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SYSTEMATIC REVIEW

Safety and efficacy of erythropoiesis-stimulating agents in critically ill patients admitted to the intensive care unit: a systematic review and meta-analysis

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Abstract

Purpose: Severe immune dysregulation is common in patients admitted to the intensive care unit (ICU) and is associated with adverse outcomes. Erythropoietin-stimulating agents (ESAs) have immune-modulating and anti-apoptotic effects. However, their safety and efficacy in critically ill patients remain uncertain. We evaluated whether ESAs, administered to critically unwell adult patients admitted to the ICU, reduced mortality at hospital discharge.

Methods: The search strategy was conducted according to a predetermined protocol and included OVID MEDLINE, OVID EMBASE and The Cochrane Central Register of Controlled Trials from inception until 20 May 2019. Publications were eligible for inclusion if they were randomized controlled trials (RCTs) including adult patients admitted to an ICU, that identified and reported a group receiving ESA therapy compared to a group not receiving ESA therapy and reported mortality. There were no language restrictions.

Results: The systematic review included 21 studies with 5452 participants. In-hospital mortality, reported in 16 studies of which only one was at low risk of bias, was lower in the ESA group (276 of 2187 patients, 12.6%) than the comparator group (339 out of 2204 patients, 15.4%), [relative risk (RR) 0.82, 95% CI 0.71–0.94, $P = 0.006$, $I^2 = 0.0\%$]. The RR of SAEs and thromboembolic events for the ESA and comparator groups were similar, RR 1.11 (95% CI 0.94–1.31, $P = 0.228$, I^2 66%) and 1.22 (95% CI 0.95–1.58, $P = 0.086$, I^2 47%), respectively.

Conclusions: In heterogenous populations of critically ill adults, evidence from RCTs of mainly low or unclear quality, suggests that ESA therapy may decrease mortality.

Keywords: Erythropoiesis-stimulating agents, Critical care, Immunomodulation

Introduction

Severe immune dysregulation is common in patients admitted to the intensive care unit (ICU) and is associated with adverse outcomes [1]. Erythropoietin is a key regulator of erythropoiesis and has immune-modulating and anti-apoptotic effects. Receptors present on a variety of cell types including parenchymal, neuronal and immune cells mediates these anti-inflammatory and anti-apoptotic effects through nuclear factor (NF)-kB-dependent pathways [2]. However, concentrations of erythropoietin are decreased in critical illness [3, 4]. Preclinical evidence suggests that erythropoiesis-stimulating agents (ESAs) may improve outcomes in a variety of severe illnesses including, sepsis, traumatic brain injury,

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hemorrhagic shock and burn injury [5–8]. As a result, ESAs have been proposed as a treatment for critical illness-associated immune dysregulation in patients admitted to the ICU [9].

However, high-quality evidence has not demonstrated a significant decrease in red blood cell requirement in anemic patients receiving ESAs in the ICU, and ESA therapy may be associated with increased adverse events in select patient groups, including an increased risk of thrombotic events possibly mediated by mechanisms including increased plasma viscosity, platelet number and aggregation [10–13].

We hypothesized that the efficacy of ESA therapy in modulating severe immune dysregulation in patients admitted to the ICU may be apparent through the aggregation of randomized clinical trial (RCT) data from the heterogeneous populations of critically unwell patients in which the therapy has been assessed. The primary aim of this study was to conduct a systematic review and meta-analysis to determine whether ESAs, administered to critically unwell adult patients admitted to the ICU, reduces mortality at hospital discharge. The effect on longer-term mortality and safety outcomes including thromboembolic events was also assessed.

Take-home message

Erythropoiesis-stimulating agent therapy may decrease mortality in ICU patients, but existing evidence is of low or unclear quality.

Methods

The study was conducted according to a predetermined protocol (PROSPERO registration number: PROSPERO 2017 CRD42017071265) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (eFigure 1) [14].

