing its prevalence or duration. However, their findings have been inconsistent or even contradictory among different studies (19–21). Therefore, we conducted a meta-analysis to assess the overall effectiveness of bundle interventions on the prevalence and duration of ICU delirium, and other important adverse outcomes, such as the hospital length of stay (LOS) and mortality.

MATERIALS AND METHODS

The meta-analysis was conducted and reported in accordance with the criteria identified by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (**Appendix File 1**, http://links.lww.com/CCM/G21) (22). The current study was a retrospective analysis of published research literature only, and no human were involved. Therefore, the Institution Review Board approval was not required based on the institutional policies. The protocol of the study was registered in International prospective register of systematic reviews (CRD42020163147).

Search Strategy

We performed a comprehensive literature search to identify RCTs and cohort studies related to delirium bundle interventions between January 2000 and July 2020. Following a preliminary PubMed search using combined key terms (delirium OR ICU delirium) AND (intervention OR critical care), the earliest published work by Slomka et al (23) relevant to the topic of this meta-analysis was identified in the year of 2000; therefore, the year of 2000 was chosen as the starting point to search available relevant published works. Databases including the Cochrane Library, PubMed, CINAHL, EMBASE, PsychINFO, and MEDLINE were searched for published articles with no language restriction applied. The search terms included a combination of key terms related to delirium: (delirium OR confusion OR acute confusional syndrome OR postoperative delirium OR cognitive dysfunction OR ICU delirium OR ICU psychosis OR ICU syndrome OR deliri*) AND

(ABCDE bundle OR ABCDEF bundle OR bundle OR PAD OR critical care* OR intensive care* OR prevention OR intervention). We also searched ongoing and unpublished trials using the clinicaltrials.gov databases. Additional relevant articles were identified by manually reviewing the reference lists of all included research articles as well as published review articles and meta-analyses. The authors of original studies were also contacted to acquire missed data to be included in the final analysis.

Study Selection

The title and abstract of all articles were screened initially, and the full text of potential studies was retrieved and further reviewed by two reviewers (S.Z. and Y.H.) independently to assess the eligibility. Articles were eligible for inclusion in the meta-analysis if they met all of the following inclusion criteria: 1) RCTs or cohort studies, (the Cochrane Handbook for Systematic Reviews of Interventions, Version 6.0 [24], identifies that the review may include nonrandomized studies, such as cohort studies, when the question of interest cannot be answered by RCTs), 2) study participants were adults (18 years old or older) administered in the ICUs, and 3) application of at least three of the components identified in the ABCDEF bundle, which includes assessment and pain management, SAT or SAT plus SBT for patients supported by ventilator, choice of analgesia and sedation, delirium monitoring/management, early exercise/mobility, and family engagement and empowerment. Articles were excluded if they were presented with any of the following reasons: 1) nonrelevant topics, 2) study protocols or case reports, 3) commentary or meta-analysis and systemic review, and 4) nonhuman study. For articles that met the above initial criteria, the following second-level inclusion criteria were applied: 1) study must be designed with control groups, 2) ICU delirium was measured by validated instruments including the diagnostic and statistical methods IV criteria, confusion assessment method (CAM), CAM for the ICU (CAM-ICU), or the intensive care delirium screening checklist (ICDSC), and 3) the study reported selected clinical outcomes of our interest (**Fig. 1**).

Outcome Measures

The primary endpoint assessed in this study was the prevalence and duration of ICU delirium. The prevalence of ICU delirium was defined as the presence of delirium among patients at the end of follow-up, and the duration of ICU delirium is defined as the total hospital days in which the patient was diagnosed with ICU delirium. The secondary endpoints included proportion of patient-days with coma, ICU and hospital LOS, number of ventilator-free days (VFDs) and MV days, as well as the ICU, inhospital, and 28-day mortalities (**Supplementary File 2**, http://links.lww.com/CCM/G22).

Quality Assessment

The quality of RCT studies was examined by two reviewers (S.Z. and Y.H.) separately, using the Modified Jadad Scale (25). The score on the Modified Jadad Scale was ranged from 0 to 7, with a score of greater than or equal to 4 being defined as high-quality studies. The quality of cohort studies was examined using the Newcastle-Ottawa Scale (NOS) (26). The score on the NOS was ranged from 0 to 9 with a score of greater than or equal to 6 being identified as an acceptable methodological design. Risk of bias of each study was further assessed based on the six domains identified by the "Cochrane Handbook for Systematic Reviews of Interventions" (27).

Data Collection

Using a predesigned standardized data-collection form, relevant data from original studies were extracted and collected independently by two researchers (S.Z. and Y.H.), including study characteristics (primary author, publication year, study design, and sample size), participant demographics (age and gender), interventions and comparisons, as well as information on the intended outcome variables. For each outcome, the reviewers extracted the means (SDs) of the variable or number of patients in each study.

