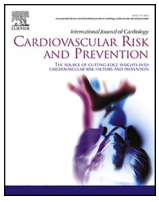
International Journal of Cardiology Cardiovascular Risk and Prevention 19 (2023) 200220

Contents lists available at ScienceDirect

International Journal of Cardiology Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention



Erythropoiesis-stimulating agents and cardiovascular mortality: A systematic review and meta-analysis of 17 studies and 372,156 hemodialysis patients

Zahra Karimi [a], Hadi Raeisi Shahraki [b], Abdollah Mohammadian-Hafshejani [c,*]

[a] Student Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran
[b] Department of Epidemiology and Biostatistics, School of Public Health, Shahrekord University of Medical Sciences, Shahrekord, Iran
[c] Modeling in Health Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

ARTICLE INFO

Handling editor: D Levy

Keywords:
Erythropoietin
Cardiovascular mortality
Hemodialysis
Meta-analysis

ABSTRACT

Introduction: Prior studies on the association between erythropoiesis-stimulating agents (ESAs) and cardiovascular mortality in hemodialysis patients have yielded conflicting findings. We aimed to clarify this relationship through a systematic review and meta-analysis of current evidence.

Methods: We comprehensively searched major databases for observational and interventional studies on ESA use and cardiovascular mortality in hemodialysis patients published from 1980 to September 2023. Pooled risk ratios (RR) with 95 % confidence intervals (CI) were calculated using random-effects models. Sources of heterogeneity were explored through subgroup analyses and meta-regression. The study data were analyzed using Stata 15 software.

Findings: Upon conducting the initial search, we extracted 792 articles and, after screening and considering the research criteria, 17 studies with 372,156 participants were included in the meta-analysis. Overall, ESA use was associated with a 27 % increased risk of cardiovascular mortality (RR 1.27, 95 % CI: 1.15–1.40, $p < 0.001$). This risk varied by geographical location, with RRs of 1.27 (95 % CI: 1.14–1.41; p-value$\leq$0.001) for America, 1.33 (95 % CI: 1.12–1.58; p-value = 0.001) for Asia, and 1.23 (95 % CI: 1.02–1.49; p-value = 0.028) for Europe. Importantly, a gender disparity was revealed, with studies involving a higher proportion of males showing greater risks (RR 1.51, 95 % CI: 1.25–1.83, $p < 0.001$) than female-predominant studies (RR 1.08, 95 % CI: 0.86–1.36, $p < 0.001$).

Conclusion: Our meta-analysis indicates ESA use is associated with heightened cardiovascular mortality in hemodialysis patients, especially in males. These findings have implications for optimizing dosing strategies while balancing efficacy and safety. Further research is warranted, particularly randomized controlled trials, to establish definitive ESA dosing guidelines.

1. Introduction

Chronic Kidney Disease (CKD) has emerged as a significant global health concern [1]. This condition is characterized by a progressive and irreversible decline in kidney nephrons, resulting in a functional capacity that is less than half of the normal level [1,2]. When kidney function falls below 10–15 % of the standard capacity, patients enter the final stage of End Stage Renal Disease (ESRD) and require kidney transplant, hemodialysis, or peritoneal dialysis for survival [3,4]. The incidence of ESRD is rapidly increasing worldwide, with the United States experiencing a tenfold rise in cases in recent years [5]. Notably, the number of patients receiving hemodialysis treatment globally is growing by approximately 7 % annually [6].

Despite the availability of dialysis treatments since the 1960s and numerous advancements in the field, the survival rate of dialysis patients remains lower than that of the general population [7]. In the United States, the average survival time on dialysis is eight years for individuals aged 40–44 and 4.5 years for those aged 60–64 [8]. Furthermore, each year of dialysis is associated with a 6 % increase in mortality risk for patients [9]. Anemia serves as a predictive factor for mortality in the majority of patients with advanced chronic renal failure. If left untreated, anemia can lead to pathophysiological disorders,

* Corresponding author.
E-mail address: mohammadian.a@skums.ac.ir (A. Mohammadian-Hafshejani).

https://doi.org/10.1016/j.ijcrp.2023.200220
Received 19 July 2023; Received in revised form 21 September 2023; Accepted 12 October 2023
Available online 18 October 2023

