# Comparative Safety of Multiple Doses of Erythropoietin for the Treatment of Traumatic Brain Injury: A Systematic Review and Network Meta-Analysis

**Qingyong Zheng**
Evidence-Based Nursing Center, School of Nursing, Lanzhou University
**Dan Duan**
Evidenced-Based Nursing Center, School of Nursing, Lanzhou University
**Jianguo Xu**
Evidence-based Medcine Center, School of Basic Medical Sciences, Lanzhou University.
**Xing Wang**
The First Clinical Medical College of Lanzhou University
**Yonggui Ge**
Department of Rehabilitation, The First Hospital of Lanzhou University.
**Xiaofeng Luo** ( luoxiaof@lzu.edu.cn )
School of Public Health, Lanzhou University

**Research**

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## Abstract

**Background:** Although many studies have shown that erythropoietin plays an important role in the prognosis of traumatic brain injury (TBI) patients, the effective dose of erythropoietin has not been clearly defined. Our aim was to systematically elucidate the safety and efficacy of erythropoietin administration regimens in TBI patients.

**Methods:** Data search included PubMed, the Cochrane Library, EMBASE and ClinicalTrials.gov for articles published before December, 2020, updated to June 2021. Network meta-analysis was performed when sufficient comparable evidence was available, and CINeMA tool was used to evaluated the quality of our evidence.

**Results:** A total of 6 RCTs involving 981 patients were included in the network meta-analysis. All studies assessed the effect of erythropoietin on mortality. Erythropoietin reduced the mortality rate in patients with TBI, and the risk of death decreased with increasing dose, but the difference was not statistically significant (odd ratio of 12,000u vs Placebo=0.98, 95%CI, 0.03-40.34; odd ratio of group 30,000u vs Placebo=0.56, 95%CI, 0.06-5.88; odd ratio of 40,000u vs Placebo=0.35, 95%CI, 0.01-9.43; odd ratio of 70,000u vs Placebo=0.29, 95%CI, 0.01-9.26; odd ratio of group 80,000u vs Placebo=0.22, 95%CI, 0.00-7.45). Three studies involving 739 patients showed that erythropoietin did not increase the incidence of deep vein thrombosis in patients with TBI. However, the risk tended to rise as the dose increases. Two studies demonstrated that erythropoietin did not increase the incidence of pulmonary embolism. The evidential quality of all the results of the evidence ranged from low to medium.

**Conclusion:** Although the efficacy of erythropoietin was not statistically demonstrated, we found a trend in the association of erythropoietin dose with reduced mortality and increased embolic events in TBI patients. We are looking forward to more high-quality original studies focusing on the dose and timing of erythropoietin for the treatment of TBI, in order to obtain stronger evidence on the optimal erythropoietin dose.

Study Registration: PROSPERO (CRD42021272500).


## Background

Traumatic brain injury (TBI) refers to a series of dull or sharp mechanical forces that induce vascular injury and hypoxia leading to glial activation, primarily astrogliosis, inflammation, cell death, and tissue loss [1]. TBI continues to plague millions of people around the world over years, disproportionately affecting the young, middle-aged and elderly [2]. Data showed that about half of the global population experienced an episode of TBI in their lifetime, causing huge economic losses to the world every year [3]. TBI has been a pressing global medical and public health problem and a leading cause of mortality and long-term disability [4].

Over the past few decades, advances in TBI pathology research updated our understanding dynamically [5]. However, the treatment and management of TBI remains a significant challenge for clinicians due to its nearly impossible to reverse brain damage. Thus, a number of neuroprotective drugs have been extensively studied, which focused on the intervention for treating patients in early stage protecting the nerve cells of the brain from secondary injury from ischemia and hypoxia [6].

Erythropoietin (EPO), a hemopoietin growth factor from the type 1 cytokine superfamily that occurs in the spleen, liver, bone marrow, lung, also expressed in the brain in small quantities, can provide neuroprotective effects [7]. The positive recovery effect of erythropoietin on traumatic brain injury has been demonstrated in many animal experimental models, including stimulating hematopoiesis, neuroregenerative and neuroprotective effects, through reduction of apoptosis, relieve inflammation, oxidative stress, and excitotoxicity [8–11].