Statistical Analysis

Meta-analysis was performed using the Review Manager (RevMan) Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark). Heterogeneity among studies was assessed using the chi-square test, and I^2 values were used to determine heterogeneity across studies, attributing to

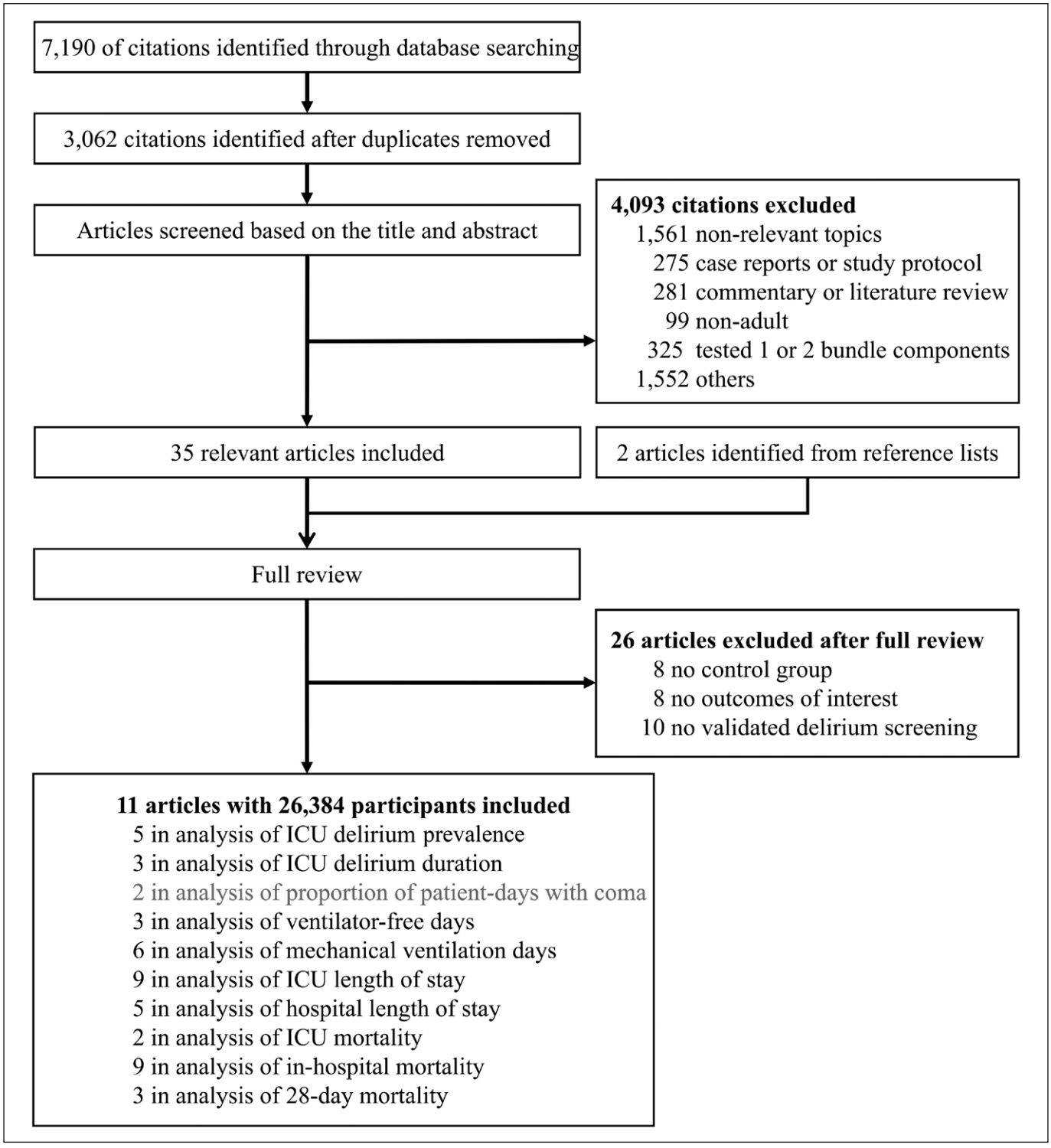

Figure 1. Flowchart of literature identification, review, and selection.

the proportion of total variation, in which the $I^2 > 50\%$ indicated substantial heterogeneity of effects and random-effects models were applied. If the $I^2 < 50\%$ was identified, which represented homogeneity, fixed-effects models were selected. For continuous data, mean difference (MD) and 95% CI were used for outcomes pooled. For dichotomous outcomes, risk ratios (RRs) with 95% CI were evaluated in accordance with intent-to-treat principles. The forest plot was applied to represent the meta-analysis results, and the funnel plots were constructed to identify publication bias using the Begg and Egger

tests with Stata software (Stata/SE 12.0; StataCorp LP, College Station, TX). Sensitivity analysis was also performed by assessing whether random-effects and fixed-effects models would bring about the same result. All statistical tests were two-tailed, and *p* value of less than 0.05 was considered statistically significant.