Search strategy

The search strategy included OVID MEDLINE, OVID EMBASE and The Cochrane Central Register of Controlled Trials from inception until 13 April 2018, then updated to 20 May 2019. We searched for RCTs comparing the use of ESAs to either placebo or standard care in critically unwell patients. The search strategies included the terms "Critical care", "erythropoietin" and "randomized controlled trial". A full list of the search terms is provided in the supplementary material. There were no date or language limitations. Conference proceedings were not searched. Two authors (JI and PL) independently searched, screened and determined study eligibility, with any disagreement adjudicated by a third author (EL). Study quality was assessed using the Cochrane Collaboration's tool for assessing risk of bias [15].

Eligibility criteria

Eligible publications were RCTs, that included patients admitted to an ICU, identified and reported a group receiving ESA therapy compared to a group not receiving ESA therapy and reported mortality. Publications were excluded if they used a crossover design without reporting any outcomes of interest prior to crossover, included neonates, or if ESA therapy was administered prior to the onset of critical illness (e.g., outside of a critical care area such as pre-admission clinic prior to major planned surgery). Where studies included two or more pre-planned treatment arms with either co-interventions (e.g., iron therapy) or differing ESA doses, the study data were limited to the treatment arm with ESA alone and the higher ESA dose.

Data collection

A case report form was piloted and refined by the study authors. Study data were then extracted from eligible studies onto a final pre-specified case report form independently, in duplicate, by four authors (JL, PA, JI, and PL). Disagreement was adjudicated by a further author (EL). Where relevant, requests were made to the corresponding authors for data not reported in the primary manuscripts.

Statistical analysis

Eligible studies were pooled for meta-analysis using a random-effects model. Trials without events in one of the trial groups were included in the meta-analysis as this has been shown to be a more reliable estimate of treatment effect. The primary outcome was hospital mortality. Key secondary outcomes included mortality beyond hospital discharge at end of follow-up, serious adverse events (SAEs), red blood cell (RBC) transfusion, hemoglobin (Hb), ICU length of stay (LOS), thromboembolic events, acute myocardial infarction (AMI) and cerebral vascular accidents (CVAs), defined according to the original reports. A full list of outcomes is provided in the protocol (PROSPERO registration number: PROSPERO 2017 CRD42017071265) to determine the risk of an outcome for categorical data, the number of participants with an event was compared with the total number of participants with and without an event. For continuous data, the participant number, mean, and standard deviation were used. Weighted mean difference (WMD) and risk ratio (RR) with a 95% confidence interval (CI) were calculated for continuous data and categorical data, respectively. A $P<0.05$ was considered significant. Heterogeneity was measured using the I^2 statistic with a $I^2>40\%$ considered significant heterogeneity. The effects of age on the association between ESA regimens and the

primary outcome were assessed using meta-regression. Publication bias was measured with a funnel plot with the odds ratio (OR) for mortality plotted against the standard error of the log OR. Two pre-specified sub-group analyses were conducted describing the trauma vs. non-trauma and brain injury vs. non-brain injury populations due to potential neurocytoprotective effects [16]. Studies that included mixed population with some trauma or brain injured patients were classified as non-trauma and non-brain injury, respectively. The statistical analysis was conducted using Stata (Intercooled Version 11.2, StataCorp, College Station, TX, USA) and Comprehensive Meta-analysis (version 2.2.034, Biostat, USA, 2006).

Trial sequential analysis was undertaken using the Copenhagen Trial Unit software and assuming a two-sided conventional test boundary with a type I error of 5% and alpha-spending function based a priori on O'Brien-Fleming with 80% power to detect a 20% relative risk reduction. The control event rate was derived from the observed event rate from the meta-analysis of the primary outcome.

Results

The search identified 1994 potentially relevant trials. Of these, 21 trials with 5452 participants were included in the systematic review [10, 17–36]. The process of identifying eligible trials is provided in Fig. 1.

Characteristics of the included trials

The included trials were published between 1998 and 2018. They were conducted in Europe, North America, Australasia, and the Middle-East. Additional data for the primary outcome were received from three authors [30, 32, 33]. There was substantial variation in the type, dose and duration of ESA used (Table 1). Overall, the quality of the included studies was moderate, with 12 out of the 21 studies including one or more criteria judged to be at high risk of bias and all but one study had at least one domain of uncertain risk of bias (Table 2). A description of the rationale for each bias assessment is provided in eTable 1.