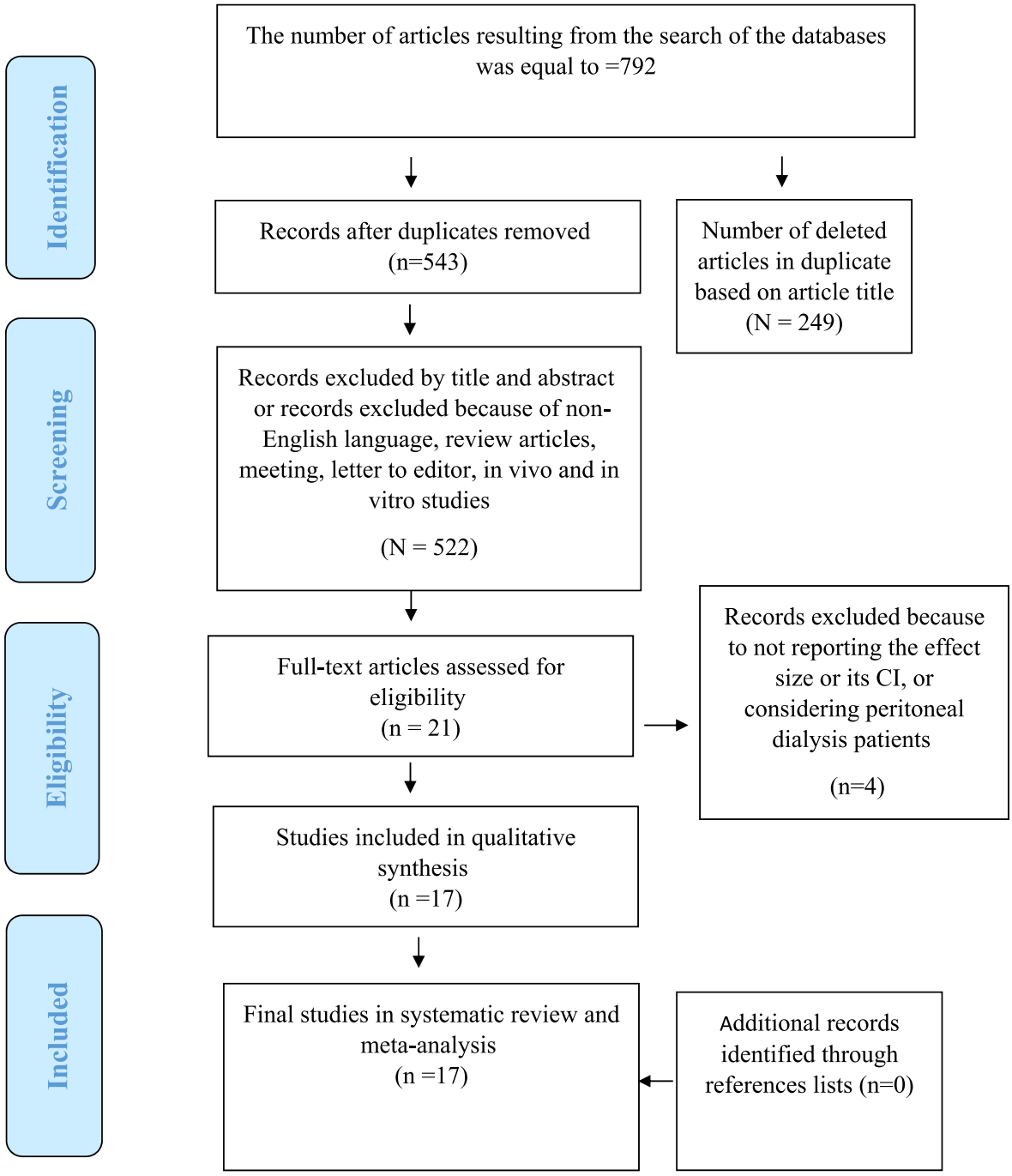


Fig. 1. Flowchart of selected studies for meta-analysis.

reduced tissue oxygenation, left ventricular hypertrophy, congestive heart failure, angina pectoris, and immune system deficiency [10]. Without proper treatment, hemoglobin levels decline, resulting in complications such as fatigue, decreased activity tolerance, weakness, and cardiac discomfort [11]. Previous studies have demonstrated the interrelationship between anemia, congestive heart failure, and CKD, with each condition exacerbating the others, establishing a detrimental cycle known as Cardio-renal anemia syndrome [12,13].

In individuals with and without anemia, the negative feedback system triggers the production of erythropoietin in response to a decrease in erythropoietin concentration caused by internal tissue hypoxia. However, this feedback mechanism is impaired in ESRD patients, resulting in erythropoietin levels approximately one-fourth of the expected level [2]. Consequently, the primary cause of anemia in CKD is the reduced production of erythropoietin [10]. As kidney function declines below 30 %, erythropoietin secretion decreases, ultimately leading to anemia [14]. In light of concerns regarding factors influencing anemia in hemodialysis patients, clinical guidelines in 2006 recommended the use of erythropoiesis-stimulating agents (ESAs) and iron agents [15]. However, high doses of ESAs may increase the risk of myocardial infarction, cardiovascular failure, and mortality in hemodialysis patients [16]. Clinical trial studies have shown that raising hemoglobin levels to the normal range through ESAs does not improve outcomes for these patients. Higher doses of ESAs in patients with higher target hemoglobin levels result in an increased risk of death and no improvement in quality of life compared to the group with lower target levels [1,17,18].

Numerous studies have been conducted worldwide to investigate the

Table 1
Characteristics of the studies included in the meta-analysis.

Number	Authors	Year	Study setting	Study design	Sample size	RR	95 % CI	Mean Follow up(month)	Quality score
1	J. Möcks [24]	2000	German	Retrospective Cohort	3111	0.82	0.44–1.66	12	8
2	Deborah L. Regidor [33]	2006	US	Prospective Cohort	58058	1.42	1.28–1.60	24	7
3	Elani Streja [19]	2008	US	Retrospective Cohort	32418	1.16	1.04–1.26	3	9
4	Joan Fort [25]	2010	Spanish	Prospective Cohort	2310	1.01	0.67–1.53	24	10
5	Xavier Cuevas [20]	2012	Spanish	Prospective Cohort	2310	1.35	1.07–1.71	24	10
6	Shingo Fukuma [21]	2012	Japan	Prospective Cohort	95460	1.61	1.23–2.11	12	10
7	Tetsuya Fujikawa [34]	2013	Japan	Prospective Cohort	2104	2.09	1.05–4.14	27.45	9
8	Marit M Suttorp [26]	2013	Netherland	Prospective Cohort	1013	1.04	0.7–1.56	60	10
9	Andreas Schneider [22]	2014	German	Prospective Cohort	1255	1.29	1.04–1.6	48	9
10	Shunji Shiohira [35]	2016	Japan	Prospective Cohort	375	3.81	1.68–8.04	36	9
11	Elani Streja [23]	2016	US	Retrospective Cohort	128598	1.26	1.16–1.38	60	10
12	Valeria Saglimbene [27]	2017	Italy	RCT	656	0.69	0.19–2.33	12	Low risk
13	Rafael Perez-Garcıa [32]	2017	Spanish	Retrospective Cohort	1679	2.38	1.32–4.29	27.7	8
14	Ko-Lin Kuo [36]	2018	Taiwan	Prospective Cohort	42230	0.98	0.91–1.05	41	10
15	Xiangxue Lu [37]	2020	China	Prospective Cohort	276	1.97	1.14–3.42	55	10
16	Takahiro Yajima [38]	2021	Japan	Retrospective Cohort	180	1.07	1.02–1.11	55.2	10
17	Hyang Yun Lee [39]	2022	Korea	Retrospective Cohort	123	2.8	1.20–6.50	24	10

*RoB 2.

relationship between ESAs intake and mortality from cardiovascular diseases. However, some of these studies suggest that ESAs intake leads to an increased risk of cardiovascular mortality [19–23], while others have not observed a significant association [24–27]. Extensive research into the effectiveness of ESAs has yielded inconsistent and, at times, contradictory findings, posing challenges for physicians and specialists in making informed decisions for their patients. Therefore, the objective of this study is to examine the relationship between ESAs administration and cardiovascular mortality in hemodialysis patients using a systematic review and meta-analysis methodology.

2. Material and method

2.1. Study design and population

This systematic review and meta-analysis included observational and interventional studies investigating the association between ESA use and cardiovascular mortality in hemodialysis patients worldwide. We included studies published from 1980 to September 2023.

2.2. Search strategies

We systematically searched major databases (Web of Science, Cochrane Library, PubMed, Embase, Scopus, Google Scholar) following PRISMA guidelines. Our search focused on erythropoietin exposure, cardiovascular mortality outcomes, in hemodialysis patients, using relevant Medical Subject Headings (MeSH) terms and keywords. No restrictions were placed on the study location, design, participants' age or gender. We adhered to the search guidelines of each database. Full search strategies for all databases are provided in supplementary files.

2.3. Selection criteria

We included clinical trials, cohort, case-control, and cross-sectional studies reporting the relationship between ESA use and cardiovascular mortality in hemodialysis patients. No restrictions were placed on study timing or location. We only included English-language studies on human participants that reported effect sizes as relative risk (RR) or odds ratio (OR) with 95 % confidence intervals (CI). Studies without accessible full texts after contacting authors and review articles, editorials, posters, and qualitative studies were excluded.

