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Original Contribution

Efficacy and safety of erythropoietin in patients with traumatic brain injury: A systematic review and meta-analysis

Juncheol Lee, MD [a,e,1], Youngsuk Cho, MD [b,e,1], Kyu-Sun Choi, MD [c,*], Wonhee Kim, MD [b], Bo-Hyoung Jang, PhD [d], Hyungoo Shin, MD [a,e], Chiwon Ahn, MD [f], Tae Ho Lim, PhD [a], Hyeong-Joong Yi, PhD [c]

[a] Department of Emergency Medicine, College of Medicine, Hanyang University, Seoul, Republic of Korea
[b] Department of Emergency Medicine, College of Medicine, Hallym University, Seoul, Republic of Korea
[c] Department of Neurosurgery, College of Medicine, Hanyang University, Seoul, Republic of Korea
[d] Department of Preventive Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
[e] Graduate School, College of Medicine, Hanyang University, Seoul, Republic of Korea
[f] Department of Emergency Medicine, Armed Forces Yangju Hospital, Yangju, Republic of Korea

A R T I C L E   I N F O

A B S T R A C T

Objective: The purpose of this study was to evaluate the effects of erythropoietin (EPO) on mortality and neurological outcomes in patients with traumatic brain injury (TBI).
Materials and methods: Electronic databases of studies published up to January 5, 2017 were searched to retrieve relevant investigations comparing the outcomes of EPO-treated patients and untreated patients following TBI. We calculated the relative risk (RR) of mortality, neurologic outcomes, and deep vein thrombosis (DVT) with corresponding 95% confidence interval (CI) using meta-analysis.
Results: Six randomized controlled clinical trials met the eligibility criteria. In total, 1041 patients were included among the studies. EPO was found to significantly reduce the occurrence of mortality (RR 0.68 [95% CI 0.50–0.95]; $P = 0.02$), but did not significantly reduce poor functional outcome (RR 1.22 [95% CI 0.82–1.81]; $P = 0.33$). There were no significant differences in the occurrence of complications, such as DVT, between the treatment groups (RR −0.02 [95% CI −0.06–0.02]; $P = 0.81$).
Conclusions: Results of the present meta-analysis suggest that the use of EPO may prevent death following TBI without causing adverse events, such as deep vein thrombosis. However, the role of EPO in improving neurological outcome(s) remains unclear. Further well-designed, randomized controlled trials using modified protocols and involving specific patient populations are required to clarify this issue, and to verify the findings.

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1. Introduction

Traumatic brain injury (TBI) is a major cause of mortality and disability worldwide [1,2], and many researchers are dedicated to finding surgical and pharmacological interventions to address this issue. Many studies have focused on promoting neuroprotective mechanisms in primary TBI because brain edema, intracranial bleeding, elevated intracranial pressure, and ischemia lead to secondary TBI and, consequently, major mortality and morbidity [3,4].

Erythropoietin (EPO), a 165 amino-acid glycoprotein with a molecular weight of 34,000 Da, is produced by the kidneys in response to

hypoxic stimulation and regulates hematopoiesis in the bone marrow [5-7]. EPO is generally effective in treating anemia and is relatively more effective in treating end-stage renal disease or hematological diseases [8]. EPO also functions as a glycoprotein hormone with pleiotropic cytokine-like neurocytoprotective effects [9], with anti-inflammatory, anti-apoptotic, and vascular actions [10,11]. Based on encouraging preliminary outcomes, several randomized controlled trials (RCTs) and prospective studies have assessed the application of EPO to treat diseases associated with neuroinflammation, apoptosis, and vascular disorders.

The use of EPO to treat TBI, however, has yielded conflicting results in the literature. For example, several studies have reported no significant differences in neurological outcomes between EPO-infused and untreated groups [12-14]. In contrast, others have reported that EPO is effective in reducing mortality and improving neurological outcome [15-18]. To resolve some of these discrepancies, one group performed a meta-analysis examining EPO treatment for TBI and revealed that the glycoprotein lowered mortality and shortened hospital stays

(without incidence of deep vein thrombosis [DVT]), but was not statistically effective in improving favorable neurological outcome [19]. However, several studies have recently reported that treatment with EPO is associated with improved functional recovery in patients who sustained severe TBI [16,18].