Mortality

The meta-analysis of in-hospital mortality included 16 studies with 4391 participants (Fig. 2). In-hospital mortality was lower in the ESA group (276 of 2187 patients, 12.6%) than the comparator group (339 out of 2204 patients, 15.4%), [relative risk (RR) 0.82, 95% CI 0.71–0.94, $P=0.006$]. There was no evidence of heterogeneity (I^2 0.0%), or publication bias on funnel plot (eFigure 2). The results were also similar to point estimate of the single study deemed at low risk of bias in all domains (RR 0.65 95% CI 0.42–1.02, $P=0.06$) [30]. Trial sequential analysis demonstrated that the required information size was reached and the cumulative z curve crossed the boundary for benefit, suggesting a true positive finding (eFigure 3).

The effect of ESA on in-hospital mortality was also similar for the seven studies exclusively enrolling patients with trauma, RR 0.64 (95% CI 0.47–0.89, $P=0.008$, I^2 0%), vs. the nine mixed or non-trauma-related studies, RR 0.87 (95% CI 0.74–1.02, $P=0.086$, I^2 0%) (test of interaction $P=0.254$) (eFigure 4). The results were also similar for the seven studies exclusively enrolling patients with brain injury RR 0.66 (95% CI 0.47–0.94, $P=0.188$, I^2 0%), vs. the nine mixed on non-brain-injury-related studies, RR 0.85 (95% CI 0.73–1.00, $P=0.05$, I^2 0%) (test of interaction $P=0.373$) (eFigure 5).

Meta-regression suggested no significant effect of age on the association between ESA therapy and in-hospital mortality (coefficient 0.01, 95% CI 0.03–0.04, $P=0.719$) (eFigure 6). Post-hoc meta-regression suggested a non-significant trend of increasing benefit of ESA therapy on mortality with increasing Acute Physiology and Chronic Health Evaluation (APACHE) score [coefficient −0.05 (95% CI −0.13–0.03, $P=0.206$)] (eFigure 7).

The meta-analysis of mortality after hospital discharge included 10 studies with 3469 participants (RR 0.94 95% CI 0.84–1.06, $P=0.33$, I^2 0%) (eFigure 8).

Secondary outcomes

There were seven studies including 3926 participants contributing to the meta-analysis of SAEs (eFigure 9). One trial with zero events in both treatment arms was excluded [23]. The RR of an SAE with ESA therapy was 1.11 (95% CI 0.94–1.31, $P=0.228$). Heterogeneity was high (I^2 66%). There were 12 studies including 3759 participants contributing to the meta-analysis of thromboembolic events (eFigure 10). Two additional studies with zero events in both treatment arms were excluded. The RR of a thromboembolic event with ESA therapy was 1.22 (95% CI 0.95–1.58, $P=0.086$, I^2 47%). The RR or SMD for secondary outcomes including RBC transfusion, Hb, ICU LOS, AMI and CVA are provided in Table 3. Other secondary outcomes identified prospectively were not reported in sufficient numbers for meta-analysis.

Discussion

Summary

In this systematic review and meta-analysis of 21 RCTs involving 5452 critically ill patients, ESA therapy decreased in-hospital mortality (RR 0.82, 95% CI 0.71–0.94, $P=0.006$). Although there was no heterogeneity and trial sequential analysis also suggested a true positive finding, only one trial was assessed as low risk of bias in all domains. Serious adverse events and thromboembolic events were increased in the ESA group. However, the results were not statistically significant, though