2.4. Specifications of study data collection tool

After collecting the articles, their bibliographic information and abstracts were entered into the Endnote version 8 reference management software. This software was used to identify and remove any duplicate papers. The titles of the remaining articles were carefully reviewed, followed by a thorough assessment of the titles, abstracts, and full texts to ensure their relevance to the study's purpose. Irrelevant items were removed. To ensure credibility, the process of searching, selecting, and collecting data from the articles was independently conducted by two researchers. In cases of disagreement, a third researcher was consulted to reach a consensus on the final selection of articles.

To collect information from the selected articles, an electronic form in the Excel environment was utilized. This form consisted of five sections: article information (title, first author, publication year, country of research, study type, and sample size), participant characteristics (average age and gender), details of the intervention and control groups (number of exposed and non-exposed groups, patient follow-up period, and receipt or non-receipt of ESAs), the effect size of the relationship between receiving ESAs and cardiovascular mortality (relative risk or odds ratio with a 95 % confidence interval), and a list of confounders adjusted in the study.

2.5. Quality appraisal

For the included randomized controlled trials (RCTs), we employed the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) to assess methodological quality and the risk of bias. This tool evaluates the risk of bias across five key domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. Each item was classified as having a "Low risk," "Some concerns," or "High risk" of bias [28].

In addition, we utilized the Newcastle Ottawa Scale (NOS) checklist to evaluate the quality of observational articles (cohort, case-control, and cross-sectional studies). This scale assesses articles based on the selection process, comparability, study design, and results. The selection process is evaluated in terms of sample representativeness, sample size, non-participation rates, and measurement tools. Comparability involves investigating confounders and other influencing factors. The study design and results are evaluated based on result evaluation and statistical tests. According to the NOS, articles are scored on a scale of zero (weakest study) to ten (strongest study). In this study, articles with a NOS score below 5 are classified as low-quality, articles with a score between 5 and 8 are classified as medium-quality, and articles with a score of 9 or higher are classified as high-quality [29].

2.6. Statistical analysis

To ensure the comprehensiveness and integrity of our meta-analysis, we employed various statistical methods. In cases where the effect size

Table 2
Adjusted variables to investigate the relationship between receiving ESAs and cardiovascular mortality of hemodialysis patients in the articles included in the study.

number	Publication first author	Year	Adjusted variables
1	J. Möcks [24]	2000	–
2	Deborah L. Regidor [33]	2006	-
3	Elani Streja [19]	2008	-
4	Joan Fort [25]	2010	-
5	Xavier Cuevas [20]	2012	Alcohol consumption; CKD etiology, dyslipidemia, previous cardiac arrhythmia, left ventricular hypertrophy, SBP before HD session; hemodialysis technique, dialysis time, glucose; potassium; iPTH; phosphorus- binder drugs, cardiovascular drugs, hypolipidemic drugs
6	Shingo Fukuma [21]	2012	Age, sex, time on dialysis therapy, post dialysis body weight, diabetes, history of cardiovascular disease, serum albumin level, and transferrin saturation.
7	Tetsuya Fujikawa [34]	2013	Age, PCR, albumin, CRP. Sex, ferritin, and 14 comorbidities
8	Marit M Suttorp [26]	2013	–
9	Andreas Schneider [22]	2014	Age and sex. Atorvastatin. 25(OH)D.
10	Shunji Shiohira [35]	2016	Age, serum albumin and C-reactive protein levels, and history of CVD
11	Elani Streja [23]	2016	Age, sex, race/ethnicity (Caucasian, African American, Hispanic, Asian, and others), marital status (married, divorced, single, and widowed), primary insurance (Medicare, Medicaid, private insurance, and others), comorbid conditions (see below), calendar quarter of cohort entry, and dialysis vintage (<6months, 6monthsto <24 months, 2to <5years, and ≥5 years), for which information was obtained from the USRDS. The following comorbidities were considered: diabetes mellitus, hypertension, ischemic heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, malignancy, no ambulatory state, and current smoking status. Hb level, serum albumin, creatinine, calcium, phosphorus, bicarbonate, total iron binding capacity, ferritin, white blood cell count, lymphocyte percentage, normalized protein nitrogen appearance (a metric of dietary protein intake), dialysis adequacy (single-pool *Kt/V*), and body mass index. Hb level was measured approximately twice per month. Most laboratory data were measured monthly, except for serum ferritin level that was measured at least quarter
12	Valeria Saglimbene [27]	2017	–
13	Rafael Perez-Garcıa [32]	2017	Age (years), CCI, VA, gender and BMI (km/m2). 'C-M' denotes case-mix adjusted. This model incorporates the demographics-adjusted model and data for CRP (mg/L), haemoglobin (g/dL), Kt (L) and iron dose (mg/month)
14	Ko-Lin Kuo [36]	2018	Age, sex, diabetes, hypertension, dialysis adequacy (Kt/V), eGFR at the start of dialysis (MDRD), white blood cell counts, the normalized protein catabolic rate (n PCR), serum albumin, cholesterol, triglyceride, hemoglobin, ferritin, transferrin saturation, calcium, phosphate, alkaline phosphatase, intact-PTH, uric acid, and intravenous iron use
15	Xiangxue Lu [37]	2020	Pre-dialysis serum albumin, pre-dialysis serum ferritin, serum transferrin saturation, pre-dialysis corrected calcium, phosphorus, high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglyceride.
16	Takahiro Yajima [38]	2021	Age, history of cardiovascular disease, creatinine, and C-reactive protein,
17	Hyang Yun Lee [39]	2022	Age, sex, and modified Charlson comorbidity index

was presented separately for different time or seasonal periods within studies, we utilized a fixed or random model meta-analysis approach. This approach allowed us to derive a total effect size from the provided values and incorporate it into our analysis. Additionally, for studies that did not explicitly report the effect size but provided sufficient information about the exposure and outcome variables, we estimated the effect size and its corresponding 95 % confidence interval. These estimated values were then included in the meta-analysis.

To assess the presence of heterogeneity among the included studies, we conducted statistical tests such as the Chi-square test and I2. These tests provided quantitative measures of heterogeneity and allowed us to determine the appropriate model for our analysis [30]. In our meta-analysis, the Chi-square test yielded a significant p-value ($p \leq 0.001$), and the I2 index indicated that 80.9 % of the heterogeneity could be attributed to differences between the results of different studies. Consequently, we employed a random-effect model.

To identify factors associated with heterogeneity in the results, we utilized the random meta-regression model. This model considered variables such as study sample size, article quality evaluation score, study design, average age of participants, follow-up period, place of study, and year of the study. Additionally, we conducted sensitivity analysis to assess the impact of excluding each individual study on the final results.