RESULTS

Study Identification

Our initial search yielded 7,190 publications based on the defined search terms (Fig. 1). After screening of the titles and abstracts, 37 potential studies with

TABLE 1.
Characteristics of Included Studies

Source	Study Type	Setting	Sample Size (*n*) Intervention Group/ Control Group	ICU Delirium Assessment Tool	Interventions	Quality Assessment[a]	Risk of Bias[b]
Girard et al (29) (2008)	RCT	ICU	167/168	CAM-ICU	3/6 (A, B, D)	5	5/6 (A, C, S, R, O)
Schweickert et al (30) (2009)	RCT	MICU	49/55	CAM-ICU	4/6 (A, B, D, E)	7	6/6 (A, B, C, S, R, O)
Mehta et al (28) (2012)	RCT	SICU and MICU	214/209	ICDSC	3/6 (A, B, D)	7	6/6 (A, B, C, S, R, O)
Mansouri et al (31) (2013)	RCT	SICU and MICU	96/105	CAM-ICU	3/6 (A, C, D)	4	4/6 (A, C, S, O)
Moon and Lee (18) (2015)	RCT	SICU and MICU	60/63	CAM-ICU	4/6 (A, C, D, E)	5	5/6 (A, C, S, R, O)
Sosnowski et al (17) (2018)	RCT	ICU	15/15	CAM-ICU	5/6 (A, B, C, D, E)	5	5/6 (A, C, S, R, O)
Olsen et al (16) (2020)	RCT	ICU	351/349	CAM-ICU	5/6 (A, B, C, D, E)	5	4/6 (A, C, S, O)
Barnes-Daly et al (32) (2017)	CS	MICU and SICU	6,064	CAM-ICU	5/6 (A, B, C, D, E)	8	3/6 (C, S, O)
Hsieh et al (20) (2019)	CS	MICU	281/366	CAM-ICU	3/6 (B, D, E)	8	3/6 (C, S, O)
Pun et al (21) (2019)	CS	ICU	NA	CAM-ICU or ICDSC	6/6 (A, B, C, D, E, F)	8	3/6 (C, S, O)
Trogrlić et al (19) (2019)	CS	SICU and MICU	1,194/ 1,337	CAM-ICU or ICDSC	5/6 (A, C, D, E, F)	8	3/6 (C, S, O)

A = assess, prevent, and manage pain, B = both spontaneous awakening trials and spontaneous breathing trials, C = choice of analgesia and sedation, CAM-ICU = confusion assessment method for the ICU, CS = cohort study, D = delirium monitoring/management, E = early exercise/mobility, F = family engagement and empowerment, ICDSC = intensive care delirium screening checklist, MICU = medical ICU, NR = not report, RCT = randomized clinical trial, SICU = surgical ICU.

[a]The quality of included RCTs articles was examined using the Modified Jadad Scale (range, 0–7). The quality of included cohort studies was examined using the Newcastle-Ottawa Scale (range, 0–9).

[b]Risk of bias include the following: A = allocation concealment, B = blinding of participants, personnel, and outcome assessors, C = completeness of outcome data, O = other sources of bias, R = random-sequence generation or balanced allocation, S = selective outcome reporting.

full-text were retrieved, in which 26 studies did not meet the second-level inclusion criteria. Therefore, a total of 11 studies (seven RCTs and four cohort studies) were included in the final analysis according to the selection criteria (**Table 1**). Two datasets were acquired from the principal investigators of the original studies (16, 28) as the data included in the articles were inadequate for analysis.

Study Characteristics

The 11 original studies included in the current study were published between 2008 and 2020, with a total of 26,384 adult participants. The reported ICU delirium prevalence varied from 20.49% (19) to 74.25% (29). All studies (with supplementary data obtained from authors of two original studies) provided relevant data on one or more targeted outcomes that were suitable for final analysis (Table 1). The selected elements of the bundle intervention used in each study were listed in **Supplementary Table 1** (http://links.lww.com/CCM/G24).

Pooled Outcomes

ICU Delirium Prevalence. Five studies (three RCTs and two cohort studies) reported on the prevalence of ICU delirium, which included a total of 18,638 patients in the meta-analysis (**Table 2**). A random-effect model showed that, when compared with control groups, the bundle interventions lowered the odds of ICU delirium prevalence by 8% (RR = 0.92; 95% CI, 0.68–1.24; $p = 0.57$), but not statistically significant (**Fig. 2**). The ICU delirium prevalence was stratified by the study design, with three RCTs comprising 441 ICU patients in intervention groups and 440 in control groups, and the pooled result showed that the bundle interventions had no effect on lowering the odds of ICU delirium (RR = 1.01; 95% CI, 0.91–1.13; $p = 0.81$) (Table 2). The two cohort studies that applied bundle interventions lowered the ICU delirium prevalence by 8% (RR = 0.92; 95% CI, 0.40–2.11; $p = 0.84$) (Table 2), but no significant differences were detected.

ICU Delirium Duration. There was no difference identified on the length of ICU delirium between the participants in the bundle-intervention group ($n = 1,410$) and usual care ($n = 1,560$) group (three studies [two RCTs and one cohort study]; MD = –1.42 d; 95% CI, –3.06 to 0.22; $p = 0.09$) (Table 2; and **Supplementary Fig. 1**, http://links.lww.com/CCM/G23).

Proportion of Patient-Days With Coma. Patients in the bundle-intervention group were associated with lower likelihood on the proportion of patient-days experiencing coma (RR = 0.47; 95% CI, 0.39–0.57; $p < 0.001$; two cohort studies; fixed-effects model) (Table 2; and **Supplementary Fig. 2**, http://links.lww.com/CCM/G23).