Therefore, the aim of the present study was to re-analyze the results of previous and newly published RCTs, and to perform a systematic review to evaluate the efficacy of EPO in the treatment of TBI.

2. Materials and methods

The present systematic review and meta-analysis of RCTs adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. The research question was based on the PICO (population, intervention, comparison, and outcome) framework. Accordingly, literature searches and critical assessments were performed, eligible studies were summarized, and outcomes were evaluated in the meta-analysis. The PICO question was as follows: "In adult patients with traumatic brain injuries (P), does the administration of EPO (I) reduce mortality and improve neurological outcome (O) when compared with the untreated group (C)?"

2.1. Search strategy

Three English literature databases—Ovid-Medline, Ovid-EMBASE, and The Cochrane Library—were searched for studies published up to January 5, 2017. To ensure high sensitivity, search strategies were designed to include pertinent MeSH and common keywords, and a comprehensive combination thereof. Details of the search strategy are described in Supplementary File 1. There were no language restrictions, and no filters were applied during the search. After removing duplicates, 2002 articles were imported for initial screening based on title and abstract.

2.2. Study selection

According to pre-determined selection criteria, two reviewers (K.-S.C. and J.L.) independently screened titles and abstracts to exclude irrelevant studies; a full-text review was subsequently performed for potentially relevant articles. Prospective-controlled studies, including RCTs published in English, were included if they met the following inclusion criteria: studies involving only patients with acute TBI; comparative investigations involving EPO- and untreated patients with TBI; and studies that reported outcomes measures—including functional outcome, thromboembolic complications (e.g., DVT), or both—with mortality.

2.3. Data extraction

Characteristics and results of the selected investigations were extracted by two independent reviewers (K.-S.C. and Y.C.) using a standardized data collection form. Any disagreement unresolved by discussion was reviewed by the other co-authors of the present article (T.L. and W.K.). The following study variables were extracted: first author; year of publication; country; study design; characteristics of the study population; EPO treatment protocol (type of EPO, dosage used, and duration of use); and definitions of favorable functional outcome, mortality, and potential side effects. The initial clinical assessment, as reflected by the Glasgow Coma Scale score, was also recorded.

Outcomes of interest included mortality, favorable functional outcome, and occurrence of DVT during follow-up periods. Favorable functional outcome was evaluated using the modified Rankin Scale or Glasgow Outcome Scale (GOS) scores. The occurrence of DVT was assessed according to the approaches used in the individual studies. If any of the above variables were not specified in the included studies,

the corresponding author of the respective study was contacted by e-mail and additional data were requested.

2.4. Quality assessment

Quality assessment was independently performed using the risk of bias tool developed by the Cochrane group. Evaluated biases included selection, performance, detection, attrition, and reporting [20]. The methodological quality of the identified studies was assessed independently by two of the authors (K.-S.C. and Y.C.). Phrases/terms, including "low risk of bias," "high risk of bias," or "unclear," were used to define each study. Any unresolved disagreements between the reviewers were resolved through discussion or review by the third author. Publication bias, however, was not assessable in these trials. Generally, tests for funnel plot asymmetry are only performed when at least 10 studies are included in a meta-analysis. Because analyses in the present study included only six RCTs, tests for asymmetry would have been be ineffective because they would be unable to differentiate chance from asymmetry. The Cochrane Collaboration format was not used to assess the risk for bias in the observational study included; therefore, only a qualitative description, in this instance, was possible.

2.5. Statistical analysis

In the primary analysis, the association between EPO use and mortality/favorable functional outcome/DVT after TBI was investigated. For dichotomous variables, a pooled risk ratio (RR) with 95% confidence interval (CI) was calculated using a fixed-effects model in the absence of significant heterogeneity [21].