At present, several randomize control trials (RCTs) have also found some efficacy of erythropoietin in treatment of TBI in humans, yet the efficacy of erythropoietin in the treatment of TBI remains controversial [6, 12–17]. A network meta-analysis (NMA) enables a coherent ranking of multiple interventions, which can thus assist decision-makers who must choose among variable treatment options [18]. In the existing meta-analysis and related original studies [19–22], the dosage of erythropoietin in the treatment of TBI varies widely. Dose optimization studies were not clear, and no dose-response studies of erythropoietin in TBI treatment had been well established. Consequently, we conducted a network meta-analysis to evaluate the efficacy of erythropoietin in TBI, which allows comparisons for the estimation of the interrelations across all dosage, to evaluate the efficacy of erythropoietin dosing regiments for TBI treatment.

## Methods

# Search strategy

We searched PubMed, the Cochrane Library, Embase and ClinicalTrials.gov for RCTs that evaluated treatment responses to pharmacological dosage management in traumatic brain injury patients. The initial search was completed on 7 December 2020. Then, the retrieval results were updated to June 24, 2021 by using the automatic push function of the database on a weekly basis. Syntax and vocabulary were adjusted across databases, including 'erythropoietin', 'Epoetin Alfa', 'Darbepoetin alfa', 'EPO', traumatic brain injur*, 'brain concussion', 'brain contusion', 'chronic traumatic encephalopathy', 'craniocerebral trauma', penetrating head injur*, 'basilar skull fracture', 'cerebrovascular trauma', 'traumatic intracranial hemorrhage', 'TBI', which were used individually or conjunctively. Full details of the search strategies used for this review are listed in Additional file 1. Related articles from the reference lists were also included to search for supplementary articles that may not have been retrieved by the searching strategy prespecified before. All included studies should be written in English. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2009)

guideline [23]. Ethical approval was not required since this review did not relate to any individual patient data. A protocol was registered a priori on PROSPERO (CRD42021272500).

## Study eligibility criteria

The studies conforming to the following criteria were included in our network meta-analysis: (1) RCTs comparing the effect of erythropoietin with placebo in TBI patients were brought in our study. Nonrandomized trials, retrospective studies, case-control studies, review articles, case reports, and letter to editors were dismissed. (2) Studies investigating the effect of pharmacological treatment of patients hospitalized for TBI management. Mild to moderate patients who have self-limiting disease courses or do not require hospitalization were not eligible for our research. (3) Medication doses should be reported accurately or approximate dose can be calculated from the management description. Studies that did not clearly report drug management and doses were excluded. (4) Significant clinical outcomes and adverse events were reported in the outcome metrics.

## Study selection

The initial search records were imported into ENDNOTE X9 literature management software, then the titles and abstracts of records were screened to select appropriate trials according to eligibility criteria by two authors (Q.Y.Z. and D.D). Subsequently, full-text versions of all potentially relevant trials were obtained and examined to ensure eligibility of the study for the network meta-analysis. The most recently reported data were analyzed in the same trial reports at different follow-up periods. Any divergences in regard to eligibility were resolved by discussion with a third reviewer (F.L.X).

## Data extraction

Data of interest were collected through a standard data extraction form created using Microsoft Excel 2021 (www.microsoft.com), including eligible studies characteristics (eg, name of the first author, published year, type of research design, follow-up time), characteristics of study participants (eg, mean age, gender, countries), drug administration (eg, route, dose arrangement, total drug dose, time to intervention) and reported clinical outcomes, including couple of adverse events. Any differences on the evaluation of these data were figured out through discussion until consensuses were reached.

## Quality evaluation

The risk of bias for individual studies was independently assessed by reviewers employing the identical bias risk assessment tool (RoB2) used for randomized trials from the Cochrane Handbook [24, 25]. A risk of bias graph was generated showing the bias levels as low risk, high risk, and unclear risk, which was demonstrated using Review Manager 5.4(Oxford, UK; The Cochrane Collaboration). The CINeMA (Confidence In Network Meta-Analysis) version 1.9.1 (https://cinema.ispm.unibe.ch/), calculating the NMA contribution matrix by using the Netmeta package of R software, based on grading of recommendations assessment, development and evaluation (GRADE) methodology was applied for assessing quality of evidence, and reported in the results [26]. A comparison-adjusted funnel plot with Egger test was constructed to assess for publication bias [27].