Mechanical Ventilation Days and Ventilator-Free Days. The length of MV was 0.83 days shorter among 1,849 ICU patients who received the bundle interventions (MD = –0.83 d; 95% CI, –1.80 to 0.14; $p = 0.09$; six studies [four RCTs and two cohort studies]) (Table 2; and **Supplementary Fig. 3**, http://links.lww.com/CCM/G23) compared with those in the control group ($n = 2,087$), but the outcome was not statistically significant. Regarding VFDs, no difference was found between the intervention group ($n = 567$) and the control group ($n = 572$) (MD = 1.56 d; 95% CI, –1.56 to 4.68; $p = 0.33$; three RCTs) (Table 2; and **Supplementary Fig. 4**, http://links.lww.com/CCM/G23).

ICU and Hospital Length of Stay. There were nine studies (seven RCTs and two cohort studies) reporting results on the ICU LOS. With a total of 5,184 ICU patients included in the meta-analysis using a random-effects model, the pooled result showed that the MD was 1.08 days shorter (95% CI, –2.16 to 0.00; $p = 0.05$) (Table 2; and **Supplementary Fig. 5**, http://links.lww.com/CCM/G23) among patients in the intervention group compared with those in the control group. In addition, five studies (four RCTs and one cohort study) measured hospital LOS (Table 2), and the meta-analysis using a fixed-effects model ($I^2 = 42\%$; $p = 0.14$) found that the MD of hospital LOS was 1.47 (95% CI, –2.80 to –0.15; $p = 0.03$) days shorter among 726 ICU patients in the intervention group compared with patients in the control group (Table 2; and **Supplementary Fig. 6**, http://links.lww.com/CCM/G23).

Mortality. Two (one RCT and one cohort study), nine (five RCTs and four cohort studies), and three (all RCTs) studies reported results on the ICU, inhospital, and 28-day mortalities, respectively (Table 2; and **Supplementary Figs. 7–9**, http://links.lww.com/CCM/G23). Meta-analysis using a fixed-effects model ($I^2 = 0\%$; $p = 0.61$) found that the bundle interventions did not decrease ICU mortality (RR = 1.01; 95%

TABLE 2.
Meta-Analysis of the Effect of Bundle Interventions

Variable	Statistical Method	Risk Ratio or Mean Difference (95% CI)	I^2 Value (%)	*p*
ICU delirium prevalence				
RCTs (18, 28, 29) (3)	M-H, fixed	1.01 (0.91–1.13)	31	0.81
Cohort studies (19, 21) (2)	M-H, random	0.92 (0.40–2.11)	98	0.84
Combined	M-H, random	0.92 (0.68–1.24)	91	0.57
ICU delirium duration				
RCTs (29, 30) (2)	IV, random	−0.89 (−2.82 to 1.06)	79	0.37
Cohort studies (19) (1)	IV, random	−2.30 (−2.83 to −1.77)	NA	< 0.001
Combined	IV, random	−1.42 (-−3.06 to 0.22)	90	0.09
Coma				
RCTs (0)	NA	NA	NA	NA
Cohort studies (19, 21) (2)	M-H, fixed	0.47 (0.39–0.57)	47	< 0.001
Combined	M-H, fixed	0.47 (0.39–0.57)	47	< 0.001
Ventilator-free days				
RCTs (16, 29, 30) (3)	IV, random	1.56 (−1.56 to 4.68)	76	0.33
Cohort studies (0)	NA	NA	NA	NA
Combined	IV, random	1.56 (−1.56 to 4.68)	76	0.33
Mechanical ventilation days				
RCTs (17, 28, 30, 31) (4)	IV, random	−0.74 (−2.22 to 0.74)	79	0.33
Cohort studies (19, 20) (2)	IV, random	−0.94 (−2.99 to 1.12)	95	0.37
Combined	IV, random	−0.83 (−1.80 to 0.14)	86	0.09
ICU LOS				
RCTs (16–18, 28, 29–31) (7)	IV, random	−1.07 (−2.62 to 0.48)	63	0.18
Cohort studies (19, 20) (2)	IV, random	−0.96 (−2.72 to 0.80)	91	0.29
Combined	IV, random	−1.08 (−2.16 to 0.00)	74	0.05
Hospital LOS				
RCTs (17, 28, 29, 30) (4)	IV, fixed	−2.24 (−4.11 to −0.37)	47	0.02
Cohort studies (20) (1)	IV, fixed	−0.70 (−2.58 to 1.18)	NA	0.47
Combined	IV, fixed	−1.47 (−2.80 to −0.15)	42	0.03
ICU mortality				
RCTs (28) (1)	M-H, fixed	0.94 (0.67–1.32)	NA	0.72
Cohort studies (19) (1)	M-H, fixed	1.05 (0.83–1.32)	NA	0.71
Combined	M-H, fixed	1.01 (0.84–1.23)	0	0.89
Inhospital mortality				
RCTs (17, 18, 28, 30, 31) (5)	M-H, random	0.73 (0.45–1.17)	53	0.19
Cohort studies (19–21, 32 (4)	M-H, random	0.92 (0.71–1.19)	80	0.52
Combined	M-H, random	0.86 (0.70–1.06)	67	0.16
28-d mortality				
RCTs (16, 18, 29) (3)	M-H, fixed	0.83 (0.71–0.98)	11	0.02
Cohort studies (0)	NA	NA	NA	NA
Combined	M-H, fixed	0.83 (0.71–0.98)	11	0.02

IV = inverse variance, LOS = length of stay, M-H = Mantel-Haenszel, NA = not applicable, RCT = randomized clinical trial.

