

SYSTEMATIC REVIEW



Intensive care unit length of stay is reduced by protocolized family support intervention: a systematic review and meta-analysis

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Abstract

Purpose: This study aimed to elucidate the impact of protocolized family support intervention on length of stay (LOS) in the intensive care unit (ICU) through a systematic review and meta-analysis.

Methods: Medline, EMBASE, the Cochrane Central Register of Controlled Trials, and other web-based databases were referenced since inception until November 26, 2018. We included randomized-controlled trials wherein protocolized family support interventions were conducted for enhanced communication and shared medical decision-making. LOS (in days) and mortality were evaluated using a random-effects model, and adjusted LOS was estimated using a mixed-effects model.

Results: We included seven randomized-controlled trials with 3477 patients. Protocolized family support interventions were found to significantly reduce the ICU LOS {mean difference = -0.89 [95% confidence interval (CI) = -1.50 to -0.27]} and hospital LOS [mean difference = -3.78 (95% CI = -5.26 to -2.29)]; the results of the mixed-effect model showed that they significantly reduced ICU LOS after adjusting for the therapeutic goal [mean difference = -1.30 (95% CI = -2.35 to -0.26)], methods of measurement [mean difference = -0.89 (95% CI = -1.55 to -0.22)], and timing of intervention [mean difference = -1.05 (95% CI = -2.05 to -0.05)]. Similar results were found after adjusting for patients' disease severity [mean difference = -1.21 (95% CI = -2.03 to -0.39)] and the trim-and-fill method [mean difference = -0.86 (95% CI = -1.44 to -0.28)]. There was no difference in mortality rate in ICU and hospital between the protocolized intervention and control groups.

Conclusions: Protocolized family support intervention for enhanced communication and shared decision-making with the family reduced ICU LOS in critically ill patients without impacting mortality.

Keywords: Intensive care units, Critical care, Professional-family relations, Decision-making, Decision support techniques

Introduction

Various types of family support interventions for critically ill patients and their surrogates have been studied to reduce the psychological problems [1–3] stemming chiefly from inadequate communication [4–6]. Although the details of each type of intervention differed across each study, these interventions commonly focused on facilitating effective communication between family and medical staff. For effective communication with family members, major professional guidelines have emphasized the concept of “family-centered care” in an intensive

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care unit (ICU) and advocated a shared decision-making approach [7, 8].

ICU length of stay (LOS) is a representative ICU index and has been shown to be a responsive measure for communication interventions in the ICU [9–11]. The previous studies have shown that patients with lengthy ICU admissions were associated with high caregiver burdens [12–14]. Moreover, the capacity strained by unnecessarily prolonged ICU LOS can be perceived as a strong barrier to patient- and family-centered care that disrupts routine opportunities for clinicians to communicate with family members [15, 16]. A lack of quality communication in the ICU often leads to confusion among the family members, which is associated with unrealistic expectations and unnecessarily prolonged ICU stays [17]. On the other hand, effective communication through well-organized protocol-based family meetings enables the caregivers to understand which intervention is being implemented, overcome the fear arising from lack of information, and cooperate with clinicians to make shared decisions [18–20].

However, the effect of protocolized family support intervention on ICU LOS has not been estimated in the previous systematic reviews (SRs) and meta-analyses. Only a few clinical trials and systematic reviews have been found to evaluate ICU LOS as the primary outcome [21, 22]. Our study focused more explicitly on protocolized interventions and includes recent research [23–26]. We hypothesized that family support intervention with well-established protocols can lead to reduced ICU LOS by promoting effective communication between family members and medical staff, and helping them reach an agreement on good, timely decisions that are in the best interests of the ICU patients.

Methods

Protocol and registration

The present study complied with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [27]. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42018117506).

Eligibility criteria

Studies that met the following inclusion criteria were considered eligible: (1) one or more family members, including surrogates and relatives, of a critically ill adult were included, (2) the critically ill patient was at a high risk of mortality, extended ventilation, or prolonged hospitalization owing to medical complications in the ICU; this criterion excluded the patients who were simply

Take-home message

Our meta-analysis found that protocolized family support intervention for enhanced communication and shared decision-making reduced ICU LOS without affecting mortality, even after adjusting for disease severity. The benefits of protocolized family support intervention were more evident in sensitivity analyses with comfort care settings, post-intervention LOS, and proactive intervention.

admitted to ICU for close observation after surgery, (3) the intervention was meant to help the patient's family and medical staff engage in shared decision-making, (4) family support intervention was performed based on the pre-established protocol, (5) an ICU LOS or hospital LOS was clearly reported, and (6) the study design was a parallel-group randomized-controlled trial (RCT). Studies based on families of pediatric patients and those in which the compliance with the intervention was too low to be evaluated were not included. Family was broadly defined as individuals whom the patients wanted involved in their care, regardless of biological or legal relations [28].