## Geometry of the network

We created a network of evidence between the comparisons using STATA (Stata Corp, College Station, Texas, United States of America, version 16.0) [28]. A network plot was drawn to present the interrelationships of comparisons across trials, which showed how each intervention connected to the others through direct or indirect comparisons. In the network, each regimen is represented by a unique node, which means different nodes were designated for different dosages of erythropoietin. Lines indicate direct head-to-head comparison of regimens, and the thickness of line corresponds to the number of trials in the comparison. Size of the node corresponds to the number of studies behind the intervention.

## Data synthesis and statistical analysis

ADDIS (IMI GetReal Initiative, EU, version 1.16.8) was used to calculate the comparison results. Parameter setting of ADDIS was follows: number of chains, 4; tuning iterations, 20,000; simulation iterations, 50,000; thinning interval, 10; inference samples, 10,000; variance scaling factor, 2.5. The consistency model was used to pool data regarding to mortality, pulmonary embolism and deep venous thrombosis (DVT). Convergence was assessed using potential scale reduction factor (PSRF) and PSRF closer to 1, indicating the better convergence; generally, PSRF less than 1.2 was acceptable [29].

# Results

## Study characteristics

In total, 544 studies were identified from PubMed, Cochrane databases, Embase and ClinicalTrials.gov by initial retrieval, and there were 10 additional record identified through other sources as shown in Fig. 1. Of these studies, 51 duplicate records were removed and another 449 studies that deviated from inclusion criteria were excluded by screening the titles and abstracts. From the remaining 54 studies, the full texts were reviewed and 48 studies were removed due to the non-randomized control trial design or unavailable specific data. Finally, 6 RCTs [6, 12–16] involving a total of 981 patients randomly assigned to receive erythropoietin or placebo treatment were included in the research. The characteristics of the 6 RCTs included were summarized in Table 1.

Table 1
Baseline characteristics of included studies

| Basic information | Study design | Follow up | Inclusion Criteria | Number of Participants (EPO/Placebo) | Age (years) | | Sex (Males%) | | Drug Administration | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | EPO | Placebo | EPO | Placebo | Route | Dosing regimen | Total dose |
| Nirula et al, 2010 | Double blind RCT<br>single center | Discharge or dead | Moderate or sTBI:<br>GCS < 13 | 16<br>(11/5) | 35 ± 19 | 40 ± 26 | 8<br>(72.7) | 3<br>(60) | IV | 40,000u | 40,000u |
| Abrishamkar et al, 2012 | Double blind<br>RCT<br>single center | Discharge or dead | sTBI with DAI:<br>GCS (4–8) | 54<br>(27/27) | 25.2 ± 5.4 | 27.3 ± 4.0 | - | - | SC | 2000u-Day 2, 4, 6, 8, 10 for 6 doses in two weeks | 12,000u |
| Aloizos et al, 2015 | RCT<br>Multicenter | 6 months | sTBI:<br>GCS < 9 | 42<br>(24/18) | 29.4 ± 1.3 | 46.5 ± 4.5 | 23 (95.8) | 16<br>(88.8) | - | 10,000u of EPO for 7 consecutive days | 70,000u |
| Nichol et al, 2015 | Double blind, RCT<br>Multicenter | 6 months | Moderate or sTBI:<br>GCS:3–12 | 603<br>(305/298) | 30.5<br>(22.9–47.5)* | 30<br>(22.9–48.3) | 256 (83.9) | 245<br>(82.5) | SC | 40,000u Day 0 then weekly for max 3 doses | 40,000u–147<br>80,000u–82<br>120,000u–75 |
| Li et al,<br>2016 | Double blind RCT<br>single center | 3 months | sTBI:<br>GCS ≤ 7 | 146<br>(75/71) | 43.4 ± 10.1 | 41.1 ± 9.6 | 49 (65.3) | 41<br>(57.7) | SC | EPO (100 u/kg) (average 6000 units) on day 1, 3, 6, 9 and 12 | 30,000u |
| Bai and Gao,<br>2018 | Triple blind<br>RCT<br>single center | 10 weeks | sTBI:<br>GCS□8 | 120<br>(60/60) | 44.5 ± 11.4 | 43.1 ± 10.9 | 41 (68.3) | 44<br>(73.3) | SC | 6000u, within<br>2h, on days 3, 5,10, and 15 | 30,000u |