To assess heterogeneity, the proportion of between-study inconsistency was estimated using the I^2 statistic, in which 25%, 50%, and 75% were considered to be low, moderate, and high, respectively [22]. In addition, a chi-squared test, with statistical significance set at $P < 0.10$, was used. In cases of substantial heterogeneity, studies were pooled and a random-effects model was used. A sensitivity analysis was performed by the sequential removal of individual studies, and subsequently determining an overall pooled approximation for the remaining studies.

All meta-analyses were performed using Review Manager, version 5.3 (RevMan, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014); $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Study and patient characteristics

A total of 1928 articles were identified using the pre-specified search strategy. After removing 608 duplicates, a total of 1320 studies remained. Based on screening of titles or abstracts, 1302 irrelevant studies were excluded, and the 18 selected citations were retrieved for full-text review among the researchers. Eleven studies were eventually excluded for one of the following reasons: review article (n = 5); animal study (n = 1); study design did not fulfil inclusion criteria (n = 3); shared identical population (n = 1); and study protocol (n = 1). Finally, a total of 1041 patients in six RCTs were included in the meta-analysis (Fig. 1).

Characteristics of the included studies are summarized in Table 1. The included studies spanned from 2010 to 2016, and sample sizes ranged from 16 to 606. A total of 1041 patients were included in the six RCTs (534 of whom were administrated EPO); thus, the total number of participants in the EPO group versus the untreated group was 534 versus 507, respectively. The mean or median age of included patients ranged from 25.2 to 46.5 years, and many were male. Administration of EPO varied widely across studies, being administered once or
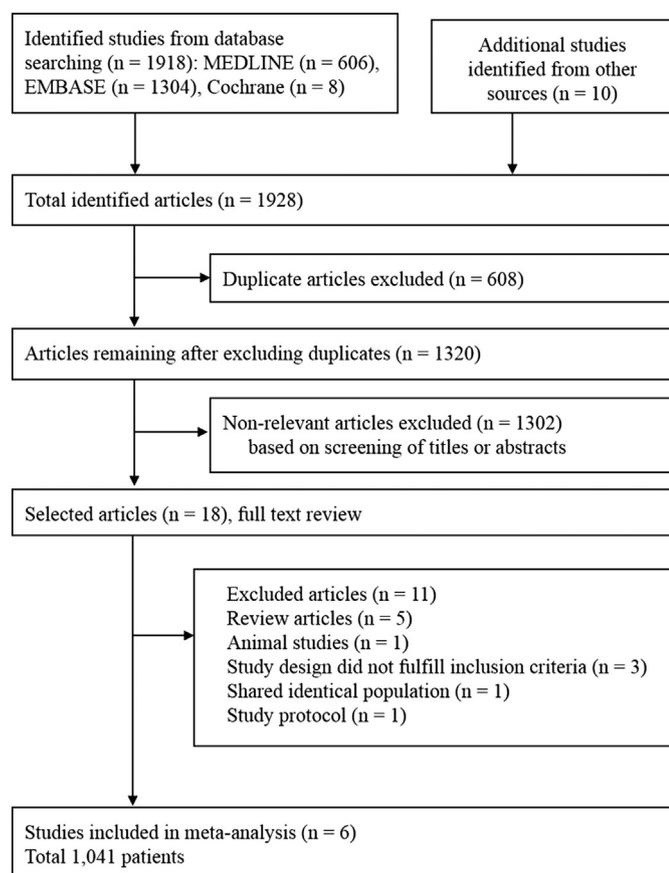
Fig. 1. Flow diagram for identification of relevant studies.

several times in small to large doses. Mortality rate was obtained from all six articles, while favorable neurological outcome and DVT were only described in three and five articles, respectively. Mortality and complications of the included studies were compared in terms of the frequency of events between patients who were administrated EPO and those untreated.