To evaluate publication bias, we employed funnel plots and conducted Begg's and Egger's tests. Furthermore, we utilized the trim-and-fill method, implemented through the Metatrim command in Stata software, to estimate the effect size of the relationship in missing studies [31]. All statistical analyses were performed using Stata statistical software (version 15.0, Stata Corp, College Station, TX), and a significance level of <0.05 was considered for this study.

3. Results

Fig. 1 illustrates the article selection process. Initially, we conducted electronic searches in the databases using Mesh keywords and Title/Abstract criteria, resulting in a total of 792 articles. After removing duplicates, 543 articles remained. Through careful examination of titles and abstracts, we excluded 522 articles for reasons such as non-English language, review articles, meetings, letters to the editor, in vivo or in vitro studies. Subsequently, we removed 2 articles that did not report the effect size, 1 article that lacked the confidence interval of the effect size, and 1 article that included peritoneal dialysis patients in addition to hemodialysis patients in the target group. Ultimately, we identified 17 articles suitable for inclusion in the current systematic review and meta-analysis. The reference lists of these articles were also reviewed, but no additional relevant studies were found.

3.1. Features of selected studies

A total of 17 studies were obtained to investigate the relationship between receiving ESAs and cardiovascular mortality in hemodialysis patients. The meta-analysis included a sample size of 372,156

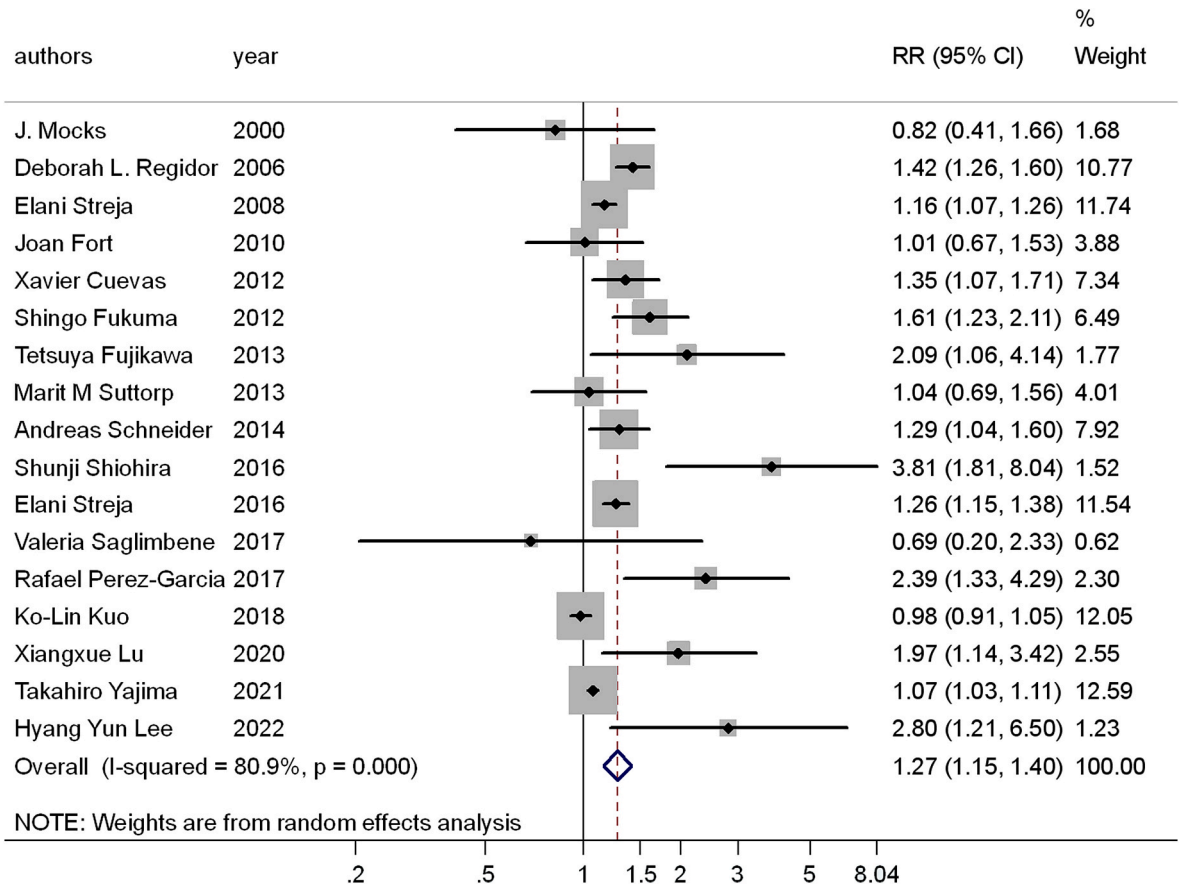


Fig. 2. Relationship between receiving ESAs and cardiovascular mortality in hemodialysis patients.

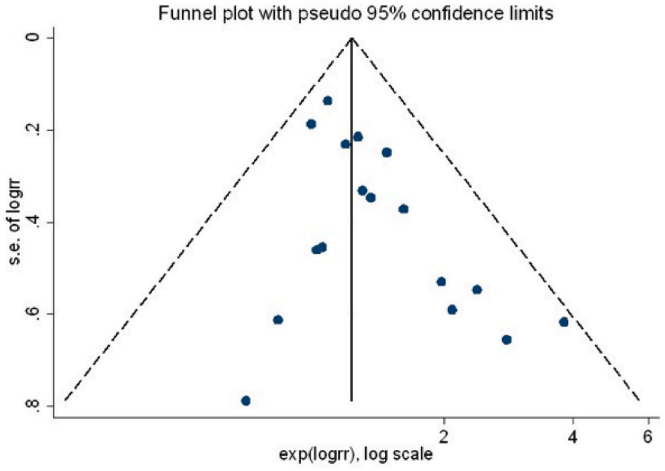


Fig. 3. Evaluation of publication bias in meta-analysis.

participants. Table 1 provides an overview of the characteristics of the studies included in the analysis. Geographically, 7 studies were conducted in Europe with 12,334 participants [20,22,24–27,32], 3 studies were conducted in the US with 219,074 participants [19,23,33], and 7 studies were conducted in Asia with 140,748 participants [21,34–39]. Out of the total studies, 16 were cohort studies [19,21–27,32–39], and 1 was a randomized controlled trial (RCT) [27] (Tables 1 and 2).

3.2. Evaluation of the relationship between receiving ESAs and cardiovascular mortality in hemodialysis patients

Meta-analysis revealed that hemodialysis patients who received erythropoiesis-stimulating agents (ESAs) had a 27 % higher risk of cardiovascular mortality compared to those non-receiving or receiving basal level of ESAs (risk ratio 1.27, 95 % CI: 1.15–1.40; $P < 0.001$) (Fig. 2).