*RCT* randomized controlled trial, *sTBI s*evere traumatic brain injury, *GCS* Glasgow Coma Scale, *NSE* Neuron Specific Enolase, *ICP* Intracranial pressure, *ICU* int blood cell, *GOS* Glasgow Outcome Scale, *GOS-E* Glasgow Outcome Scale Extended, *APACHE* acute Physiology and Chronic Health Evaluation, *BP* blood press *SC* subcutaneous injection, *u* units, *** age range.

Among all researches, the intervention (EPO) and control treatment (Placebo) were administered as adjunctive therapy to standard care. These included studies were published between 2010 and 2018, and the participants were distributed in America, Iran, Athens, Australia, New Zealand, France, Germany, Finland, Ireland, Saudi Arabia and China. There were no significant differences in demographic characteristics including Age, Sex, Severity of disease and GCS. The total dosage of erythropoietin among all the trials ranged from 12,000u to 80,000u. Medical treatment included intravenous injections and subcutaneous injection, which was not reported in only one research [14]. The total duration of drug interventions ranged from 1 to 7 sessions.

## Risk Of Bias And Quality Of Evidence Evaluation

In general, the results indicated an acceptable risk of bias among these RCTs as summarized in Fig. 2. Of the 6 RCTs, 3 trials [6, 12, 16] (50%) were judged to have a low risk of bias for randomization methods, 4 [6, 12, 15, 16] (66.7%) for concealment allocation, 5 [6, 12, 13, 15, 16] (83.3%) for blinding of participants and personnel, 4 [6, 12, 13, 15] (66.7%) for blinding of outcome assessment, 4 [12–15] (66.7%) for incomplete outcome data, 1 [12] (16.7%) for selective reporting, and 5 [6, 12–14, 16] (83.3%) for other bias. Most of studies reported the differences in dropouts and the reasons for patient withdrawal. Only 1 study [15] was judged to be high risk among other bias because it reported inequality at baseline. The specific item score for each study is available in the Additional file 1. The funnel plots of each outcome indicator were asymmetrical, which might be due to the small number of studies. The Egger test result can be found in Additional file 1.

The level of quality of evidence is represented by a bubble chart. As shown in Fig. 3, the overall quality of evidence for mortality, DVT and pulmonary embolism was moderate in both the EPO and placebo groups. Partial individual comparison groups in mortality and DVT group were judged to have a low quality of evidence.

## Statistical analysis

Comparisons between all doses of erythropoietin and placebo were presented in a network diagram in Fig. 4. The placebo acted as an intermediary to establish comparisons between all doses. The pooled ORs and 95% CIs of the treatment efficacy among the different groups in the network meta-analysis were given in Fig. 5 and Additional file 1. Specific indicators were analyzed as follows.

## Mortality

Regarding to mortality. Compared with the placebo, erythropoietin could reduce the incidence of mortality from traumatic brain injury but the difference was not statistically significant (OR of 12,000u vs Placebo = 0.98, 95%CI, 0.03–40.34; OR of group 30,000u vs Placebo = 0.56, 95%CI, 0.06–5.88; OR of 40,000u vs Placebo = 0.35, 95%CI, 0.01–9.43; OR of 70,000u vs Placebo = 0.29, 95%CI, 0.01–9.26; OR of group 80,000u vs Placebo = 0.22, 95%CI, 0.00-7.45). As could be clearly seen in the as-generated sequence diagram (see Additional file 1), EPO (80,000u) had the highest therapeutic effect on TBI patients. Figure 5 displays that, the probability of mortality risk decreases with the increase of erythropoietin dose.