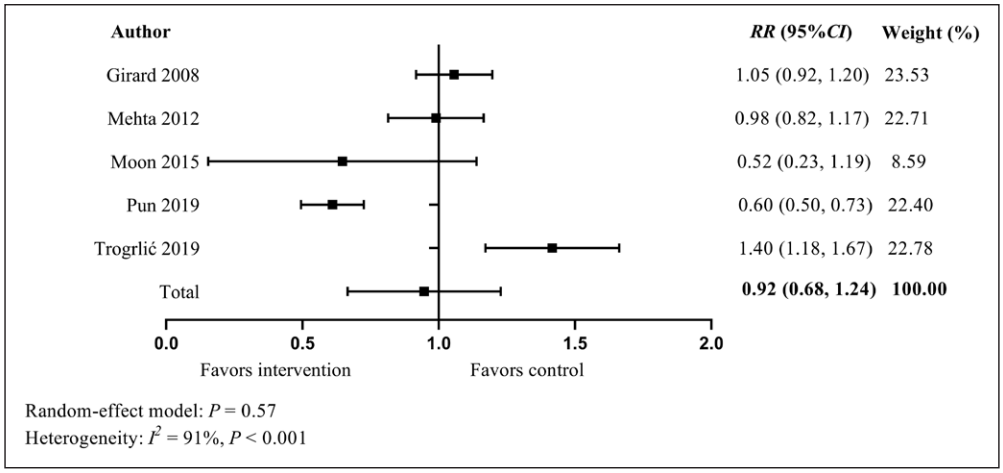

Figure 2. Meta-analysis of ICU delirium prevalence. RR = risk ratio.

CI, 0.84–1.23; p = 0.89) among 2,954 ICU patients. Additionally, the RR for inhospital mortality was 0.86 (95% CI, 0.70–1.06; p = 0.16) among 25,349 ICU patients, with nonsignificant findings. However, the 28-day mortality was decreased by 18% (RR = 0.82; 95% CI, 0.69–0.99; p = 0.04) among 1,158 ICU patients in the intervention group.

Sensitivity Analysis. In the sensitivity analysis on the ICU delirium prevalence, there was still heterogeneity among studies (p < 0.001; I^2 = 93%) after excluding the study from Mehta et al (28), which used the ICDSC to assess ICU delirium. The RRs obtained by the random-effect model were 0.89 (95% CI, 0.59–1.33), Z = 0.59, and p = 0.56, with no substantial changes observed in the results.

Meanwhile, the sensitivity analysis was also performed by excluding the study from Pun et al(21), which underwent extensive modeling and adjusted for 18 confounding factors, and therefore could have affected the result on ICU delirium prevalence. However, the result was similar to the general pooled analysis (RR = 1.08; 95% CI, 0.87–1.34; p = 0.49).

The ICU delirium duration was stratified based on the number of bundle interventions, which was dichotomized using the median of 4 as the cutoff point and was divided into two groups among patients received the intervention (**Supplementary Table 2**, http://links.lww.com/CCM/G24). In patients who received interventions with equal or less than four elements identified in the bundle approach (two studies), the MD obtained by the random-effect model was –0.89 (95% CI, –2.83 to 1.06; p = 0.37), and the MD was –2.30 (95% CI, –2.83 to –1.77; p < 0.01) among those who received more than four elements of the bundle interventions (one study).

In the sensitivity analysis on inhospital mortality, heterogeneity was still identified among studies (I^2 = 69%; p = 0.002) after excluding the study from Sosnowski et al (17), which is a pilot study reported with very high inhospital mortality in the intervention group.

The result was in line with that from the general pooled data (RR = 0.85; 95% CI, 0.70–1.04; p = 0.12).

The sensitivity analysis shows that regardless of which effect model was applied, the outcomes remained similar.

Publication Bias. As shown in **Supplementary Fig. 10** (http://links.lww.com/CCM/G23), the funnel plot is generally symmetric, which implied no publication bias existed for the ICU delirium prevalence (Egger test, p = 0.66; Begg test, p = 0.46). Similar findings were observed for ICU LOS, MV days, hospital LOS, and inhospital mortality (**Supplementary Figs. 11–14**, http://links.lww.com/CCM/G23). However, the number of studies reported on the relationship of bundle interventions with other outcomes was too small and a funnel plot analysis was not performed.