3.3. Evaluation of publication bias

Evidence of publication bias was detected through Egger's test ($P = 0.012$), but not Begg's test ($P = 0.592$) (Fig. 3). After adjusting for potentially missing studies using trim-and-fill analysis, the risk ratio was attenuated to 1.24 (95 % CI: 1.12–1.37; $P \leq 0.001$), but remained statistically significant (Fig. 4).

3.4. Meta-regression and sensitivity analysis

To explore the observed heterogeneity among the results of the included studies in this meta-analysis, we conducted a random meta-regression analysis. Several factors were considered, including the study sample size, quality assessment score, study design (randomized controlled trials or cohort studies), average participant age, follow-up period, geographical location of the studies, and the year of study. The analysis revealed that the year of study (p-value = 0.092), quality assessment score (p-value = 0.137), and study design (p-value = 0.133) significantly influenced the observed heterogeneity (Table 3).

Furthermore, we performed a sensitivity analysis by systematically excluding each study from the analysis in consecutive runs. Notably, the final estimate of the relative risk (RR) remained largely unchanged,

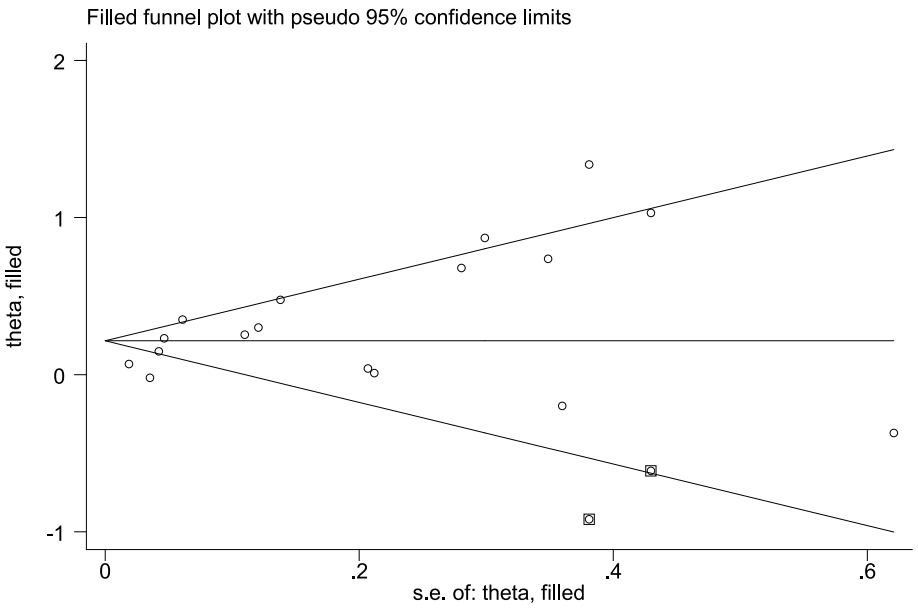


Fig. 4. Estimate the amount of effect size in the missing studies.

Table 3
Meta-regression results in the studies that investigate the relationship between receiving ESAs and cardiovascular mortality in the hemodialysis patients.

Meta-regression REML estimate of between-study variance					Number of obs = 17	
% residual variation due to heterogeneity					Taue2 = 0.0829	
Proportion of between—study variance explained					I-suuared_res = 81.95	
Joint test for all covariates					Model F [7,16] = 1.01	
With Knapp-Hartung modification					Prob>F = 0.4805	
logor	Coef.	Std. Err.	t	p>|t|	[95 % Conf. Interval]	
Year	.0649007	.0344502	1.88	0.092	−.013031	.1428324
Quality Assessment Score	−.2179692	.1335103	−1.63	0.137	−.5199905	.0840521
Study design	−1.233883	.7479469	−1.65	0.133	−2.925857	.4580902
Sample size	1.32e-06	3.61e-06	0.37	0.722	−6.83e-06	9.48e-06
Average participant age	−.0027308	.2781639	−0.01	0.992	−.6319814	.6265197
Geographical location	.0787102	.1870765	0.42	0.684	−.3444861	.5019066
Follow-up period	−.0098762	.0064309	−1.54	0.159	−.024424	.0046716
_cons	−126.9593	68.31878	−1.86	0.096	−281.5071	27.58852

Table 4
Sensitivity analysis of the relationship between receiving ESAs and cardiovascular mortality in the hemodialysis patients.

Study omitted	YEAR	RR (95 % CI)
J. Möcks [24]	2000	1.28 (1.16–1.41)
Deborah L. Regidor [33]	2006	1.25 (1.13–1.37)
Elani Streja [19]	2008	1.30 (1.16–1.45)
Joan Fort [25]	2010	1.28 (1.16–1.42)
Xavier Cuevas [20]	2012	1.27 (1.14–1.40)
Shingo Fukuma [21]	2012	1.25 (1.13–1.38)
Tetsuya Fujikawa [34]	2013	1.26 (1.14–1.39)
Marit M Suttorp [26]	2013	1.28 (1.16–1.42)
Andreas Schneider [22]	2014	1.27 (1.15–1.41)
Shunji Shiohira [35]	2016	1.24 (1.13–1.37)
Elani Streja [23]	2016	1.28 (1.15–1.42)
Valeria Saglimbene [27]	2017	1.28 (1.16–1.40)
Rafael Perez-Garcıa [32]	2017	1.25 (1.13–1.38)
Ko-Lin Kuo [36]	2018	1.32 (1.19–1.47)
Xiangxue Lu [37]	2020	1.25 (1.14–1.38)
Takahiro Yajima [38]	2021	1.33 (1.17–1.50)
Hyang Yun Lee [39]	2022	1.26 (1.14–1.38)
Combined		1.27 (1.15–1.40)

confirming the robustness of the meta-analysis results. For more detailed information, please refer to Table 4 and Fig. 5.

3.5. Subgroup analysis

To explore the relationship between receiving ESAs and cardiovascular mortality in hemodialysis patients, we conducted a subgroup analysis based on various study variables including sample size, duration of study, study design, geographical location, gender ratio, average age of participants, follow-up period, and quality assessment score. We observed that compared to the non-receiving group or group receiving basal level of ESAs, the RR of cardiovascular mortality in the receiving ESAs group remained significant across different geographical regions, including American (RR 1.27, 95 % CI 1.14–1.41; $P \leq 0.001$), Asian (RR 1.33, 95 % CI: 1.12–1.58; $P = 0.001$), and European (RR 1.23, 95 % CI: 1.02–1.49; $P = 0.028$) countries. The risk was higher in studies where the gender ratio (male/female) was ≥ 1 (RR 1.51, 95 % CI: 1.25–1.83; $P \leq 0.001$) versus <1 (RR 1.08, 95 % CI: 0.86–1.36; $P = 0.511$). It was similar between age groups, with a RR of 1.27 (95 % CI: 1.10–1.47; $P = 0.001$) for studies with average age <60 years and 1.28 (95 % CI: 1.12–1.45; $P \leq 0.001$) for ≥ 60 years. See Table 5 for a full overview of subgroup analysis results.