Information sources and search strategy

Medline, EMBASE, and the Cochrane Central Register of Controlled Trials were referenced for potentially eligible published or unpublished clinical studies (Search date: November 26, 2018). The Peer Review of Electronic Search Strategies checklist was used to design the search strategy [29]. Additional data sources included the United States National Library of Medicine (www.clinicaltrials.gov), the European Union Clinical Trials Register (<https://www.clinicaltrialsregister.eu>), and conference abstracts from the international congress of the American Thoracic Society, British Thoracic Society, and European Respiratory Society. Our search strategy was complemented by manual searches for references cited in recent articles, SRs, and meta-analyses. No restrictions were applied on study period, ethnicity, or language. The detailed search strategy is described in Supplementary appendix 1.

Study selection

We selected pertinent studies based on the PRISMA flow diagram [30]. After removing duplicate studies, two independent reviewers (HWL and YKP) undertook a calibration exercise with a sample of 200 randomly selected studies and achieved over 95% agreement. All potentially eligible studies were individually screened by the reviewers for conducting a full-text review to assess whether they met the eligibility criteria. Any conflicts or disagreements regarding eligibility were resolved by referring to the original articles and discussing them with a third reviewer (YJL).

Data extraction and quality assessment

A standardized format was prepared [31]. HWL and YKP extracted data on study characteristics (first author, published year, and study design), baseline features of the patients and their families (number of participants, age, sex, ethnicity, and relationship), the patient's therapeutic goal (comfort care or curative care), types of family support interventions (providing medical information or emotional support), the timing of intervention (a proactive intervention beginning since ≤ 72 h of ICU admission or randomization), and the range of medical staff involved. Two continuous variables (ICU LOS and hospital LOS) and two dichotomous variables (number of deceased patients in ICU and hospital) were used as clinical outcomes. Data on ICU LOS were collected using two different methods of measurement: post-intervention LOS versus LOS at baseline. We extracted unadjusted and adjusted LOS data in all studies, if they were available.

The risk of bias (ROB) of eligible studies was assessed using the Cochrane Collaboration's tool for assessing ROB for RCTs [32]. However, the results of the ROB assessment were not used to exclude any individual study from our analysis.

Outcomes

The primary outcome was ICU LOS in the intervention and control groups. Secondary outcomes included hospital LOS and the all-cause mortality rate in the ICU and hospital.

Data synthesis and analysis

Primary and secondary outcomes were analyzed using a random-effects model, because heterogeneity regarding study protocol and participants was detected in all the included studies. A fixed-effects model was only used as a sensitivity analysis to check if similar results were yielded. LOS was presented as mean difference with 95% confidence interval (CI) and mortality was presented as odds ratio (OR) with 95% CI, in terms of summary statistics. If the mean and standard deviation (SD) were not given, other values including the median and range, the median and interquartile range (IQR) [33], and the mean and p value (Chapter 7.3.3) [31] were converted to mean and SD to obtain mean difference. Heterogeneity was statistically evaluated with I^2 statistics and Cochran's Q test.

Subgroup analyses of ICU LOS were conducted to determine how effect size and heterogeneity changed according to the pre-defined variables (therapeutic goal, method of measuring LOS, and timing of intervention) using a random-effects model. Considering the influence of these pre-defined variables on ICU LOS, a

meta-regression analysis was conducted using a mixed-effect model. We also adjusted ICU LOS and hospital LOS by predicted probability of mortality estimated by disease severity with a mixed-effect model. Publication bias was qualitatively assessed by funnel plot asymmetry and quantitatively analyzed by Egger's and Begg's test (Chapter 10.4.3.1) [31]. Funnel plot asymmetry was analyzed: if asymmetry was detected in the funnel plot, the trim-and-fill method was used to calculate a corrected OR by estimating the number of missing studies [34].