Association Between Quality Ratings and Effectiveness. The quality assessment based on the Modified Jadad Scale showed that seven RCTs were rated as high-quality study designs (Modified Jadad Score 4–7) (Table 1). The four cohort studies were also identified with high quality, among which the NOSs score were ranged from 6 to 8 (Table 1). No significant difference was observed between the score on risk of bias and the effectiveness of bundle interventions.

DISCUSSION

In this meta-analysis, we included 11 studies with a total of 26,384 adult ICU patients to evaluate the effectiveness of bundle interventions on either prevention and/or management of ICU delirium. Our findings failed to provide evidence in supporting that

the bundle interventions were effective measures on reducing either ICU delirium prevalence or duration. However, the result should be interpreted with caution, as there was substantial heterogeneity among studies even though sensitivity analysis was applied in terms of the result on ICU delirium prevalence and duration, but the results were not changed from the pooled effects. To the best of our knowledge, this is the first meta-analysis conducted to evaluate the effect of the ABCDEF bundle on ICU delirium prevalence and duration and other related adverse outcomes.

The PADIS Guidelines have recommended to use all components of the ABCDEF bundle to reduce the modifiable risk factors (e.g., pain, deep sedation, use of MV, analgesics and sedatives, and immobility) relevant to the development of the ICU delirium. However, the majority of the studies in the current analysis only used selected elements from the bundle. Among all the studies included, four studies used three elements, two studies used four elements, another four studies used five elements, and only one study reported the use of all ABCDEF bundle elements. This indicates that most of the interventions described by authors may not tailor to patients' every specific risk factors targeted by the ABCDEF bundle.

Our meta-analysis found that there were no significant differences in reducing the prevalence and duration of ICU delirium between the bundle-intervention group and the control group in the pooled analysis. These findings may be explained by the following possible reasons. First, the majority of the included studies in this meta-analysis did not focus on all the elements identified in the ABCDEF bundle, so not all modifiable ICU delirium risk factors were appropriately addressed by the interventions applied. For example, the PADIS Guidelines recommend to use nonbenzodiazepine sedatives (e.g., dexmedetomidine) over benzodiazepines for sedation in ICU patients (9, 33). However, as identified by authors in three of the included studies (28, 29, 30), benzodiazepines were commonly prescribed for sedation in patients in the ICU. In addition, one study (19) used five elements of the bundle interventions, which significantly decreased the ICU delirium duration by 2.30 days among patients in the intervention group. However, the result must be interpreted with caution, as only one study used interventions that included more than four elements of the bundle approach among those examined the effects of the intervention on ICU delirium duration. In addition, the cohort study conducted by Pun et al (21) used all ABCDEF bundle elements and demonstrated that the bundle approach significantly reduced the delirium prevalence and improved selected outcomes such as coma and MV use. However, there is a lack of sufficient evidence from RCTs to support the effectiveness of ABCDEF bundle in improving ICU delirium prevalence and duration. Future well-designed RCTs are needed to evaluate the effects of all the ABCDEF bundle components as a whole intervention on ICU delirium.

Second, due to the complexity of the ABCDEF bundle approach, the adoption and adherence of the bundle interventions were suboptimal among included studies (28, 34). Healthcare providers were often reluctant to implement fully the bundle interventions in ICU patients, concerning practical difficulty, patient safety, workload burden, etc (5, 35); therefore, even the bundle interventions were implemented and they were not executed in their full extent (such as the dosage of sedatives is not adequately titrated) (28).

The proportion of patient-days experiencing coma was reduced by 53% in the bundle-intervention group. Although only two cohort studies (19, 21) reported the proportion of patient-days with coma in the current meta-analysis, there are one RCT study and two cohort studies revealed that the bundle intervention significantly shortened the duration of coma, decreased the proportion of patients with coma, or experienced more days free of coma, respectively. However, we failed to combine these coma-related outcomes due to inconsistent data formats among studies (20, 29, 32). The possible effect of bundle approach on coma improvement may be explained in part by the application of bundle intervention targeting on daily awakening, which attempts to stimulate the reticular activating system in the brain of comatose patient, and therefore promoted arousal (36, 37). Evidences have shown that the awakening trial is necessary for sustaining cortical arousal, which promoted further recovery of the nervous system and improved functional efficiency of the brain (36, 38). In addition, as demonstrated in previous research, passive range-of-motion activities (the "E" element) could also stimulate the brain activities that might have contributed to the decrease in the proportion of patient-days with coma (39, 40). Further studies are necessary to verify this result. The improvement of coma by the

bundle intervention may also explained our result on decreased LOS (1.47 d) in the current analysis.

As indicated by the results on mortality, the 28-day mortality was reduced after implementation of the bundle intervention but not with the ICU or inhospital mortality. The possible reason may be that the prevalence and duration of delirium were not changed in patients receiving the bundle intervention in the current meta-analysis; therefore, it could not reverse the adverse effect of delirium such as ICU and inhospital mortality. The other reason may be that none of the included studies were designed to test the effectiveness of bundle intervention on ICU mortality as primary outcomes; therefore, they were not powered to test the differences between the groups. However, a longer follow up period, such as 28 days, will increase the power to test the differences on 28-day mortality (1, 29).