## Deep vein thrombosis

Regarding to DVT events. Compared with the placebo, erythropoietin could reduce the incidence of DVT from traumatic brain injury with no significant difference (OR of 30,000u vs Placebo = 0.24, 95%CI, 0.00-7.43; OR of group 40,000u vs Placebo = 0.42, 95%CI, 0.02–2.69; OR of 80,000u vs Placebo = 0.44, 95%CI, 0.03–6.38). As could be obviously seen in the as-generated sequence diagram (see Additional file 1), EPO (30,000u) had the highest therapeutic effect on TBI patients. Additional file 1 shows that, the likelihood of DVT increased with the increase in erythropoietin dose.

## Pulmonary embolism

Regarding to pulmonary embolism events. Compared with the placebo, EPO (30,000u) groups could increase the incidence of pulmonary embolism from traumatic brain injury while 40,000u and 80,000u decrease the risk, although there was no statistically significant difference in either of them (OR of 30,000u vs Placebo = 1.88, 95%CI, 0.17–30.16; OR of group 40,000u vs Placebo = 0.96, 95%CI, 0.11–7.41; OR of 80,000u vs Placebo = 0.39, 95%CI, 0.02–3.67). As could be clearly seen in the as-generated sequence diagram (see Additional file 1), EPO (80,000u) had the highest therapeutic effect on TBI patients. Additional file 1 shows that, erythropoietin changed from a deleterious to a beneficial factor with increasing dose.

### Discussion

In this network meta-analysis, different doses of erythropoietin and placebo were compared in the treatment of TBI patients. Erythropoietin had a significant trend advantage in patient prognostic factors. Erythropoietin had advantage over placebo in reducing mortality in patients with TBI and showed a trend advantage as the total dose increased. At present, we cannot determine the association between erythropoietin use and embolic events.

Although erythropoietin has been found to improve the prognosis of neurological function after the treatment of TBI in most animal experiments, the improvement of neurological function has not been statistically significant in human studies in the recent meta-studies [19, 20, 22] based on RCT studies, which may be related to insufficient sample size and number of studies or the failure to adopt the most appropriate clinical observation indicators. But it's worth noting that erythropoietin plays an important role in reducing mortality in patients with TBI. In the subgroup analysis, there was a statistically significant in reducing 6 months mortality [19, 21, 22]. Liu's research [22] found that erythropoietin has some effect on shortening the length of hospital stay of patients. In addition to this, EPO did not increase the incidence of various adverse events, such as severe disability, vegetative state, DVT, pulmonary embolism, cardiac arrest, myocardial infarction, pneumonia, sepsis, incidence of RBC transfusion, seizure and gastrointestinal complications, etc.

Erythropoietin drugs have evolved over several generations, and the specific model or batch of erythropoietin used was not described in detail in the original studies included. Each generation of erythropoietin has a different half-life, and diverse injection methods affect the way EPO is metabolized in the body, but erythropoietin has a short half-life in the body and these factors do not differ greatly [30]. The pharmacokinetic properties of erythropoietin were fully considered, our network meta-analysis collected useful and comprehensive evidence regarding the efficacy of different total doses of erythropoietin used for the treatment of TBI rather than the treatment duration.

The results of our network meta-analysis displayed that erythropoietin did not show a statistically significant in reducing in mortality among TBI patients, which differs from previous studies [19–22]. The probable reason is that we excluded relevant RCT studies that did not accurately report drug doses and did not distinguish when mortality occurred, as well as the algorithm mechanism differences between traditional pairwise meta-analysis and network meta-analysis produced by Addis software. However, cogent evidence in the network meta-analysis showed that the effect value gradually decreased with the increase of the total dose of erythropoietin, which strongly implied that the higher dose of erythropoietin was more likely to reduce the mortality of TBI patients. Nevertheless, even with such a network meta-analysis, we are still unable to detect the exact size of the differences between the various dosing regiments.

With regard to the occurrence of deep vein thrombosis, the results of our research showed that EPO use did not increase the risk of its occurrence, which was similar to the results of previous traditional meta-analyses [19–22]. EPO may become a risk factor for the increased incidence of DVT for TBI patients with further study or increase of EPO dose. Regarding the Incidence of pulmonary embolism events. Since the number of studies is small and the relationship is not prominent, we believe that the use of EPO did not increase the possibility of its occurrence temporarily, which is similar to the results of previous traditional meta-analyses [19], too. It's worth noting that EPO has been proved to be associated with increased blood viscosity, elevated hemoglobin concentration, and vasoconstriction, which may contribute to the incidence of thromboembolism and the risk of cardiovascular events, including death [7]. While this has not yet been demonstrated in patients with TBI, we do find that certain propensity and improper dosage may increase the risk of embolism in this high-risk group. The purpose of our study is to determine the optimal erythropoietin dose for TBI patients, so as to ensure that the incidence of adverse events could be reduced based on the optimal treatment outcome.