Effect size estimates with two-tailed significance of $P < 0.05$ were regarded statistically significant. All the analyses were performed using Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) and R version 3.4.0 statistical computing software (R Foundation for Statistical Computing, Vienna, Austria) with the metafor package [35].

Results

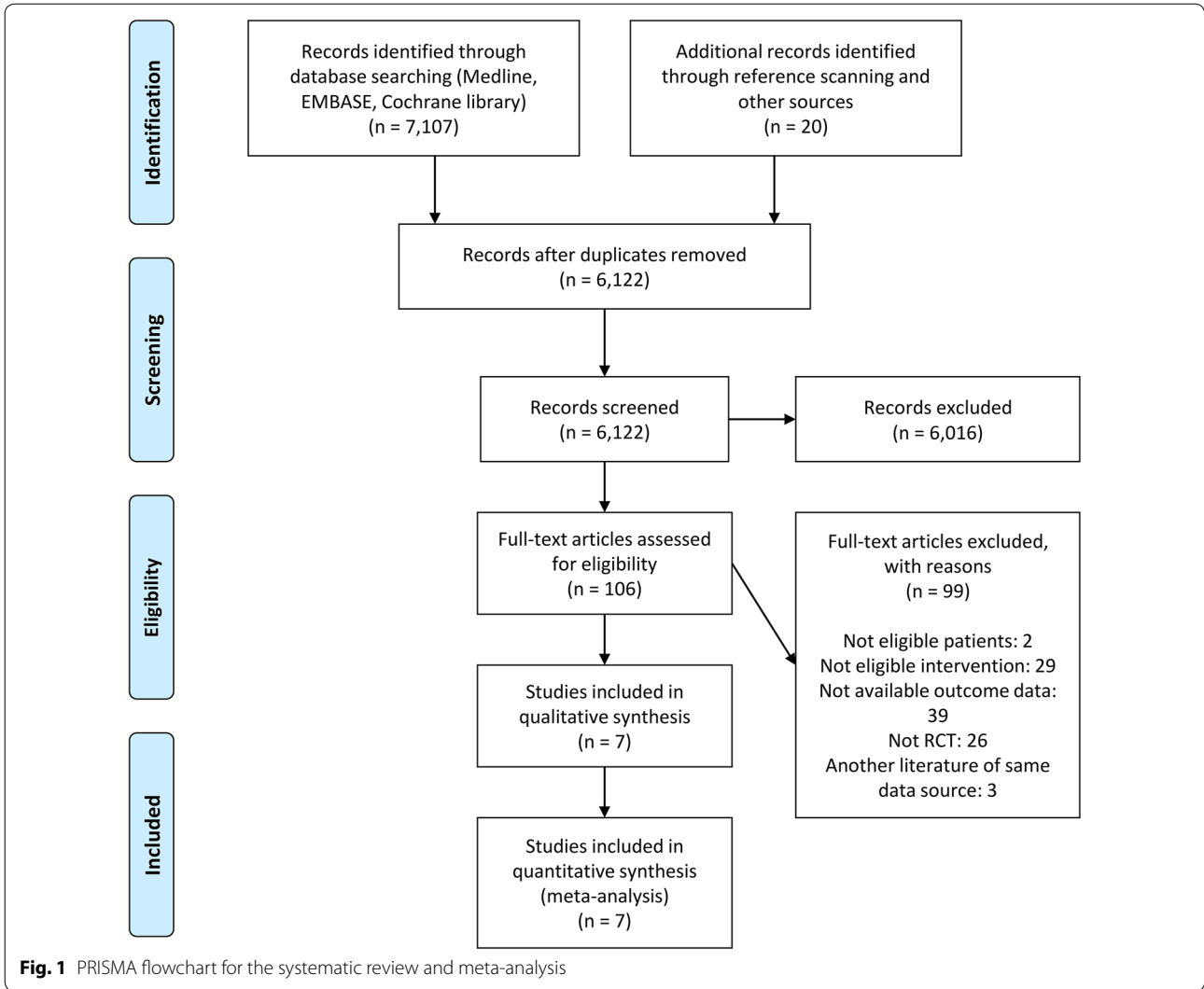
Study selection

A total of 6122 studies were identified after removal of duplicates, and 106 potentially relevant articles were retrieved for full-text review (Fig. 1). The final 7 RCTs selected met the eligibility criteria and included 3477 patients [18, 21, 23–26, 36]. The reasons for excluding the other 99 articles are summarized in Supplementary appendix 2. ICU LOS and hospital LOS were reported in seven and four RCTs, respectively. Inter-observer reliability for study selection was high ($\kappa = 0.92$), which was assessed with a sample of 300 randomly selected studies.