3.2. Quality assessment of the included studies

Details of the quality assessment of the included studies are shown in Fig. 2. Briefly, four of the RCTs performed randomization, double-blinding, and had controls, whereas two of the RCTs were unclear as to their randomization process and allocation concealment.

Among the six included studies, four were deemed to be high quality based on their control measures [12-14,16], while the other two did not use effective control measures (e.g., random sequence generation, allo-cation concealment, and selective reporting domains) and, therefore, did not meet quality criteria [15,17]. Through discussion and agreement among the authors, the quality assessment was confirmed. When a clear description of the study control criteria could not be found, quality was assessed as "unclear."

3.3. Effect of EPO use on mortality

Six studies, accounting for 1041 patients, were analyzed in terms of the efficacy of EPO in preventing mortality. With regard to the six RCTs, EPO administration was associated with decreased mortality compared with the untreated group (RR 0.68 [95% CI 0.50–0.95]; $P = 0.02$) (Fig. 3). The mortality rate in the EPO-treated groups of the RCTs was 10.3% (55 of 534), and 15% (76 of 507) in the untreated groups. Moreover, no def-inite evidence of heterogeneity was demonstrated ($I^2 = 0\%$; $P = 0.91$).

3.4. Effect of EPO use on neurological outcome

Functional neurological outcome was assessed using a GOS score or an extended GOS score in five of the six RCTs; a favorable neurological outcome was defined as a score of 4–5. The outcome assessment was made over a variety of time periods, ranging from 120 h to six months. However, only three studies were included in the meta-analysis be-cause the others did not have comparable forms, such as odds ratio. Of the three included studies, favorable outcome occurred in 256 of 469 (54.5%) individuals who received EPO compared with 223 of 454 (49.1%) of untreated individuals. The pooled analysis of included studies demonstrated that EPO administration tended to result in a more favor-able neurological outcome than untreated patients; however, this find-ing was not statistically significant (RR 1.22 [95% CI 0.82–1.81]; $P =$

Table 1
Characteristics of studies included in the review

Study & year	Recruitment period and country	Study design	Follow-up duration	Inclusion criteria	Number of participants (EPO/Placebo)	Age (yrs)[a]		Number of males (%)		Intervention	Outcome
						EPO	Placebo	EPO	Placebo		
Li, 2016	2010–2014 China	RCT	3 mos	Severe TBI	146 (75/71)	43.4 ± 10.1	41.1 ± 9.6	49 (65.3)	41 (57.7)	100 units/kg, on days 3, 6, 9, and 12	Itemized GOS, Serum NSE, S-100B protein
Nichol, 2015	2010–2014 Australia	RCT	6 mos	Moderate or severe TBI	606 (302/294)	30.5 (22.4–47.5)	30.5 (22.9–48.3)	256 (82.8)	246 (83)	40,000 IU, 1st dose within 24 h, weekly for a max of 3 doses	Extended GOS & adverse events
Aloizos, 2015	Not checked Greece	RCT	6 mos	Severe TBI	42 (24/18)	29.4 ± 1.3	46.5 ± 4.5	23 (95.8)	16 (88.8)	10,000 IU, 7 consecutive days	Extended GOS, adverse events
Robertson, 2014	2006–2012 USA	RCT	6 mos	TBI	200 (102/98)	31.5 (23–48)	29.0 (23–47)	88 (85.9)	84 (85.7)	500 IU, 1st dose within 6 h, weekly for 2 more wks	GOS, DRS & adverse events
Abrishamkar, 2012	Not checked Iran	RCT	2 wks	Severe TBI with DAI	54 (27/27)	25.2 ± 5.4	27.3 ± 4.0	Not checked	Not checked	2000 U, on days 2, 4, 6, 8, and 10	GOS & mortality
Nirula, 2010	Not checked USA	RCT	120 h	Moderate or severe TBI	16 (11/5)	35 ± 19	40 ± 26	8 (72.7)	3 (60.0)	40,000 units within 6 h	Serum NSE, S-100B, ICP values, mortality & adverse events
Talving, 2012	2009–2010 USA	PCT	Not checked	TBI (head AIS > 3)	150 (75/75)	42.2 (2.2)	44.0.2 (2.2)	63 (84.0)	57 (76.0)	0.40 μg/kg, by subcutaneous injection weekly	Mortality, ΔGCS, complication, length of stay