The end of the other related indicators also was reported in the original study, such as the neural function recovery, the hospitalization time and cardiovascular events, and so on. However, due to its small amount, it could not constitute our dose study network and there was no certain statistical significance in traditional Meta-analysis [19–22], and we didn’t analyze it. The number of RCTs included in this study was small, and we are looking forward to more original studies to better confirm the optimal dose of erythropoietin and its therapeutic relationship with patients with TBI.

There are also some limitations in our studies. First and foremost, because of the need for relatively accurate dose calculations, we have had to abandon a few studies where complete data cannot be obtained, which accounted for the small number of studies and may have a certain impact on our data analysis. Besides, one study reported inconsistencies between the experimental group and the control group at baseline, which we identified as a high risk of bias. Multiple studies have been judged inconclusive in selective reporting and the overall quality level of the study was not enough high. Those reasons may have influenced the results of the network meta-analysis. Finally, we don't have complete data on which treatments patients received in addition to erythropoietin, and we don't know if these basic treatments are comparable. We are looking forward to more high-quality original studies focusing on the dose and timing of EPO for the treatment of TBI, in order to obtain stronger evidence on the optimal EPO dose.

## Conclusion

The results of the network meta-analysis did not indicate a statistically significant therapeutic relationship between erythropoietin and TBI, nor did it increase the risk of adverse events. But the dosimetry effect relationship has been gradually reflected in the data analysis process. We are looking forward to more high-quality original studies focusing on the dose and timing of erythropoietin for the treatment of TBI, in order to obtain stronger evidence on the optimal erythropoietin dose.

## Abbreviations

TBI
Traumatic brain injury; EPO:Erythropoietin; RCTs:Randomize control trials; NMA:network meta-analysis; PRISMA:Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RoB2:Risk of bias 2 tool; CINeMA:Confidence In Network Meta-Analysis; GRADE:Grading of recommendations assessment, development and evaluation; DVT:deep venous thrombosis; PSRF:potential scale reduction factor; OR:Odd ratio; sTBI:severe traumatic brain injury; GCS:Glasgow Coma Scale; NSE:Neuron Specific Enolase; ICP:Intracranial pressure; ICU:intensive care unit; RBC:red blood cell; GOS:Glasgow Outcome Scale; GOS-E:Glasgow Outcome Scale Extended; APACHE:acute Physiology and Chronic Health Evaluation; BP:blood pressure; IV:Intravenous injection; SC:subcutaneous injection; u:units.

## Declarations

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### Authors’ contributions

QYZ, DD contributed to the conception and design of this review. QYZ, DD and XFL performed the two-stage literature screening, extracted the data and conducted the risk of bias assessment. QYZ and JGX statistically analyzed the data and interpreted and synthesized the data. XFL functioned as a senior reviewer, supervised the analysis and advised the interpretation of results. QYZ wrote the draft manuscript. DD, XW, YGG and XFL critically revised the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

All data generated and/or analyzed during the current study are included within the published article and its additional files.

**Ethics approval and consent to participate**

As a systematic review and net meta-analysis based on aggregate-level data from published RCTs, this study does not require ethics approval under the Swiss Human Research Act.

**Consent for publication**

Not applicable.

**Competing interests**

All authors declare that they have no competing interests.

**Author details**

[1]Evidence-based Nursing Center, School of Nursing, Lanzhou University, Gansu Lanzhou 730000, China.[2]Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Gansu Lanzhou 730000, China.[3]The First Clinical Medical College of Lanzhou University, Gansu Lanzhou 730000, China.[4]Department of Rehabilitation, The First Hospital of Lanzhou University, Gansu Lanzhou 730000, China.[5]School of Public Health, Lanzhou University, Gansu Lanzhou 730000, China.