Characteristics of the included studies and participants

The characteristics are summarized in Table 1. Medical information was provided to the patients' family members in seven RCTs, while emotional support was provided in five. Protocolized family support interventions were implemented with clinicians in five, nurses in six, and other facilitators in four RCTs. These interventions were conducted in several countries: five in the United States and two in France. Although eligibility criteria in each study were heterogeneous, the included patients can be summarized into five categories: deceased patients (one RCT), patients at a high risk of mortality (four RCTs), patients with prolonged mechanical ventilation (one RCT), patients at a high risk of mechanical ventilation (one RCT), and patients at a high risk of prolonged hospitalization (one RCT).

The characteristics of the included patients are described in Table 1. Mean age was about 66.2 years and about 53.7% of them were male. In about 69.4% of cases, women made medical decisions as a surrogate



for families. Among family members, spouses had the largest share (40.2%) in terms of decision-making, followed by children (32%), parents (9.4%), and siblings (11.4%). The disease severity was reported in five studies. Mean in-hospital mortality was 62.4%.

Risk-of-bias assessment within studies

The quality of eligible studies is described in Supplementary appendix 3. All seven RCTs had low ROB in random sequence generation. Specific methodology for allocation concealment was described in four RCTs. One RCT blinded medical personnel. Although description about blinding of outcome assessment was not found in any RCT, our primary and secondary outcomes were not likely to be influenced by lack of blinding, because these outcomes were objective findings. Low risk of attrition bias and reporting bias was found in six RCTs. No additional sources of bias were found in any of the RCTs.

Intensive care unit length of stay

For 3,477 patients in seven RCTs, the estimated mean difference of ICU LOS was -0.89 days (95% CI -1.50 to -0.27) determined in a meta-analysis using a random-effects model (Fig. 2). A fixed-effects model yielded the same results. Significant heterogeneity was not detected by either model ($I^2=0\%$, $P=0.62$).

In a subgroup analysis by therapeutic goal, the benefit of protocolized family support intervention was only evident in comfort care settings [estimated mean difference = -1.26 (95% CI -2.21 to -0.31), $P=0.009$] (Supplementary appendix 4). The pooled effect of protocolized family support intervention was differently estimated according to method of measurement; only post-intervention LOS showed significant results [estimated mean difference = -0.89 (95% CI -1.55 to -0.22), $P=0.009$] (Supplementary appendix 5). Results of a subgroup analysis by timing of intervention

Table 1 Characteristics of the seven included RCTs

Study (year)	Summarized characteristics of included patients					Summarized description of interventions for family meetings with pre-established protocols			Type of intervention	Medical staff involvement	Country
Schneiderman et al. [21] (2003)	Patients at high risk of mortality					A general process model of ethics consultation			I, E	C, N	US
Lautrette et al. [18] (2007)	Patients at high risk of mortality					A proactive communication strategy that consists of end-of-life family conferences according to guidelines			I, E	C, N, F	France
Curtis et al. [36] (2011)	Patients who died in the ICU or within 24 h of ICU discharge					Changes in clinicians by increasing knowledge, enhancing attitudes, and modeling appropriate behaviors			I	C, N	US
Carson et al. [25] (2016)	Prolonged MV in ICU					Meetings where families receive informational and emotional support from palliative care specialists			I, E	C, N, F	US
Curtis et al. [24] (2016)	Patients at high risk of mortality					A facilitator to increase families' and clinicians' self-efficacy expectations about communication			I, E	F	US
Garrouste-Orgeas et al. [26] (2016)	Patients at high risk of prolonged MV					Proactive nurse participation in ICU family conferences			I	N	France
White et al. [23] (2018)	Patients at high risk of mortality or prolonged hospitalization					Family support intervention delivered by an inter-professional ICU team providing emotional support to families and ensuring frequent clinician-family communication			I, E	C, N, F	US