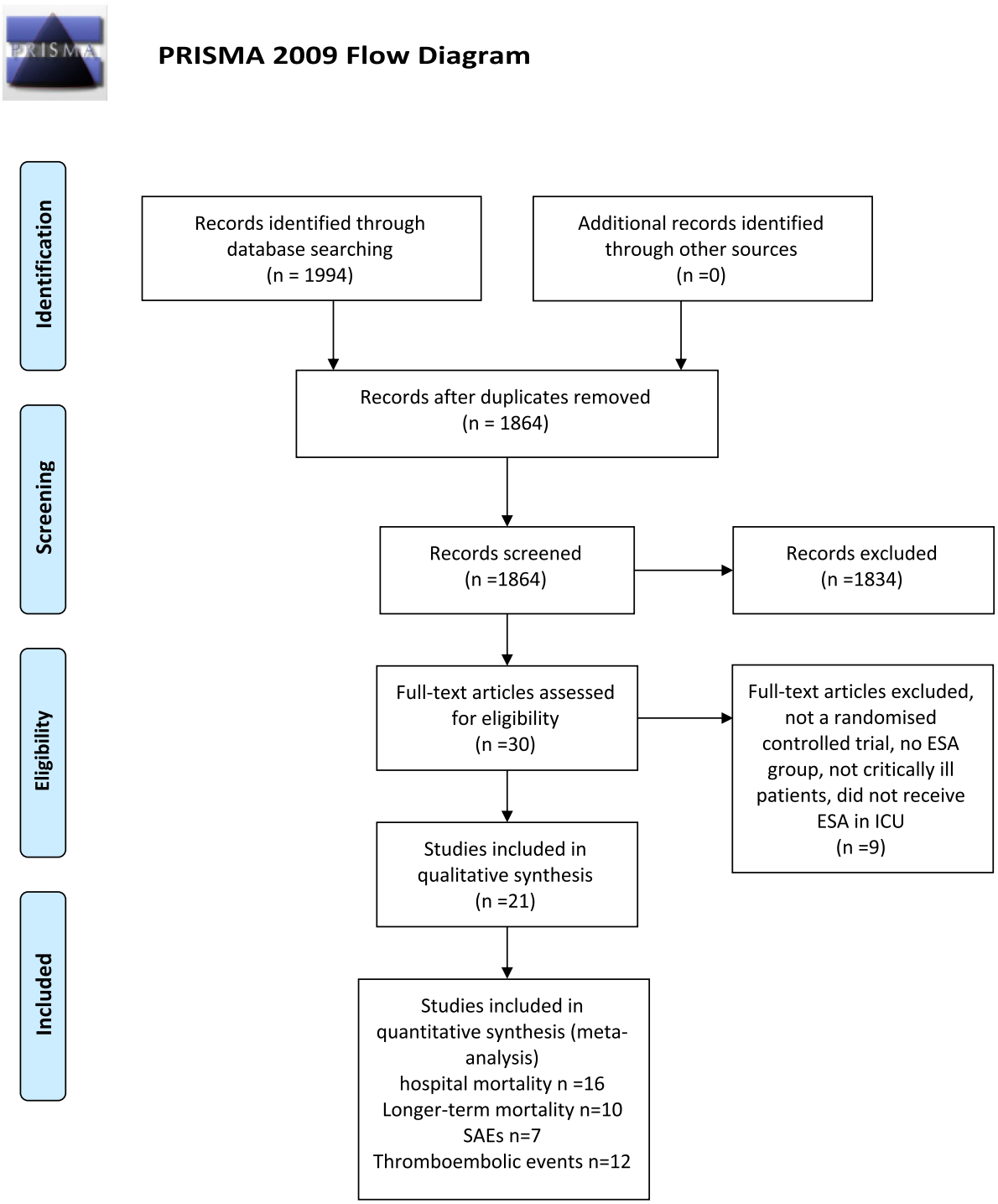


Fig. 1 Preferred reporting items for systematic reviews and meta-analyses study screening, inclusion and meta-analysis