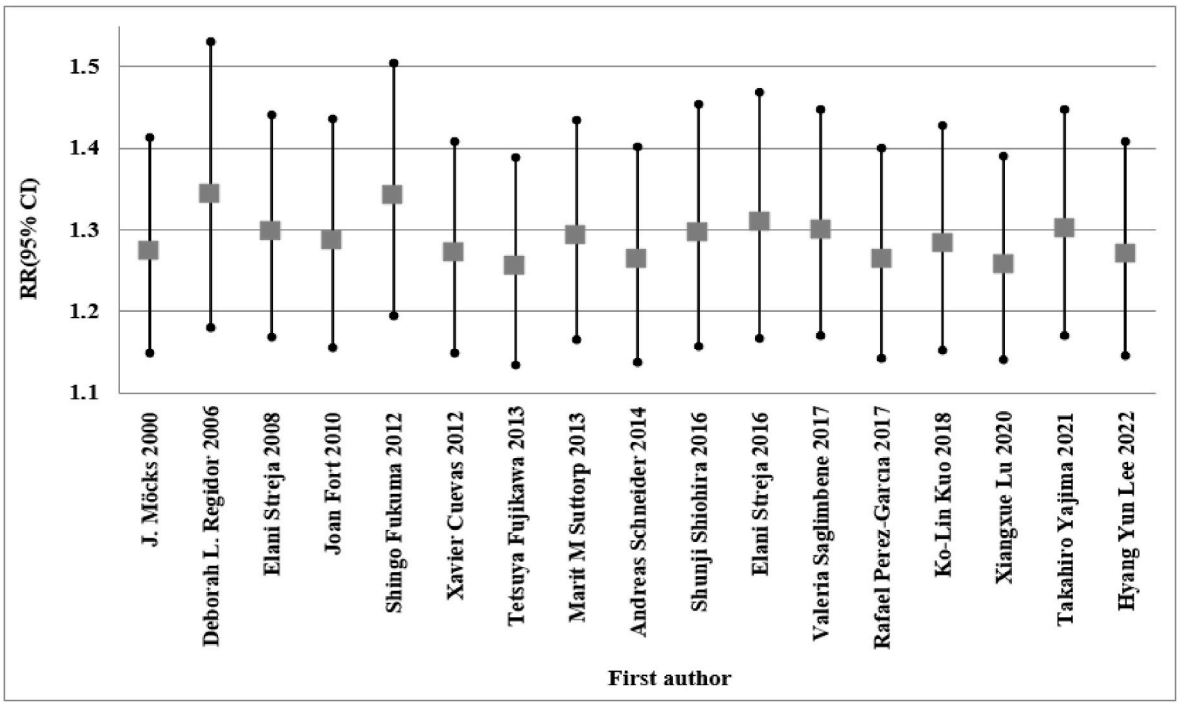


Fig. 5. Sensitivity analysis of the relationship between receiving ESAs and cardiovascular mortality in hemodialysis patients.

Table 5
Subgroup analysis in the relationship between receiving ESAs and cardiovascular mortality in hemodialysis patients.

Features of Studies		Number of studies	I^2	RR (95 % CI)	P-value
Gender ratio (M/Female)	Less than one	3	89.6	1.08 (0.86–1.36)	0.511
	Equal to or more than one	11	83.1	1.51 (1.25–1.83)	<0.001
Follow-up period	Equal to or less than 2 years	8	61.3	1.30 (1.12–1.51)	<0.001
	More than 2 years	9	83.2	1.24 (1.09–1.41)	0.001
Geographical location	America	3	73.5	1.27 (1.14–1.41)	<0.001
	Europe	7	35.2	1.23 (1.02–1.49)	0.028
	Asia	7	84.8	1.33 (1.12–1.58)	0.001
The time studying	2015 and before	9	52.1	1.29 (1.15–1.44)	<0.001
	2016 and after	8	85.1	1.26 (1.08–1.46)	0.003
Sample size	Equal to or less than 2000	8	77.3	1.52 (1.16–2.0)	0.003
	More than 2000	9	83.5	1.24 (1.09–1.41)	0.001
Quality Assessment Score	Medium	3	62.6	1.45 (0.94–2.24)	0.096
	High	14	78.2	1.23 (1.12–1.36)	<0.001
Average participant age	Less than 60 years	6	61.3	1.27 (1.10–1.47)	0.001
	Equal to or more than 60	11	82.4	1.28 (1.12–1.45)	<0.001
Study design	Clinical Trial	1	0	0.69 (0.20–2.33)	0.55
	Cohort	16	82.8	1.28 (1.16–1.41)	<0.001

4. Discussion

In this systematic review and meta-analysis, which evaluated the relationship between ESAs and the risk of cardiovascular mortality, most studies reported an increase in the risk of mortality due to exposure to the drug in question. The study included 17 articles, which involved more than 372,000 people in 9 countries from all over the world. This meta-analysis found a significant 27 % increased risk of cardiovascular mortality associated with ESA use. The risk was consistent across studies from Europe, the United States, and Asia.

Costa NA et al. conducted a study entitled "Relationship between response to erythropoietin and mortality" in the United States, involving 36,450 hemodialysis patients. The findings indicated that patients receiving higher doses of erythropoiesis-stimulating agent (75,000, 100,000, and 200,000 U/week, respectively) had increased mortality risks of 1.85 (1.55–2.23), 1.89 (1.53–2.3), and 2.07 (1.46–2.95) [40]. A study by Cuevas X et al. investigated the risk factors related to cardiovascular morbidity and mortality in Spanish hemodialysis patients and revealed a higher mortality risk in individuals receiving higher doses of erythropoietin [20]. Prez-García R et al. explored increased mortality in hemodialysis patients receiving high doses of ESA drugs within a sample of 1679 subjects. Their study demonstrated that Kaplan-Meier survival curves exhibited a significant increase in the risk of mortality among patients treated with high doses of ESAs (more than 8127.4 U/week). The application of a multivariate Cox regression model in this study revealed that a high dose of ESA independently predicted cardiovascular mortality and mortality from all causes [32], which aligns with the results of the present study. Fujikawa T et al. and Shiohira S et al. also reported that the use of high doses of erythropoietin, compared to standard doses, increased the risk of cardiovascular mortality [34,35]. Another American study demonstrated that receiving a weekly dose of ESA ≥30,000 U/week raised the risk of cardiovascular mortality by 44 % [23]. Regidor DL et al. found that hemodialysis patients requiring higher ESA doses to maintain normal hemoglobin levels faced a greater risk of death [33]. Similarly, a US study indicated significantly higher odds ratio estimates for ESA doses exceeding 18,000 U/week compared to doses below 6000 U/week, and weekly ESA doses ≥30,000 U/week

were associated with a 52 % increased risk of mortality [23]. The lower survival rates observed in patients requiring high ESA doses but failing to achieve the hemoglobin goal may be attributed to underlying pathologies such as inflammation or malnutrition. Monitoring the response to ESA therapy can aid in identifying this vulnerable population. Zhang Y et al. identified ESA dose as an independent predictor of mortality, even after adjusting for hematocrit values and other variables [41]. Although the results of Fort J et al.'s research with a 2-year follow-up period demonstrated the protective role of ESA in mortality, they observed that this protective effect diminished with increasing drug dosage [25]. Furthermore, Saglimbene V et al. conducted a clinical trial study comparing low and high doses of ESA in hemodialysis patients. They reported that receiving a high dose, compared to a low dose, had a non-significant effect against the occurrence of fatal heart attacks at 0.69 (0.19–2.33) [27]. These findings are inconsistent with the results of the present study.