Number of patients	Age of patients, mean	Male in patients, %	Age of family members, mean	Male in family members, %	Relationship with patients, % (Spouse)	Relationship with patients, % (Child)	Relationship with patients, % (Parent)	Relationship with patients, % (Sibling)	Disease severity, mean	In-hospital mortality, %
329 ^a	67.5	53.6	NR	NR	NR	NR	NR	NR	NR	100 ^a
126	68.4	55.5	54	26.6	38.9	48.2	6.9	NR	SAPS II: 61.5 ^b	NR
1079	71.1	56.2	59	30.6	44	NR	NR	NR	NR	100 ^c
256	57.5	48.5	51	29	28.5	22.5	9.6	7.1	APACHE II: 26.0	39.1
168	53.7	64.3	51	29.5	29.1	27.2	19.4	11.6	SOFA: 9.9	29.2
99	68.9	57.6	58.4	37.3	33.7	37.2	12.8	NR	SAPS II: 56.0	NR
1420	64.9	51.1	56.7	30.9	41.2	32.5	8.2	12.1	Modified SAPS III: 50.0	33.2

APACHE acute physiology and chronic health evaluation, C clinician, E providing emotional support, F facilitator other than clinician and nurse at bedside, I providing medical information, ICU intensive care unit, MV mechanical ventilation, N nurse at bedside, NR not reported, RCT randomized-controlled trial, SAPS simplified acute physiology score, SOFA sequential organ failure assessment, US United States

^a Data on LOS were only available in dead patients. In-hospital mortality rate in ITT patients was 60.3%

^b Mean was estimated with median and interquartile range using a formula of Wan et al. [33]

^c Eligible patients were those who died in an ICU or within 30 h of transfer to another hospital location

showed that only proactive (≤ 72 h) intervention had a significant effect on reducing LOS [estimated mean difference = -1.07 (95% CI -2.12 to -0.02), $P=0.05$] (Supplementary appendix 6). Significant heterogeneity was not found in these subgroups.

In a sensitivity analysis adjusted by pre-defined variables using a mixed-effects model, protocolized family support intervention significantly decreased ICU LOS after adjustment by therapeutic goal [comfort care, estimated mean difference = -1.30 (95% CI -2.35

to -0.26), $P=0.01$], method of measurement of LOS [post-intervention, estimated mean difference = -0.89 (95% CI -1.55 to -0.22), $P=0.01$], and the timing of intervention [proactive intervention, estimated mean difference = -1.05 (95% CI -2.05 to -0.05), $P=0.04$]. After adjusting for disease severity (predicted probability of mortality), a significantly reduced ICU LOS was found in the group with protocolized intervention [adjusted mean difference = -1.21 (95% CI -2.03 to -0.39), $P=0.004$].

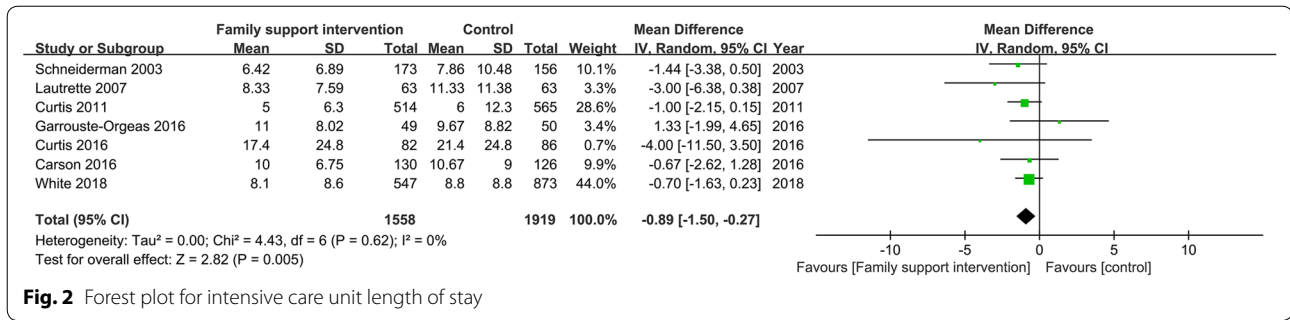


Fig. 2 Forest plot for intensive care unit length of stay

Adjusted LOS could be extracted only in one study [23]. In the sensitivity analysis including adjusted LOS instead of unadjusted LOS, similar results were obtained [estimated mean difference = -0.79 (95% CI -1.23 to -0.36), $P < 0.001$].