Table 1 Description of included studies

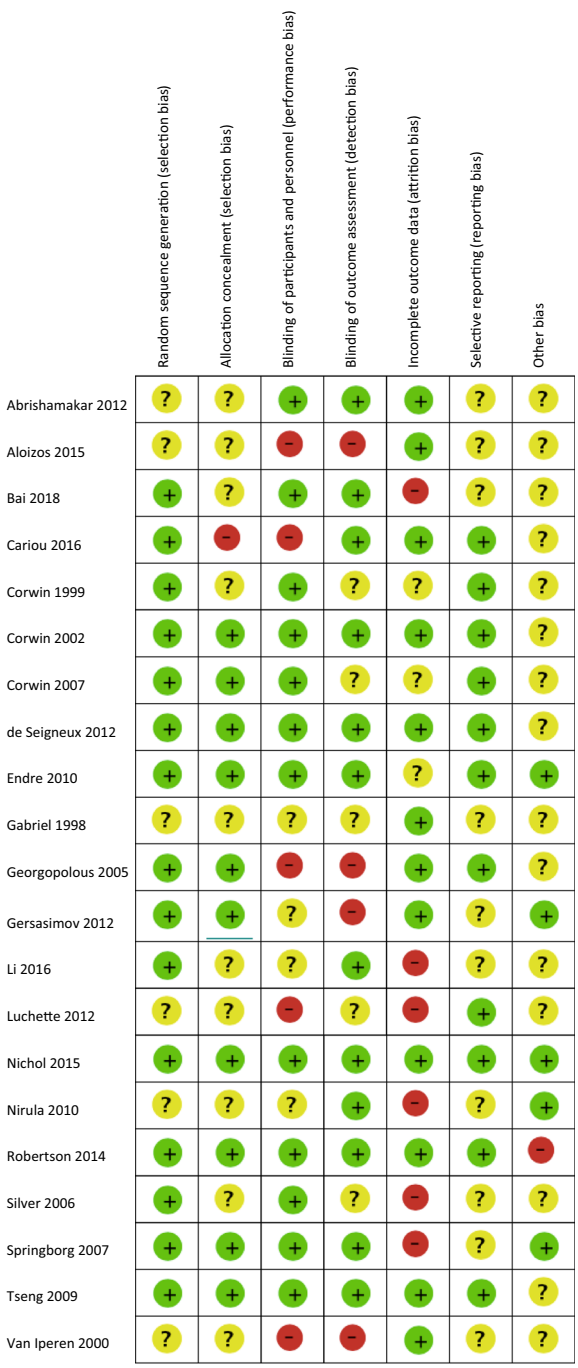
Name	Year	Population	ESA	Dose (units)	Dose schedule	Comparator	Location	*N*	Primary outcome	Follow-up (days)	Secondary outcomes
Abrishamkar	2012	TBI	Epo α	2000	Six doses in 2 weeks	0.9% NaCl	Iran	54	GCS and GOS	28	Hospitalisation, extubation
Aloizos	2015	TBI	rHuEPO	10,000	Daily for 7 days	Nil stated	Greece	42	GOS, GOS-E	183	6-Month mortality
Bai	2018	TBI	rHuEPO	6000	Five doses over 15 days	0.9% NaCl	China	120	GOS	70	Mortality 70 days, ADVERSE events
Cariou	2016	Cardiac arrest	Epo α	40,000	Five doses over 48 h	Nil stated	France	476	CPC	60	CPC, ICU and hospital mortality, adverse events
Corwin	1999	Mixed	rHuEPO	300/kg	Daily for 5 days, then alt. day for min 2 weeks	Placebo (not revealed)	USA	160	RBC transfusion	42	Nil stated
Corwin	2002	Mixed	rHuEPO	40,000	Weekly for at least three doses	Placebo (not revealed)	USA	1302	Transfusion independence	28	RBC transfusion, mortality, Hb
Corwin	2007	Mixed	Epo α	40,000	Three doses over 15 days	Placebo	USA	1460	RBC transfusion	140	RBC transfusion, Hb, mortality
de Seigneux	2012	Surgical	Epo α	40,000	Single dose	0.9% NaCl	Switzerland	60	Urinary NGAL	28	Renal function, cytokine Levels
Endre	2010	Mixed	Epo β	500/kg	Two doses in 24 h	0.9% NaCl	New Zealand	163	creatinine	90	Renal function, renal replacement therapy, mortality
Gabriel	1998	Mixed	rHuEPO	600/kg	Three doses weekly for 21 days	0.9% NaCl	Austria	21	Reticulocyte Blood Level	21	Erythropoietin serum concentrations, circulating, cytokine levels, red cell indices, iron metabolic indices, peripheral progenitor cells
Georgopoulos	2005	Mixed	rHuEPO	40,000	Three doses weekly for min 3 weeks	Nil stated	Greece	97	Hb and Hct	28	ICU LOS, cumulative mortality, adverse effects
Gerasimov	2012	Trauma	Epo α	40,000	One dose	Nil stated	Russia	78	RBC transfusions	29	Thrombotic events, ICU-free days, mortality
Li	2016	TBI	rHuEPO	100/kg	Five doses over 12 days	0.9% NaCl	China	159	Serum NSE[1], S-100 beta protein, GOS	90	Blood pressure, Hb, pneumonia, sepsis, VTE
Luchette	2012	Mixed	Epo α	40,000	Weekly dose based on Hb for 12 weeks	Placebo (not revealed)	USA	192	SF-36[2]	168	Anaemia, fatigue, functional independence measure, Hb
Nichol	2015	TBI	Epo α	40,000	Weekly for three doses	0.9% NaCl	Multiple	606	GOS-E	183	6-Month QoL assessment, six-month mortality, DVT, thrombotic events, cost effectiveness