GCS, Glasgow Coma Scale score; RCT, randomized controlled trial; PCT, prospective controlled trial; EPO, erythropoietin; DAI, diffuse axonal injury; GOS, Glasgow Outcome Scale; DRS, Disability Rating Scale.
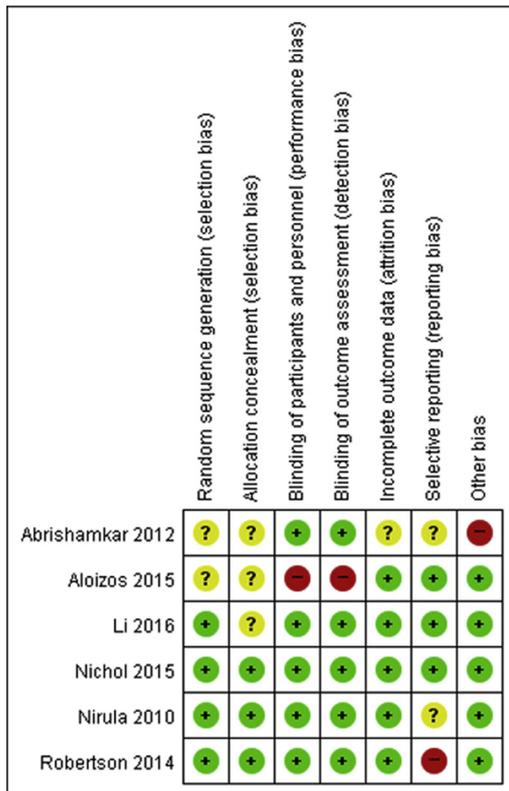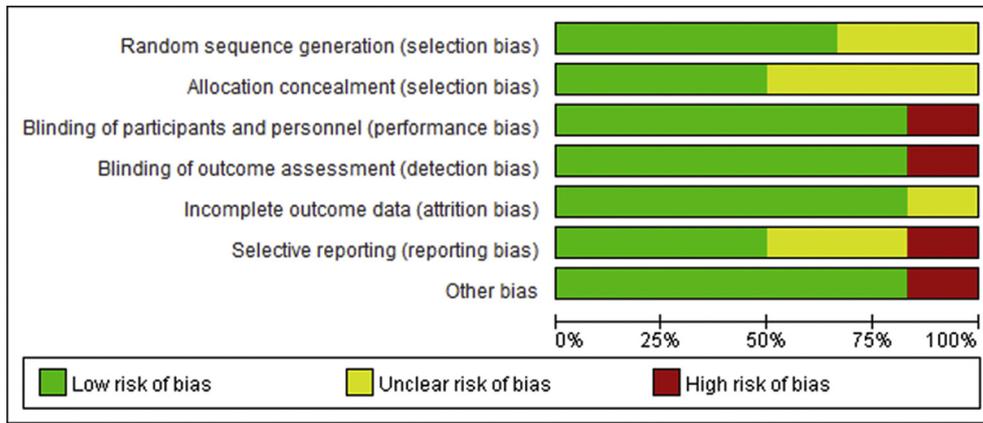[a] Age was presented as median (IQR) or mean.