Hospital length of stay

For 1,562 patients in four RCTs, the estimated mean difference of hospital LOS was -3.78 days (95% CI -5.26 to -2.29) in a meta-analysis using a random-effects model (Fig. 3). A fixed-effects model yielded similar results [estimated mean difference = -3.88 (95% CI -5.84 to -1.91), $P < 0.001$]. Small heterogeneity was detected in both models ($I^2 = 31%$, $P = 0.23$). After adjusting for the predicted probability of mortality, a significantly reduced hospital LOS was found in the group with protocolized intervention [adjusted mean difference = -5.24 (95% CI -9.79 to -0.70), $P = 0.02$].

Adjusted LOS was found only in one study [23]. In the sensitivity analysis including adjusted LOS instead of unadjusted LOS, results were also significant [estimated mean difference = -3.54 (95% CI -5.36 to -1.72), $P < 0.001$].

Mortality in ICU and hospital

In two RCTs, the observed mortality rate in ICU was not significantly different between the intervention group and the control group [estimated OR = 0.76 (95% CI 0.45 – 1.29)] (Supplementary appendix 7). In four RCTs, the observed mortality rate in hospital also was not

significantly different between the two groups [estimated OR = 1.13 (95% CI 0.85 – 1.49)] (Supplementary appendix 8). Significant heterogeneity was not detected in both meta-analyses.

Publication bias

The results of funnel plots supported by Egger's and Begg's tests indicate no publication bias for ICU LOS and hospital LOS (Fig. 4). The adjusted mean difference for ICU LOS by the trim-and-fill method showed similar results [estimated mean difference = -0.86 (95% CI -1.44 to -0.28), $P = 0.004$]. No adjustment for publication bias was needed for the analysis of hospital LOS.

Discussion

Our SR and meta-analysis focused on the effect of protocolized family support interventions on reducing ICU LOS and hospital LOS in critically ill patients. We found that such interventions significantly decreased ICU LOS by a mean of about 1 day and hospital LOS by that of about 4 days. Subgroup and sensitivity analyses showed that these interventions were beneficial in comfort care settings, post-intervention LOS, and proactive intervention. Even after adjusting for patients' disease severity and the trim-and-fill method, the effect was similar. There was no significant difference in mortality rate between the intervention and control groups. Protocolized family support interventions may decrease ICU LOS by reducing the potentially inappropriate life-sustaining treatments for patients requiring comfort care, while not