Table 1 (continued)

Name	Year	Population	ESA	Dose (units)	Dose schedule	Comparator	Location	*N*	Primary outcome	Follow-up (days)	Secondary outcomes
Nirula	2010	TBI	EPO	40,000	One dose	0.9% NaCl	USA	23	S-100B, NSE concentration	5	ICU LOS, GCS at ICU discharge, in-hospital mortality
Robertson	2014	TBI	Epo α	500/kg	Three doses over 16 days	0.9% NaCl	USA	162	GOS-E, DRS[3]	183	DAR, mortality rate, ARDS, Infection
Silver	2006	Mixed	rHuEPO	40,000	Weekly dose for max 12 doses	Placebo (not revealed)	USA	86	RBC units transfused	84	RBC transfusion, mortality, Hb
Springborg	2007	SAH	Epo α	500/kg	Three doses in 48 h	0.9% NaCl	Denmark	73	GOS	183	Vasospasm, cerebral infarction, cerebral metabolism, jugular venous oximetry, drug safety
Tseng	2009	SAH	Epo β	30,000	Three doses every other day	0.9% NaCl	UK	80	Cerebral vasospasm	183	Modified Rankin Score, GOS, NISS
van Iperen	2000	Mixed	Epo α	300/kg	Dose every other day for five doses	Nil stated	Netherlands	24	Erythropoiesis and iron metabolism	21	ICU LOS, mortality

ICU intensive care unit, *LOS* length of stay, *ESA* erythropoietin-stimulating agent, *NSE* neuron-specific enolase, *Hb* hemoglobin, *Hct* hematocrit, *VTE* venous thromboembolism, *TBI* traumatic brain injury, *ARDS* acute respiratory distress syndrome, *SF-36* short form health assessment questionnaire, *GCS* glasgow coma scale, *GOS* glasgow outcome scale, *GOS-E* glasgow outcome scale extended, *DRS* disability rating scale, *CPC* cerebral performance category, *DAR* disability rating scale, *NISS* National Institute of Health Stroke Scale, *QoL* quality of life

Table 2 Risk of bias assessment



it is plausible that these findings may differ if trials that reported SAEs without reporting mortality were eligible for inclusion in our primary search.

Comparison to the published literature

A trial by French et al. found that ESA therapy decreased hospital mortality in trauma patients [37]. Our results expand on these findings and are consistent with the observation that immune dysregulation is a feature of critical illness generally rather than a specific population such as trauma. Indeed, our results were similar when evaluating the trauma vs. heterogeneous comparator subgroups and support the hypothesis that the beneficial effects of ESA therapy in critical illness may be mediated through anti-inflammatory and anti-apoptotic effects that target a common pathway of severe systemic inflammation that occurs in a broad range of critically ill patients. The erythropoietin receptor is expressed on immune cells as well as the parenchymal cells of several organ systems including myocardium, lung liver, kidneys and central and peripheral nerves. Animal models of ESA therapy consistently demonstrate anti-apoptotic and tissue protective effects at these sites [2]. However, mechanistic data in human, critically ill subjects are lacking. For example, our study found a positive, though not statistically significant, correlation between APACHE II score and benefit associated with ESA therapy. It is plausible that the APACHE II score, as a surrogate measure of the severity of immune dysregulation demonstrates an increasing immunomodulatory benefits of ESA therapy in patients with greater baseline immune dysfunction. Future studies are required to describe the relationship between erythropoietin concentration, receptor expression and inflammatory cytokine levels.