This meta-analysis has limitations typical of observational data, including potential residual confounding. The lack of randomized controlled trials is another weakness. However, multiple sensitivity and subgroup analyses demonstrated the robustness of the observed association. Additional high-quality studies are still needed to clarify the relationship between ESA dose and cardiovascular mortality risk in hemodialysis patients. Mechanistic studies on the biological effects of ESAs are also warranted.

5. Conclusion

In conclusion, this large meta-analysis indicates that ESA therapy, particularly at higher doses, is associated with increased cardiovascular mortality in hemodialysis patients. Conservative ESA dosing protocols are appropriate given the evidence of harm at higher doses. Further research can help refine the risk-benefit profile of ESAs for managing anemia in this vulnerable population.

Funding source

We received support for this work from the research deputy of Shahrekord University of Medical Sciences in Iran, with grant number 6365 and ethical code IR.SKUMS.REC.1401.097.

Data availability

All relevant data are within the paper and its Supporting **information files**.

Registration and protocol

This study has not been previously registered. Also, the study implementation protocol has not been published before.

Author's contributions

Zahra Karimi contributed to Conceptualization, Writing – original draft, and Investigation. Hadi Raeisi contributed to Writing – original draft, Visualization, reviewing, and editing. Abdollah Mohammadian-Hafshejani contributed to Data curation, Writing – original draft, preparation, Visualization, Investigation, Project administration, Validation, reviewing, editing, Methodology, and Software.

Declaration of competing interest

There is no conflict of interest in this study.

Acknowledge

We acknowledge that the project leading to the publication of this paper is fully funded by the research deputy of Shahrekord University of Medical Sciences in Iran, with grant number 6365 and ethical code IR.SKUMS. REC.1401.097.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2023.200220.

References

[1] M. Mohammadian, H. Salehiniya, S. Khazaei, A. Mohammadian-Hafshejani, Erythropoietin dose and survival of hemodialysis patients, Biomed. Res. Therapy 4 (7) (2017) 1432–1434.
[2] M.Z.E. Khodaverdi, S.N. Mousavinasab, S. Khodaverdi, H.R. Amirmoghadami, J. Ahmadi, Evaluation of the influence of intravenous carnitine on hemoglobin and hematocrit levels in End stage chronic renal failure patients under hemodialysis, J. Zanjan Univ. Med. Sci. 18 (73) (2010) 58–66.
[3] A.S. Levey, J. Coresh, K. Bolton, B. Culleton, K.S. Harvey, T.A. Ikizler, et al., K/DOQI clinical practice guidelines for chronic kidney disease, Am. J. Kidney Dis. 39 (2) (2002). SUPPL 1.
[4] M.A. Abbasi, G.M. Chertow, Y.N. Hall, End-stage renal disease, Clin. Evid. 2010 (2010).
[5] US Department of Health Human Services, Kidney Disease Statistics for the United States, National Kidney and Urologic Diseases Information Clearinghouse, National Institutes of Health, Bethesda, MD, 2011.
[6] M.J. Lysaght, Maintenance dialysis population dynamics: current trends and long-term implications, J. Am. Soc. Nephrol. 13 (suppl 1) (2002) S37–S40.
[7] S.W. Murphy, R.N. Foley, B.J. Barrett, G.M. Kent, J. Morgan, P. Barré, et al., Comparative mortality of hemodialysis and peritoneal dialysis in Canada, Kidney Int. 57 (4) (2000) 1720–1726.
[8] A.J. Collins, R.N. Foley, C. Herzog, B.M. Chavers, D. Gilbertson, A. Ishani, et al., Excerpts from the US renal data system 2009 annual data report, Am. J. Kidney Dis.: the off. J. National Kidney Foundation 55 (1 Suppl 1) (2010) S1.
[9] G.M. Chertow, K.L. Johansen, N. Lew, J.M. Lazarus, E.G. Lowrie, Vintage, nutritional status, and survival in hemodialysis patients, Kidney Int. 57 (3) (2000) 1176–1181.
[10] F.N.M. Nazemian, Comparison of the results of anemia treatment with erythropoietin in patients undergoing hemodialysis and peritoneal dialysis, Med. J. Mashad Univ. Med. Sci. 49 (94) (2007) 351–356.
[11] H.D.S. Khalili, S. Seifi, M. Hadjibabaie, S. Shafiei, Erythropoietin utilization evaluation and two brand products comparison, eprex and eposim, Tehran Univ. Med. J. 64 (2) (2006) 133–140.
[12] T. Hayashi, N. Joki, Y. Tanaka, M. Iwasaki, S. Kubo, A. Matsukane, et al., Resistance to erythropoiesis-stimulating agents in pre-dialysis and post-dialysis mortality in Japanese incident hemodialysis patients, Blood Purif. 47 (Suppl 1) (2019) 31–37. Suppl 2.
[13] D. Silverberg, Outcomes of Anaemia Management in Renal Insufficiency and Cardiac Disease, vol. 18, Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 2003, pp. ii7–12. Suppl 2.
[14] H. Noshad, Blood pressure increase after erythropoietin injection in hemodialysis and predialysis patients, Iranian J. kidney diseases 7 (3) (2013) 220–225.
[15] H. Yokoyama, T. Kawaguchi, T. Wada, Y. Takahashi, T. Higashi, S. Yamazaki, et al., Biocompatibility and permeability of dialyzer membranes do not affect anemia, erythropoietin dosage or mortality in Japanese patients on chronic non-reuse hemodialysis: a prospective cohort study from the J-DOPPS II study, Nephron Clin. Pract. 109 (2) (2008) c100–c108.
[16] Y. Sakaguchi, T. Hamano, A. Wada, I. Masakane, Types of erythropoietin-stimulating agents and mortality among patients undergoing hemodialysis, J. Am. Soc. Nephrol. : JASN (J. Am. Soc. Nephrol.) 30 (6) (2019) 1037–1048.
[17] A.K. Singh, L. Szczech, K.L. Tang, H. Barnhart, S. Sapp, M. Wolfson, et al., Correction of anemia with epoetin alfa in chronic kidney disease, N. Engl. J. Med. 355 (20) (2006) 2085–2098.
[18] M.A. Pfeffer, E.A. Burdmann, C.Y. Chen, M.E. Cooper, D. de Zeeuw, K.U. Eckardt, et al., A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease, N. Engl. J. Med. 361 (21) (2009) 2019–2032.
[19] E. Streja, C.P. Kovesdy, S. Greenland, J.D. Kopple, C.J. McAllister, A.R. Nissenson, et al., Erythropoietin, iron depletion, and relative thrombocytosis: a possible explanation for hemoglobin-survival paradox in hemodialysis, Am. J. Kidney Dis. : the off. Journal. National Kidney Foundation 52 (4) (2008) 727–736.
[20] X. Cuevas, F. García, A. Martín-Malo, J. Fort, F. Lladós, J. Lozano, et al., Risk factors associated with cardiovascular morbidity and mortality in Spanish incident hemodialysis patients: two-year results from the ANSWER study, Blood Purif. 33 (1–3) (2012) 21–29.
[21] S. Fukuma, T. Yamaguchi, S. Hashimoto, S. Nakai, K. Iseki, Y. Tsubakihara, et al., Erythropoiesis-stimulating agent responsiveness and mortality in hemodialysis patients: results from a cohort study from the dialysis registry in Japan, Am. J. Kidney Dis. 59 (1) (2012) 108–116.
[22] A. Schneider, L. Gutjahr-Lengsfeld, E. Ritz, H. Scharnagl, G. Gelbrich, S. Pilz, et al., Longitudinal assessments of erythropoietin-stimulating agent responsiveness and the association with specific clinical outcomes in dialysis patients, Nephron Clin. Pract. 128 (1–2) (2014) 147–152.