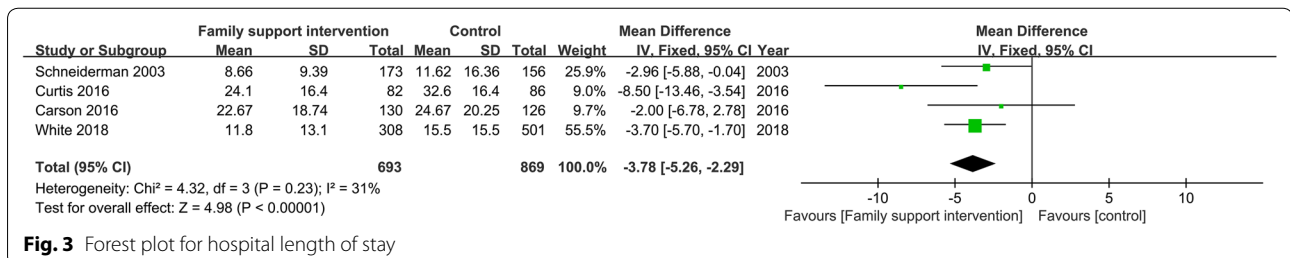


Fig. 3 Forest plot for hospital length of stay

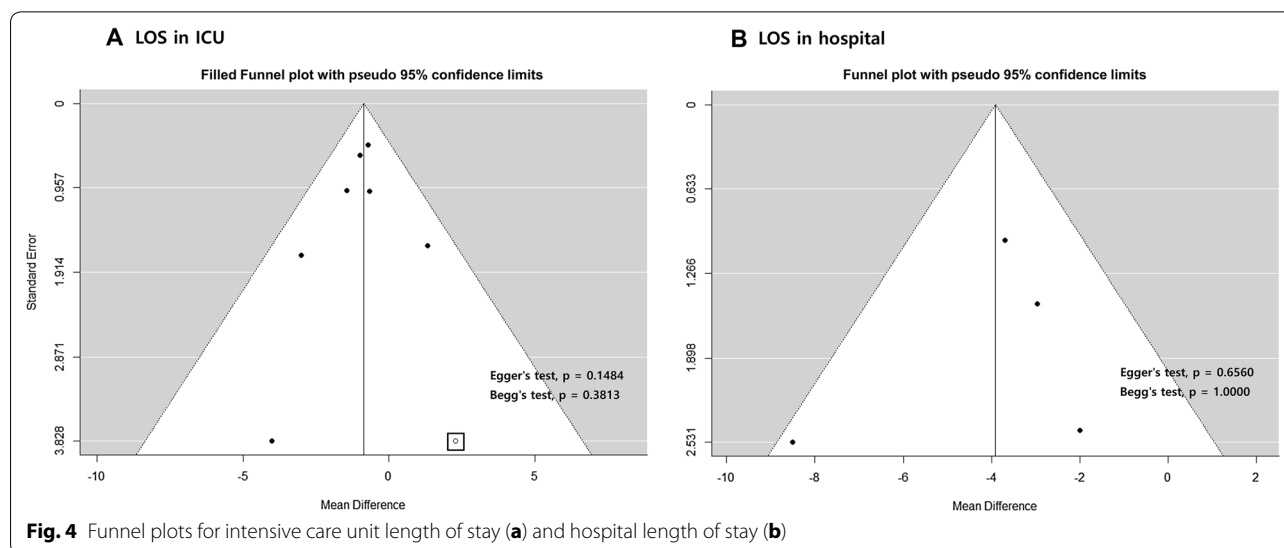
increasing mortality by hindering the discontinuance of lifesaving treatments for patients who could survive.

One of the most reasonable and efficient goals of ICU care is decreasing ICU LOS [17], when medically appropriate, as well as to improve the quality of care, reduce medical cost [37], and efficiently use limited ICU resources [38]. However, in most previous RCTs about the effect of family support intervention, the primary measured outcome was the family members' psychological symptoms (post-traumatic stress disorder, depression, and anxiety) [18, 23–26] or satisfaction with ICU care [36]. In one SR, LOS was qualitatively evaluated in individual-level studies, and a pooled effect of family support intervention was not estimated [1]. Another meta-analysis similarly showed that family-centered care intervention may decrease ICU LOS by about one day [2]. The previous SRs reported descriptive information about LOS reductions by palliative ICU care in several studies [3, 39]. Our study, on the other hand, focused on pre-established protocol-based family support interventions using rigorous inclusion criteria to include high-quality RCTs. In addition, the sensitivity analysis of the present study elucidates specific medical settings in which a more obvious effect of protocolized family support intervention is derived.

Among the various types of family support interventions [1–3, 39], there are reasons to analyze interventions for well-organized protocol-based interventions in our study. To achieve efficient communication between family members and medical staff and make appropriate timely decisions, there should be well-organized protocols containing detailed key components as follows: establishing a trusting partnership with empathetic attitudes and emotional support, assessing patient's or

family's situation and preference, reviewing prognosis and treatment options, being realistic and empathetic, and frequently asking family members if they have any questions about the current status, medical decisions, and prognosis [7, 18, 40]. Based on pre-established protocols with these items, medical staff can prepare family meetings without inadvertently missing out on important information points or key questions and maintain an appropriate and consistent quality of interventions. In fact, some RCTs showed that protocolized family support intervention was associated with lower psychological symptoms in family members [18, 24] and higher family ratings of quality of communication and patient-centeredness of care [23]. On the other hand, interventions that merely involve sharing educational materials or leaflets without any direct communication or conducting family meetings without a unified protocol are likely to be ineffective, and shared decision-making may be unsatisfactory.