In addition to anti-apoptotic and anti-inflammatory effects, it is plausible that increased erythropoiesis leading to higher hemoglobin and lower requirement for RBC transfusion also contributed to improved outcomes. Although a large RCT by Corwin et al. was not able to demonstrate a significant decrease in RBC transfusion requirement, our study found that ESA therapy was associated with a significant increase in hemoglobin at hospital discharge and decrease in RBC transfusion requirement.

Mesgarpour et al. conducted a systematic review focusing primarily on the harms of off-label ESA therapy in critically ill patients. However, the review included observational studies and less severely ill patients such as patients admitted to the coronary care unit and patients with isolated intratrochanteric fractures, limiting assessment of causality in critically ill patients [38]. Nevertheless, the risk of death was similar to our study and there was a similar non-significant increased risk of adverse events. Given these findings, harm attributable to ESA therapy in critically ill patients remains uncertain. Recent larger RCTs have not demonstrated an increased risk of thrombosis and it appears as if the overall effect, based on mortality reduction, is beneficial [30].

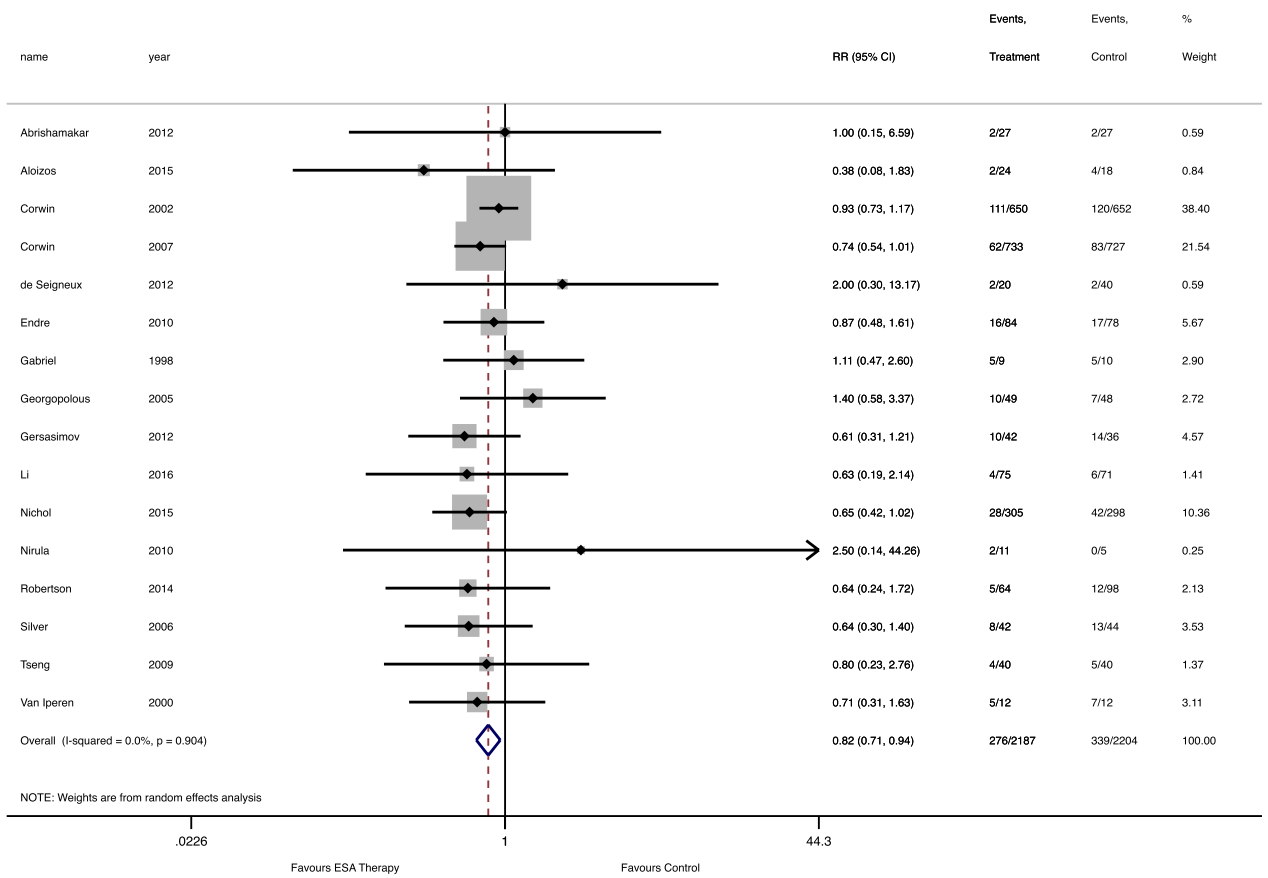


Fig. 2 Forrest plot for the association between erythropoietin-stimulating agent therapy and mortality

Table 3 Secondary outcomes

Outcome	Trials (*n*)	Participants (*n*)	Treatment effect (RR[a] or WMD[b])	95% CI	*P* value	I^2 (%)
Serious adverse events	7	3926	1.11[a]	0.94–1.31	0.228	66
Thromboembolic events	12	3759	1.17[a]	0.87–1.58	0.302	47
Transfused one or more RBC units	10	4075	0.88[a]	0.78–0.98	0.024	54
Hb at hospital discharge (g/dL)	6	1891	0.61[b]	0.24–0.97	0.001	68
ICU LOS (days)	4	182	− 4.88[b]	− 11.66–1.91	0.159	76
Acute myocardial infarction	6	3135	1.97[a]	0.84–4.61	0.120	15
Cerebrovascular accident	3	388	0.77[a]	0.41–1.45	0.414	0

RR relative risk, *WMD* weighted mean difference, *Hb* hemoglobin, *ICU* intensive care unit, *LOS* length of stay

Implications of the findings