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## Figures

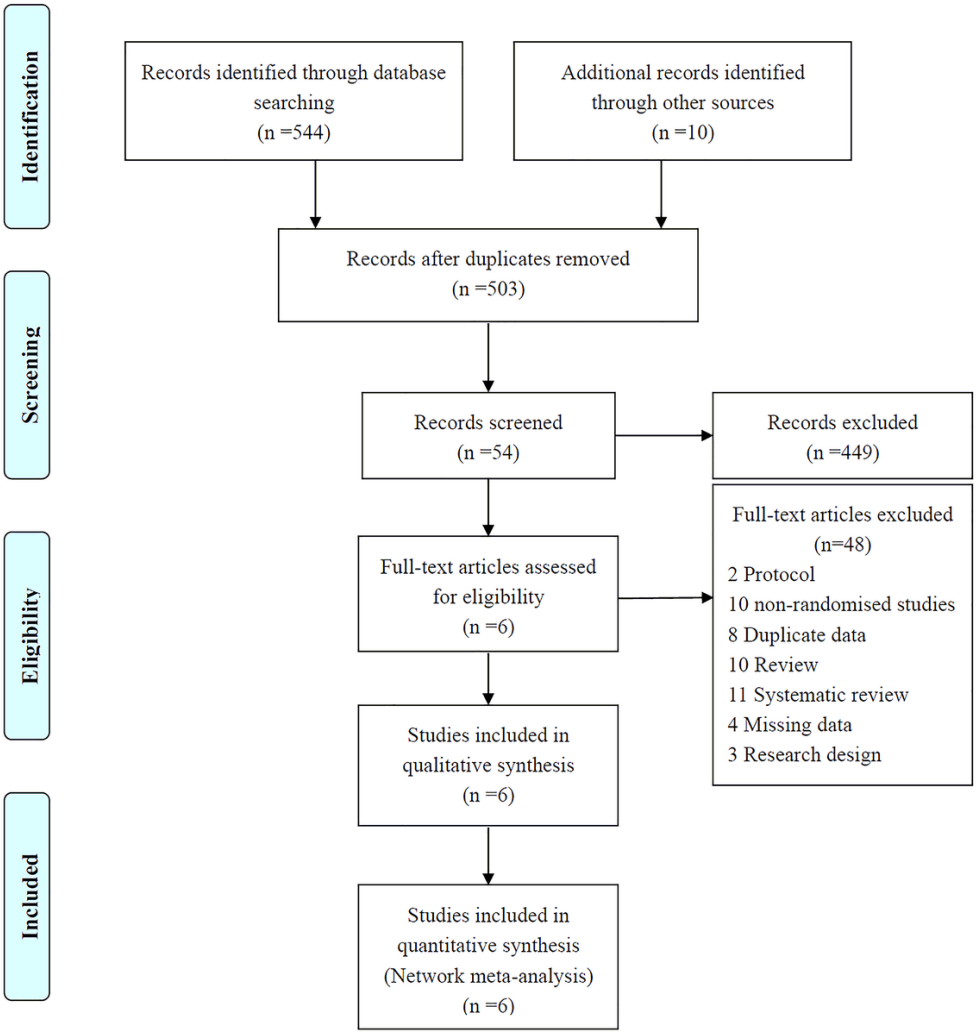


**Figure 1**

Flowchart of literature identification, review, and selection.

