Therapeutic targets for the anemia of predialysis chronic kidney disease: a meta-analysis of randomized, controlled trials

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ABSTRACT

Anemia is one of the major complications in predialysis patients with chronic kidney disease (CKD). A clearer cognition of the prognostic impact of hemoglobin (Hb) or hematocrit (Hct) target on the outcomes of predialysis patients with CKD is significant. This article aims to establish the suitable hemoglobin target to provide clinical guidance. MEDLINE, EmBase, the Cochrane Library and other databases were searched with both MeSH terms and keywords to gather researches that assessed all-cause mortality, stroke, treatment of renal replacement, and transfusion. The meta-analysis was accomplished via Revman 5.3 version. Totally, 13 eligible studies involving 7606 patients were included. There was a significantly lower risk of transfusion (risk ratio (RR) 0.59, 95% CI 0.52 to 0.67; p<0.00001) in the higher hemoglobin group than in the lower one. However, no significant difference was found in all-cause mortality (RR 1.10, 95% CI 0.98 to 1.23; p=0.11), stroke (RR 1.32, 95% CI 0.82 to 2.10; p=0.25) and treatment of renal replacement including hemodialysis, peritoneal dialysis and renal transplant (RR 1.08, 95% CI 0.95 to 1.22; p= 0.23) between the higher hemoglobin group and the lower one. The results favor the higher hemoglobin target. To target the higher hemoglobin when treating predialysis patients with CKD may decrease the risk of transfusion without increasing the risk of death, stoke, and treatment of renal replacement.

Significance of this study

What is already known about this subject?

- To our best knowledge, anemia aggravates exercise tolerance, cognitive competence, and reduces the quality of life both in predialysis and dialysis patients.
- Kidney Disease Improving Global Outcomes Guidelines have been developed for the hemoglobin targets, but there remains considerable controversy regarding the appropriate Hb or Hct levels as shown by the wide variation that still exists in anemia management practices between and within countries.
- Interventional evidence has been pointing in a different direction. A meta-analysis found that predialysis and dialysis patients treated with erythropoiesis-stimulating agents targeting the higher hemoglobin do not lower mortality and may increase cardiovascular risk.

What are the new findings?

- There was a significantly lower risk of transfusion in the higher hemoglobin group than in the lower one.
- No significant difference was found in all-cause mortality, stroke, and treatment of renal replacement including hemodialysis, peritoneal dialysis and renal transplant between the higher hemoglobin group and the lower one. The results favor the higher hemoglobin target.
- Due to lack of relative articles of studying higher Hb (such as >150 g/L), we cannot summarize and give the answer of upper limit of Hb concentration.

How might these results change the focus of research or clinical practice?

- Overall, our studies favor the higher hemoglobin target in predialysis patients.

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem, because of its high prevalence, heavy economic burden, and poor prognosis.[1 2] Patients with CKD easily suffered from anemia due to endogenous erythropoietin deficiency, shortened red blood cell (RBC) survival, and uremic inhibitors.[3] Recombinant human erythropoietin and the analogues are widely used to treat anemia. To our best knowledge, anemia aggravates exercise tolerance, cognitive competence, and reduces quality of life both in predialysis and dialysis patients.[4–6] Anemia also can exert adverse influence on cardiovascular system such as left ventricular hypertrophy or dilation, arrhythmia, and myocardial ischemia.[7 8] Reversing anemia may reduce the risk. However, it is reported that adverse effects of