Fig. 2. Risk of bias assessment. Authors' judgments regarding each risk of bias item for each included study.
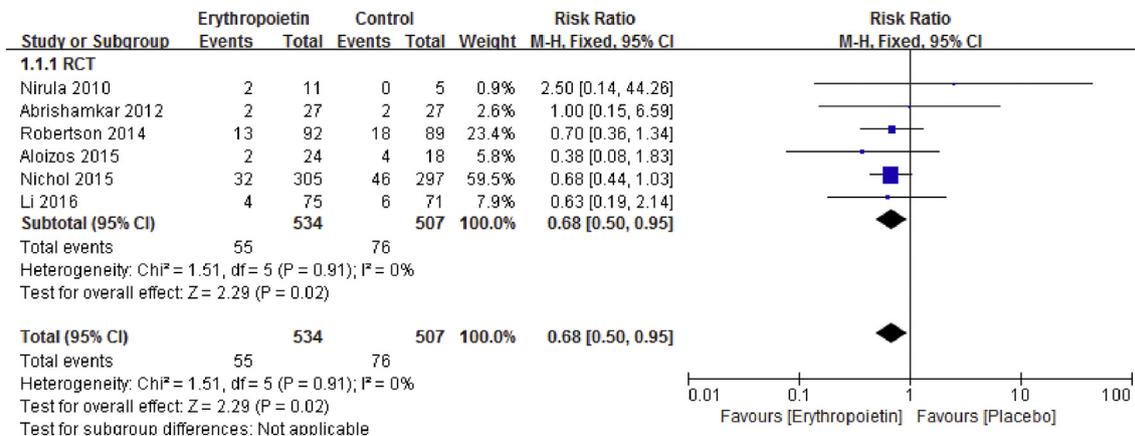

Fig. 3. Meta-analysis of relevant studies assessing mortality according to erythropoietin (EPO) treatment (fixed-effects model). Six randomized controlled trials included. CI, confidence interval.
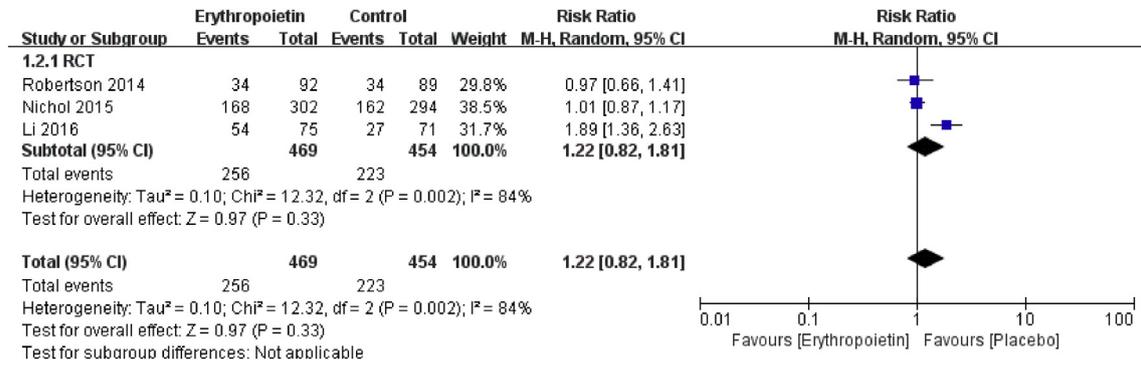
Fig. 4. Meta-analysis of relevant studies assessing favorable neurological outcome after TBI according to EPO treatment (random-effects model). Three randomized controlled trials included. CI, confidence interval.

0.33) (Fig. 4). Furthermore, there was statistically significant heterogeneity between studies ($I^2 = 84\%$; $P = 0.002$).

Negative neurological outcomes in patients who survived TBI were defined as unfavorable outcomes excluding mortality. Unfavorable outcome(s) in surviving patients were the result in 164 of 469 (34.9%) EPO-treated individuals and 161 of 454 (35.4%) untreated subjects. The pooled analysis revealed that EPO administration was associated with less unfavorable outcomes in patients who survived TBI; however, this finding was not statistically significant (RR 0.86 [95% CI 0.51–1.46]; $P = 0.58$) (Fig. 5). There was statistically significant heterogeneity among the studies ($I^2 = 87\%$; $P < 0.001$).