In our study, protocolized family support interventions were found to significantly reduce ICU LOS especially in comfort care settings. The mean difference of LOS can be an indicator for withdrawal of futile life support through effective shared decision-making [41]. Family members of ICU patients with impaired consciousness often find themselves in distress while making important decisions, because these decisions include complicated and potentially distressing issues, such as the dilemma between their duty to preserve the patient's life and the patient's right to a dignified death [42]. Effective and high-quality communication between family members and medical staff could help family members to make timely appropriate decisions related to this issue [43], and earlier withdrawal of potentially inappropriate life support is



associated with reduced length of stay and increased family member satisfaction in ICU [23, 44]. Therefore, our study suggests setting up treatment goals for care in a timely manner through well-organized family meetings, especially in the setting of comfort care, which could prevent inappropriate use of potentially futile treatments [1] and improve patient- and family-centered outcomes.

There have been conflicting results about the benefit of proactive communication with family members in the ICU. The previous studies reported that the early integration of family communication was associated with a higher quality of death as rated by family members [45] and reduced ICU LOS [11, 46]. On the other hand, Garroute-Orgeas's study showed that LOS did not reduce after the proactive participation of a nurse in family conferences [26]. In that study, a nurse facilitated mutual understanding between medical staff and family members, but played a limited role in family conferences. In our study, sensitivity analysis by timing of intervention showed that reduction in ICU LOS was only found in proactive intervention, which supports the American College of Critical Care Medicine guideline that recommends holding a family meeting with a multi-professional ICU team within 24–48 h of ICU admission [7]. Proactive intervention with empathetic attitudes would help clinicians develop an intimate relationship with the families earlier, leading to an early consensus to avoid delayed decisions of essential treatment and potentially futile treatments in a timely manner.

Methodological variabilities were found in each protocol of trials. The first is the frequency of family interventions. Additional family meetings could be held according to the patient's request or medical need without prescribed rules. The number of family meetings was not fully reported in all included RCTs. It was unclear whether there was a difference in the actual number of meetings for each protocol or how such a difference would affect the results. The second is the purpose of the communication with family. While there were studies in which protocols were written to focus on emotional support [23, 25], other studies focused on providing medical information to family members [26, 36]. However, providing emotional support and medical information cannot be performed separately, and in most cases, the two would be conducted together. The third is the degree of medical staff's involvement. Clinicians usually play a major role in family conferences to make shared decisions. However, two studies were centered on the role of nurse or facilitator [24, 26]. Considering that the nurse and facilitator could help the family conference proceed smoothly and effectively, most medical staff needs to be involved in efforts for better communication with patient's family.

This study has its limitations. First, although rigorous eligibility criteria were applied in our systematic review and meta-analysis, the characteristics of protocolized family support interventions were varied in detailed implementations. Some studies seemed to have different objectives for family support intervention. For example, Schneiderman et al.'s study [21] involved a trial of ethical consultation and Curtis et al.'s [36] involved a trial of quality improvement of communication. Despite this major concern about heterogeneity, the reason for pooling these studies was to determine if using pre-established protocols can be an important factor for successful family support intervention. In fact, all the included studies were under a common umbrella in that family support interventions were conducted according to pre-established protocol. Second, we did not control for all the variables that affect LOS reduction in ICU or hospital. However, it is unlikely that other variables had a significant impact on LOS when considering the effective randomization in individual RCTs. After adjusting for predicted probability of mortality, we still obtained significant reduction in ICU LOS or hospital LOS. Third, unblinded medical staff might affect the discharge decision. Owing to the nature of intervention, performance bias is likely. Only Carson et al. [25] described about blinding of study staff to group assignment.

In conclusion, ICU LOS significantly reduced without impacting mortality after implementation of protocolized family support intervention for shared decision-making. The benefits of the intervention were more evident when conducted proactively or in the context of comfort care or high risk of death.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-019-05681-3>) contains supplementary material, which is available to authorized users.

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Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

Study concept and design: HWL and YJL. Data acquisition: HWL and YKP. Data analysis and interpretation: HWL and EJJ. Drafting of the manuscript: HWL. Critical revision of the manuscript and important intellectual content: HWL and YJL. Study supervision: YJL.

Funding

The authors declare that they have taken no support from any organization for the submitted work. The authors also have no conflicts of interest to declare.

Availability of data and material

The data sets used and/or analyzed can be obtained from the corresponding author on reasonable request.

Compliance with ethical standards

Conflicts of interest

The authors have no conflicts of interest to declare.

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Received: 5 March 2019 Accepted: 26 June 2019

Published online: 3 July 2019

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