[23] E. Streja, J. Park, T.Y. Chan, J. Lee, M. Soohoo, C.M. Rhee, et al., Erythropoietin dose and mortality in hemodialysis patients: marginal structural model to examine causality, Int. J. nephrol. 2016 (2016), 6087134.
[24] J. Mocks, Cardiovascular mortality in haemodialysis patients treated with epoetin beta - a retrospective study, Nephron 86 (4) (2000) 455–462.
[25] J. Fort, X. Cuevas, F. García, R. Pérez-García, F. Lladós, J. Lozano, et al., Mortality in incident haemodialysis patients: time-dependent haemoglobin levels and erythropoiesis-stimulating agent dose are independent predictive factors in the ANSWER study, Nephrol. Dial. Transplant. 25 (8) (2010) 2702–2710.
[26] M.M. Suttorp, T. Hoekstra, J.I. Rotmans, I. Ott, M. Mittelman, R.T. Krediet, et al., Erythropoiesis-stimulating agent resistance and mortality in hemodialysis and peritoneal dialysis patients, BMC Nephrol. 14 (1) (2013) 1–10.
[27] V. Saglimbene, S.C. Palmer, J.C. Craig, M. Ruospo, A. Nicolucci, M. Tonelli, et al., Low versus high dose erythropoiesis-stimulating agents in hemodialysis patients with anemia: a randomized clinical trial, PLoS One 12 (3) (2017), e0172735.
[28] J.A.C. Sterne, J. Savović, M.J. Page, R.G. Elbers, N.S. Blencowe, I. Boutron, et al., RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ 366 (2019) l4898.
[29] M.Z.M. Adib-Hajbaghery, The barriers to patient education from the viewpoint of nurses in Iran: a systematic review, Nurs Midwifery J. 15 (7) (2017) 544–558.
[30] F. Barili, A. Parolari, P.A. Kappetein, N. Freemantle, Statistical Primer: heterogeneity, random- or fixed-effects model analyses? Interact. Cardiovasc. Thorac. Surg. 27 (3) (2018) 317–321.
[31] L. Shi, L. Lin, The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses, Medicine 98 (23) (2019), e15987.
[32] R. Írez-García, J. Varas, A. Cives, A. Martín-Malo, P. Aljama, R. Ramos, et al., Increased mortality in haemodialysis patients administered high doses of erythropoiesis-stimulating agents: a propensity score-matched analysis, Nephrol. Dial. Transplant. 33 (4) (2018) 690–699.
[33] D.L. Regidor, J.D. Kopple, C.P. Kovesdy, R.D. Kilpatrick, C.J. McAllister, J. Aronovitz, et al., Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients, J. Am. Soc. Nephrol. 17 (4) (2006) 1181–1191.
[34] T. Fujikawa, Y. Ikeda, S. Fukuhara, T. Akiba, T. Akizawa, K. Kurokawa, et al., Time-dependent resistance to erythropoiesis-stimulating agent and mortality in hemodialysis patients in the Japan dialysis outcomes and practice patterns study, Nephron Clin. Pract. 122 (1–2) (2013) 24–32.
[35] S. Shiohira, K. Tsuchiya, H. Kataoaka, M. Okazaki, M. Komatsu, T. Naganuma, et al., Relationship between variations in time-dependent response to erythropoiesis-stimulating agents and mortality in hemodialysis patients: a single-center study, Ren. Replace Ther. 2 (2016) 10.
[36] K.L. Kuo, S.C. Hung, W.C. Tseng, M.T. Tsai, J.S. Liu, M.H. Lin, et al., Association of anemia and iron parameters with mortality among patients undergoing prevalent hemodialysis in taiwan: the AIM - HD study, J. Am. Heart Assoc. 7 (15) (2018), e009206.
[37] X.X. Lu, J.L. Zhang, S.X. Wang, Q. Yu, H. Li, High erythropoiesis resistance index is a significant predictor of cardiovascular and all-cause mortality in Chinese maintenance hemodialysis patients, Mediat. Inflamm. (2020) 2020.
[38] T. Yajima, K. Yajima, H. Takahashi, Association of the erythropoiesis-stimulating agent resistance index and the geriatric nutritional risk index with cardiovascular mortality in maintenance hemodialysis patients, PLoS One 16 (2021).
[39] H.Y. Lee, S.-W. Suh, J.H. Hwang, J. Shin, Responsiveness to an erythropoiesis-stimulating agent is correlated with body composition in patients undergoing chronic hemodialysis, Front. Nutr. 9 (2022).
[40] N.A. Costa, A.V. Kshirsagar, L. Wang, R.K. Detwiler, M.A. Brookhart, Pretransplantation erythropoiesis-stimulating agent hyporesponsiveness is associated with increased kidney allograft failure and mortality, Transplantation 96 (9) (2013) 807–813.
[41] Y. Zhang, M. Thamer, K. Stefanik, J. Kaufman, D.J. Cotter, Epoetin requirements predict mortality in hemodialysis patients, Am. J. Kidney Dis. 44 (5) (2004) 866–876.