3.5. Effect of EPO use on DVT as a complication

DVT occurred 61 of 517 (11.8%) patients in the EPO-treated group and 69 of 490 (14.1%) in the control (i.e., untreated) group. When five RCTs were assessed using pooled analysis, no benefit of EPO use on DVT incidence was observed (RR −0.02 [95% CI −0.06–0.02]; $P = 0.81$) (Fig. 6). There was no statistically significant heterogeneity ($I^2 = 0\%$; $P = 0.81$).

4. Discussion

Our research team conducted a systematic review and meta-analysis of RCTs with the expectation that EPO would be found to be helpful in the prognosis of TBI. In this study, our evaluation revealed that EPO treatment yielded a lower mortality in patients with TBI than in the control group, and that EPO was not associated with adverse events such as DVT. However, there was no significant difference between EPO- and untreated patients in terms of favorable or unfavorable neurological outcome(s).

To reduce the mortality rate and improve neurological outcome in patients with TBI, several studies have investigated the efficacy of various neuroprotective agents. To date, however, no agent(s) has been identified to have definitive efficacy. EPO—a cytokine that regulates red blood cell production—has recently emerged as a potential neuroprotective agent that is present in both the central and peripheral nervous systems [9]. EPO has direct and indirect effects on nerve cells, promoting the production of antioxidant enzymes, antagonizing the cytotoxic effects of glutamate, metabolizing free radicals, normalizing cerebral blood flow, and effecting neurotransmitter release [9]. Based on preclinical reports [9,23], several studies have evaluated the effects of EPO using an animal model of TBI. These studies have shown that EPO maintains oxygenation in the brain and improves anemia, is involved in anti-oxidative mechanisms, has anti-inflammatory effects and protective actions on glia, and defense against nitric oxide-mediated injury in patients with TBI [24-30].

Collectively, the majority of preclinical and clinical studies investigating EPO suggest that it acts as a neuroprotective agent in TBI. Although the mechanisms by which EPO exerts these actions are not clear, several RCTs and prospective studies have aimed to determine the efficacy of EPO treatment in humans; the effect of EPO among these studies, however, remains inconsistent. A meta-analysis based on these RCTs revealed a positive effect of EPO—in terms of reducing mortality rate—but no effect in improving neurological prognosis [19]. However, typical of preclinical and clinical studies, continuous research is needed to verify such findings. Since then, research investigating the neuroprotective effect of EPO in TBI has proceeded; thus, our team conducted a meta-analysis to include the additional study. Although the results of the current study are not significantly different from the previous meta-analysis, they provide meaningful support for continued research on the effects of EPO in TBI.

Although several studies suggest that EPO improves neurological outcome, this was difficult to verify in the current study because, among those included in our meta-analysis, few actually compared
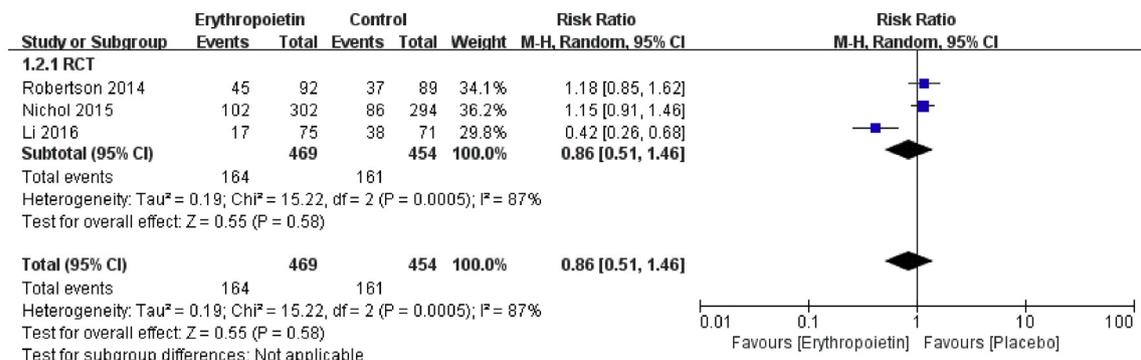