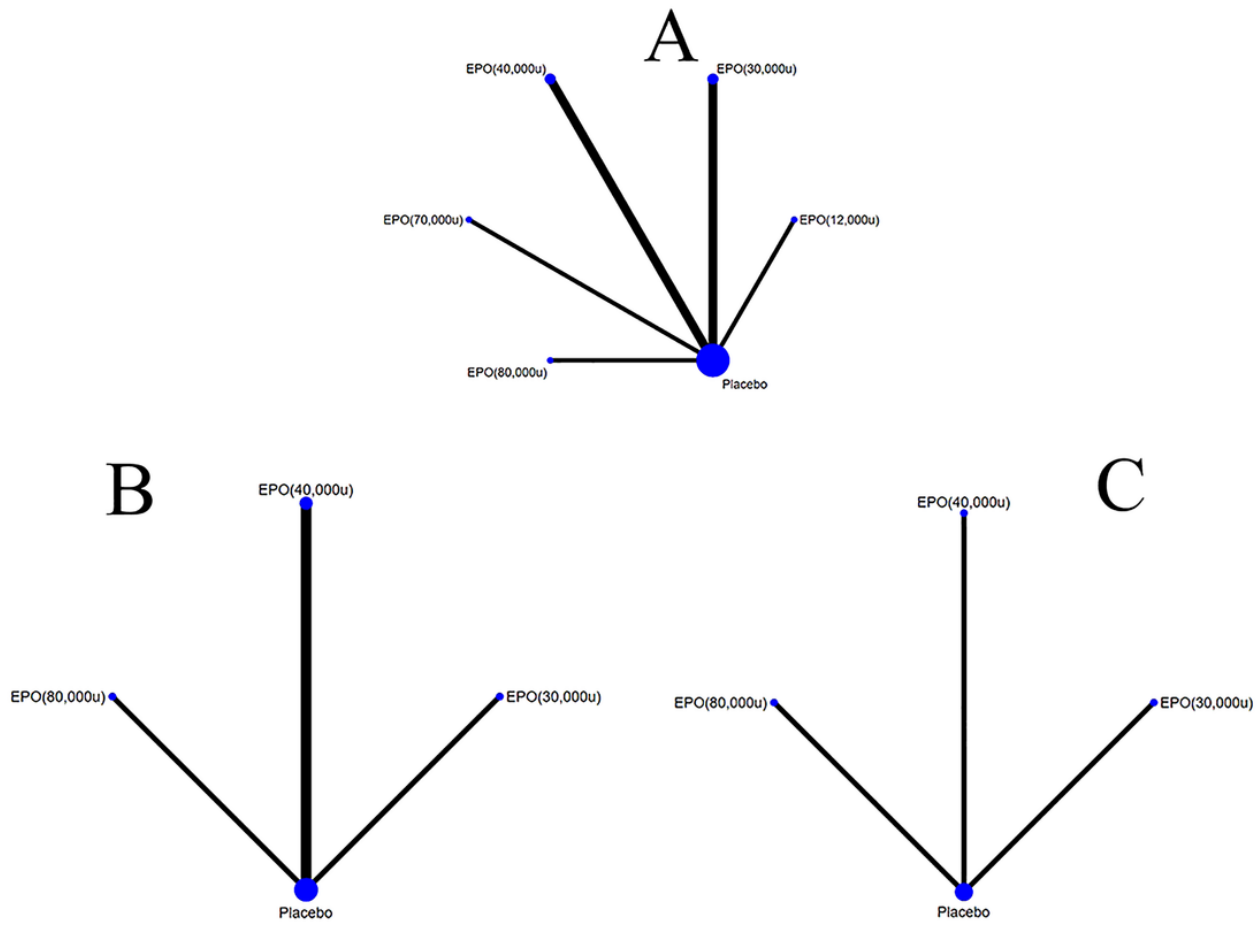


**Figure 4**

Network plot for adverse incidences produced by STATA network plot command. Legends: EPO, erythropoietin; DVT, deep vein thrombosis; u, unit. A, mortality; B, deep vein thrombosis; C, pulmonary embolism.

| | | | | | |
|---|---|---|---|---|---|
| EPO (12000u) | | | | | |
| 1.76 (0.02, 146.81) | EPO (30000u) | | | | |
| 2.86 (0.02, 379.96) | 1.62 (0.03, 88.24) | EPO (40000u) | | | |
| 3.52 (0.02, 590.41) | 1.99 (0.03, 139.06) | 1.22 (0.01, 154.40) | EPO (70000u) | | |
| 4.80 (0.03, 1099.44) | 2.62 (0.04, 347.72) | 1.56 (0.01, 389.53) | 1.31 (0.01, 321.17) | EPO (80000u) | |
| 0.98 (0.03, 40.34) | 0.56 (0.06, 5.88) | 0.35 (0.01, 9.43) | 0.29 (0.01, 9.26) | 0.22 (0.00, 7.45) | Placebo |

**Figure 5**

Effects of different doses of erythropoietin on mortality compared with placebo based on network meta-analysis. Legends: EPO, erythropoietin; DVT, deep vein thrombosis; u, unit.

## Supplementary Files

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