Our findings support the need for further, high-quality studies investigating both the underlying mechanisms and the clinical outcomes associated with ESA therapy in heterogenous populations of critically ill patients. There is also an unmet need to investigate whether novel erythropoietin derivatives that preserve the beneficial effects of ESA therapy with theoretically lower risk of thromboembolism and other adverse effects provide additional benefit in critically ill patients [9].

Limitations

Of the 16 trials included in the analysis of the primary outcome, eight were at high risk of bias in one or

more domain and only one was at low risk of bias in all domains. Variations in the specific ESA, timing and dosing strategy prevented comparative analysis of regimes and the optimal dose and timing of ESA therapy remain uncertain. In the minority of trials with more than one intervention arm, a decision was made a priori to limit the analysis to the treatment arm with ESA alone and the higher ESA dose. The effect of this choice on the primary outcome remains uncertain. Trial sequential analysis suggests a true positive result, but it is likely that the study was underpowered for important secondary outcomes and analysis of covariates. The primary outcome of in-hospital mortality will not capture the effects of the intervention after hospital discharge. Some pre-defined secondary outcomes were not reported in sufficient numbers to allow meta-analysis. An alternative search based on broader eligibility criteria, and not based on outcome as ours did, may report on other aspects and result in different findings. Although TSA suggests a true positive finding, this only applies to a relative risk reduction of 20% and not smaller. Finally, meta-analysis does not assist in providing mechanistic data to help elucidate the underlying pathophysiological processes involved.

Conclusion

The available evidence from randomized controlled trials of mainly low or unclear quality suggests that in heterogenous populations of critically ill patients admitted to the ICU, ESA therapy may be associated with decreased in-hospital mortality, a finding that should be considered hypothesis generating. Although no difference in serious adverse events was found, a clinically important increase associated with ESA therapy cannot be excluded.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05686-y) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

The authors declare no conflict of interests in relation to this manuscript.

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