Fig. 5. Meta-analysis of relevant studies assessing unfavorable neurological outcome in survived patients after TBI according to EPO treatment (random-effects model). Three randomized controlled trials included. CI, confidence interval.
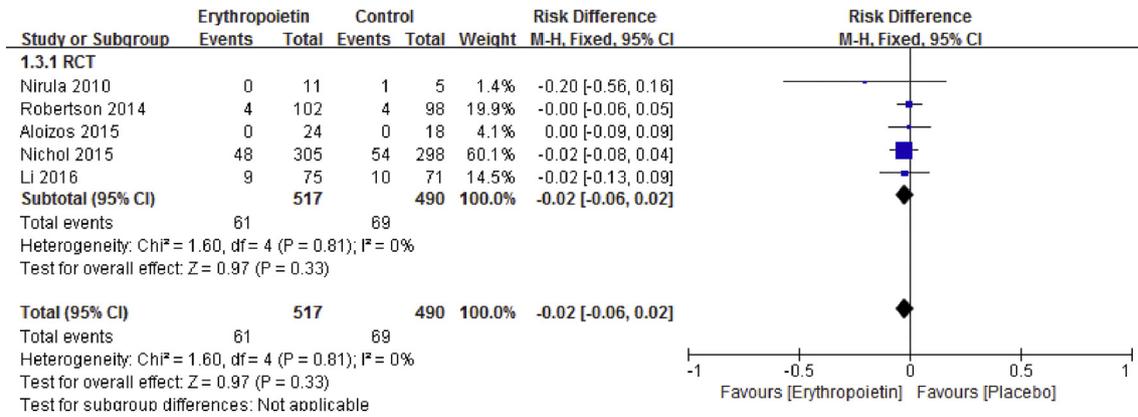
Fig. 6. Meta-analysis of relevant studies assessing deep vein thrombosis (DVT) as a complication according to erythropoietin (EPO) treatment (fixed-effects model). Five randomized controlled trials included. CI, confidence interval.

functional outcome(s). In addition, patient and disease characteristics varied across studies, as did the protocols used for EPO administration. However, we were able to compare EPO efficacy with other commonly used techniques to treat TBI. Puetz et al. presented that there is controversy regarding whether an inability to walk unassisted, and requiring aid in performing various bodily activities, can be considered a favorable outcome [31]. In this study, unfavorable outcomes excluding mortality in TBI survivors were compared across studies and no significant difference was observed between the EPO- and untreated groups. Thus, although EPO reduced mortality among patients with TBI, the fact that treatment with this glycoprotein did not affect the functional outcome of survivors raises questions pertaining to its actual efficacy.

Several limitations to this study should be addressed. First, we were unable to analyze the efficacy of EPO according to TBI severity. Further studies examining the efficacy of EPO in patients with TBI are needed for subgroup analysis. Second, the dose and timing of EPO injections varied greatly across studies. Because these factors may influence the course of TBI, additional studies should be conducted. Third, our meta-analysis failed to obtain individual patient-level data from the assessed studies, limiting further evaluation of potential confounding factors in the assessment of functional outcome after TBI. Finally, withdrawal of care due to the predicted poor prognosis of the patient might affect mortality. However, the studies that included in this meta-analysis did not describe the cause of death in detail.

5. Conclusions

This systematic review and meta-analysis revealed that EPO could help lower TBI-related mortality without causing adverse events such as DVT. However, the role of EPO in improving neurological outcome remains unclear. Because potential biases and confounding factors could not be fully excluded in our analysis, well-designed RCTs that consider EPO potency are required to confirm its association with clinical outcomes.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2018.08.072.

Authors' contributions

All authors contributed to the design of the study. K-SC, Y.C. and J.L. undertook the searches and screened the citations for eligibility. TH.L. and B-H.J. assessed the quality of articles and performed statistical analysis. J.L. and Y.C. drafted the manuscript. H-J.Y and C. A moderated disagreements during data collection and analyzed data. TH.L. and W.K. revised the manuscript critically for important intellectual content. All authors revised the manuscript and approved the final version.

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