One of the strengths of this study is that our meta-analysis strictly followed the PRISMA statement and used a comprehensive search strategy to identify potential studies in all available databases to ensure the generalizability of the results. Meanwhile, we included a relevantly large number of studies in the meta-analysis to extend the conclusion beyond the population contained in previous meta-analyses and systematic reviews. In our meta-analysis, bundle interventions were applied in all 11 studies that were identified as methodologically high-quality studies. Therefore, our findings appear to be largely driven by the findings from high-quality RCTs, allowing us to draw more reliable and valid conclusions. In addition, we avoided publication bias by following comprehensive search strategies that included studies with a large sample size.

Several limitations should be noted in this meta-analysis. First, we included both RCT and cohort studies in the current analysis, and heterogeneity was identified among studies in terms of results on the ICU delirium prevalence and duration, MV days, ICU, or hospital LOS. These could be due to differentiation existed in terms of study designs and inconsistent inclusion and exclusion criteria among studies; these all restricted the power to draw conclusions. However, we rigorously limited the heterogeneity by including only high-quality studies in the analysis and used sensitivity analysis that applied random-effects models and fixed-effects models simultaneously to examine the effect of bundle interventions. In addition, the results of the sensitivity analyses on related outcomes showed no different findings from the pooled effects. Second, the number of studies included in the current analysis reporting outcomes on ICU mortality is small, which may have insufficient power to assess the differences and limited the interpretation of our pooled data. Third, although some studies reported coma-related outcomes, we failed to combine these data for analysis due to different presented data formats. Although authors of the original studies were contacted several times, no responses were obtained. Therefore, this limited the reliability when interpreting this result. Finally, as majority of the studies in this analysis did not include all elements of the bundle approach, the modifiable risk factors identified by the PADIS Guidelines are not fully addressed in the interventions. Therefore, it is limited to draw conclusions on the collective effect of the full bundle approach with current evidence. Further studies are needed to examine the full implementation of the ABCDEF bundle on the prevalence and duration of ICU delirium in the future. Despite these limitations, the results of this meta-analysis are clinically relevant and reliable for the prevention and management of delirium in the ICU settings.

CONCLUSIONS

The current meta-analysis did not support the effects of bundle interventions on decreasing the prevalence and shortening the duration of ICU delirium, although there is clear evidence in supporting that the bundle interventions are effective in reducing the proportion of patient-days with coma, hospital LOS, and 28-day mortality in ICU patients. The modifiable risk factors for ICU delirium were not fully addressed by interventions in the majority of the included studies, which may limit the effectiveness of bundle interventions to be shown on ICU delirium prevalence and duration. Future studies, especially well and rigorously designed RCTs and full implementation of ABCDEF bundle intervention, should be considered to test the effect of bundle interventions on ICU delirium prevalence and duration, as well as other related adverse outcomes.

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1 *Department of Adult Care, School of Nursing, Capital Medical University, Beijing, China.*

2 *Department of Epidemiology and Health Statistics, School of Public Heath, Capital Medical University, Beijing, China.*

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For information regarding this article, E-mail: helenywu@vip.163.com

REFERENCES

1. Klein Klouwenberg PM, Zaal IJ, Spitoni C, et al: The attributable mortality of delirium in critically ill patients: Prospective cohort study. *BMJ* 2014; 349:g6652
2. Ely EW, Shintani A, Truman B, et al: Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004; 291:1753–1762
3. Noriega FJ, Vidán MT, Sánchez E, et al: Incidence and impact of delirium on clinical and functional outcomes in older patients hospitalized for acute cardiac diseases. *Am Heart J* 2015; 170:938–944
4. Pandharipande PP, Girard TD, Jackson JC, et al; BRAIN-ICU Study Investigators: Long-term cognitive impairment after critical illness. *N Engl J Med* 2013; 369:1306–1316
5. Hshieh TT, Yue J, Oh E, et al: Effectiveness of multicomponent nonpharmacological delirium interventions: A meta-analysis. *JAMA Intern Med* 2015; 175:512–520
6. Barr J, Fraser GL, Puntillo K, et al; American College of Critical Care Medicine: Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; 41:263–306
7. Hsieh SJ, Ely EW, Gong MN: Can intensive care unit delirium be prevented and reduced? Lessons learned and future directions. *Ann Am Thorac Soc* 2013; 10:648–656
8. Guo Y, Fan Y: A preoperative, nurse-led intervention program reduces acute postoperative delirium. *J Neurosci Nurs* 2016; 48:229–35
9. Devlin JW, Skrobik Y, Gélinas C, et al: Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018; 46:e825–e873
10. Balas MC, Vasilevskis EE, Olsen KM, et al: Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. *Crit Care Med* 2014; 42:1024–1036
11. Balas MC, Burke WJ, Gannon D, et al: Implementing the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle into everyday care: Opportunities, challenges, and lessons learned for implementing the ICU pain, agitation, and delirium guidelines. *Crit Care Med* 2013; 41:S116–S127
12. Colombo R, Corona A, Praga F, et al: A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study. *Minerva Anestesiol* 2012; 78:1026–1033
13. Rivosecchi RM, Kane-Gill SL, Svec S, et al: The implementation of a nonpharmacologic protocol to prevent intensive care delirium. *J Crit Care* 2016; 31:206–211
14. Foster J, Kelly M: A pilot study to test the feasibility of a nonpharmacologic intervention for the prevention of delirium in the medical intensive care unit. *Clin Nurse Spec* 2013; 27:231–238
15. Brummel NE, Girard TD, Ely EW, et al: Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: The activity and cognitive therapy in ICU (ACT-ICU) trial. *Intensive Care Med* 2014; 40:370–379
16. Olsen HT, Nedergaard HK, Strøm T, et al: Nonsedation or light sedation in critically ill, mechanically ventilated patients. *N Engl J Med* 2020; 382:1103–1111
17. Sosnowski K, Mitchell ML, White H, et al: A feasibility study of a randomised controlled trial to examine the impact of the ABCDE bundle on quality of life in ICU survivors. *Pilot Feasibility Stud* 2018; 4:32
18. Moon KJ, Lee SM: The effects of a tailored intensive care unit delirium prevention protocol: A randomized controlled trial. *Int J Nurs Stud* 2015; 52:1423–1432
19. Trogrlić Z, van der Jagt M, Lingsma H, et al: Improved guideline adherence and reduced brain dysfunction after a multicenter multifaceted implementation of ICU delirium guidelines in 3,930 patients. *Crit Care Med* 2019; 47:419–427
20. Hsieh SJ, Otusanya O, Gershengorn HB, et al: Staged implementation of awakening and breathing, coordination, delirium monitoring and management, and early mobilization bundle improves patient outcomes and reduces hospital costs. *Crit Care Med* 2019; 47:885–893
21. Pun BT, Balas MC, Barnes-Daly MA, et al: Caring for critically ill patients with the ABCDEF bundle: Results of the ICU liberation collaborative in over 15,000 adults. *Crit Care Med* 2019; 47:3–14
22. Liberati A, Altman DG, Tetzlaff J, et al: The PRISMA statement for reporting systematic reviews and meta-analyses of studies

that evaluate healthcare interventions: Explanation and elaboration. *BMJ* 2009; 339:b2700

23. Slomka J, Hoffman-Hogg L, Mion LC, et al: Influence of clinicians' values and perceptions on use of clinical practice guidelines for sedation and neuromuscular blockade in patients receiving mechanical ventilation. *Am J Crit Care* 2000; 9:412–418
24. Reeves BC, Deeks JJ, Higgins JPT, et al: Chapter 24: Including non-randomized studies on intervention effects. *In:* Cochrane Handbook for Systematic Reviews of Interventions Version 6.0. Higgins JPT, Thomas J, Chandler J, et al (Eds). Cochrane, 2019
25. Jadad AR, Moore RA, Carroll D, et al: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996; 17:1–12
26. Wells G, Shea B, O'Connell D, et al: The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses, 2019
27. Higgins J, Altman D, Sterne J, et al: Chapter 8: Assessing risk of bias in included studies. *In:* Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011
28. Mehta S, Burry L, Cook D, et al; SLEAP Investigators; Canadian Critical Care Trials Group: Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: A randomized controlled trial. *JAMA* 2012; 308:1985–1992
29. Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): A randomised controlled trial. *Lancet* 2008; 371:126–134
30. Schweickert WD, Pohlman MC, Pohlman AS, et al: Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. *Lancet* 2009; 373:1874–1882
31. Mansouri P, Javadpour S, Zand F, et al: Implementation of a protocol for integrated management of pain, agitation, and delirium can improve clinical outcomes in the intensive care unit: A randomized clinical trial. *J Crit Care* 2013; 28:918–922
32. Barnes-Daly MA, Phillips G, Ely EW: Improving hospital survival and reducing brain dysfunction at Seven California Community Hospitals: Implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. *Crit Care Med* 2017; 45:171–178
33. Mehta S, Cook D, Devlin JW, et al; SLEAP Investigators; Canadian Critical Care Trials Group: Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med* 2015; 43:557–566
34. Trogrlić Z, van der Jagt M, Bakker J, et al: A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. *Crit Care* 2015; 19:157
35. Boehm LM, Dietrich MS, Vasilevskis EE, et al: Perceptions of workload burden and adherence to ABCDE bundle among intensive care providers. *Am J Crit Care* 2017; 26:e38–e47
36. Mitchell S, Bradley VA, Welch JL, et al: Coma arousal procedure: A therapeutic intervention in the treatment of head injury. *Brain Inj* 1990; 4:273–279
37. Sosnowski C, Ustik M: Early intervention: Coma stimulation in the intensive care unit. *J Neurosci Nurs* 1994; 26:336–341
38. Claassen J: Coma science: Intensive care as the new frontier. *Intensive Care Med* 2020; 46:97–101
39. Mart MF, Brummel NE, Ely EW: The ABCDEF bundle for the respiratory therapist. *Respir Care* 2019; 64:1561–1573
40. Bartolo M, Bargellesi S, Castioni CA, et al; Intensive Care and Neurorehabilitation Italian Study Group: Mobilization in early rehabilitation in intensive care unit patients with severe acquired brain injury: An observational study. *J Rehabil Med* 2017; 49:715–722