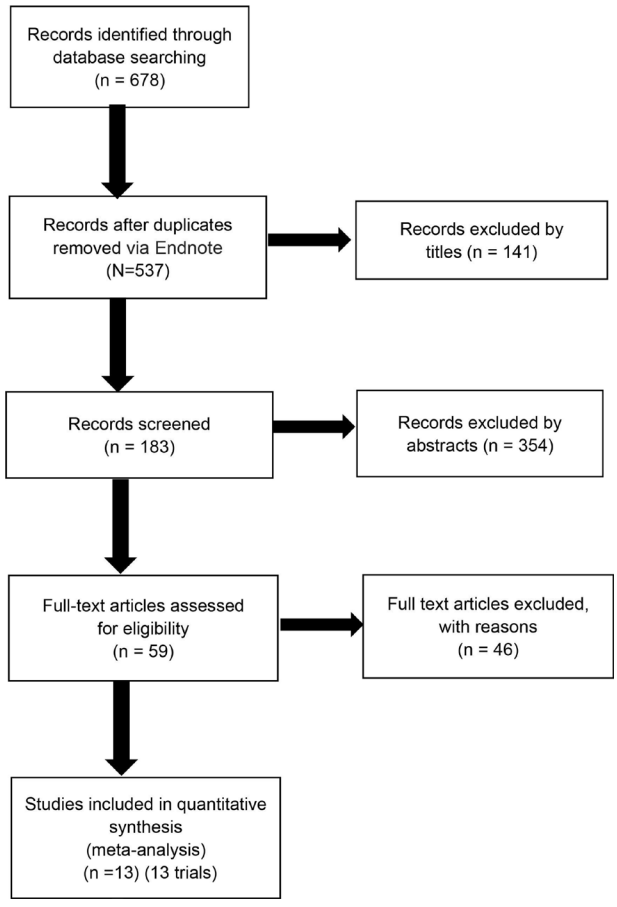

Figure 1 Flow diagram of studies considered for inclusion.

the higher hemoglobin level include the development of systemic hypertension, site access thrombosis in dialysis patients with arteriovenous shunts, and increased risk of cardiovascular events.[9] Interventional evidence has been pointing in a different direction. A meta-analysis[10] found that predialysis and dialysis patients treated with erythropoiesis-stimulating agents (ESAs) targeting the higher hemoglobin do not lower mortality and may increase cardiovascular risk.

Kidney Disease Improving Global Outcomes (KDIGO) Guidelines have been developed for the hemoglobin targets, but there remains considerable controversy regarding the appropriate Hb or Hct levels as shown by the wide variation that still exists in anemia management practices between and within countries. The aim of this systematic review is to summarize the benefits and harms of lower versus higher hemoglobin in the treatment of the anemia of only predialysis CKD using existing randomized controlled trial data.

MATERIALS AND METHODS

Data sources and literature searches

We conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (see supplementary file S1 Appendix 1).[11] We electronically searched MEDLINE literature to collect all relevant literature using the search terms or synonyms *'Chronic kidney disease', 'CKD', hemoglobin, Hb, Hematocrit, Hct, 'erythropoiesis stimulating agent, recombinant human erythropoietin, rhuEPO, darbepoetin, erythropoietin,'* from inception to December 25, 2017. Randomized controlled clinical trials were also searched via EMBASE (1974 to December 2017), the Cochrane Controlled Clinical Trials Register Database (through December 2017), the Cochrane Renal Group Specialized Register of Randomized Controlled Trials (through December 2017) and the ClinicalTrials.gov website.

We also searched (manually) the abstracts of conference proceedings of the American Society of Nephrology from 1998 to 2017. However, we did not have access to RCTs that were not reported. Our searches have no restriction on language. Finally, we found 786 studies for the analysis. After screening, 13 studies[12–24] were included in the analysis (figure 1).

Study selection

All RCTs that studied predialysis CKD adults (age >18 years) and compared higher Hb target to lower ones were included. We excluded the studies as follows: duplicate publication; personal perspective, academic conferences, reviews, and meta-analysis articles; animal and cell experiment; literature that studies dialysis patients; population age<18 years; sample size <50. Titles and abstracts were reviewed and evaluated by two reviewers independently, as well as the full-text articles.

Data extraction and quality assessment

Data were independently extracted by two authors (Yuqiu Ye and Shaomin Li). Search strategies of all databases could be found in online supplementary file 2. The following data were extracted: country of origin; year of publication; sample size; mean age; percentage of men; mean or median follow-up time; prevalence of diabetes; prevalence of hypertension; different Hb (or Hct) targets; number of endpoints outcomes.

We also extracted trial characteristics, trial intervention. Regularly, several items such as independent randomization center, random allocation, blindness, adequate allocation concealment, intention-to-treat for RCTs were recorded. The quality of trials was assessed by Review Manager 5.3 (Oxford, UK) according to the Cochrane Handbook for Systematic Reviews of Interventions. Discrepancies concerning extraction and/or assessment of the quality of data were addressed by the third person if necessary.

Synthesis and analysis of data

The software Review Manager 5.3 was used to implement meta-analysis. Risk ratios (RRs) were used to pool results for dichotomous outcomes (eg, all-cause mortality). We use a fixed-effects (used if $I^2<25\%$) and a random-effects model (used if $I^2>50\%$) to analyze data. 95% CIs were provided for all pooled estimates. Heterogeneity was assessed using the Cochrane Q test. I^2 index (which describes the percentage of total variation across studies due to true heterogeneity rather than chance) and p values were also used. Publication bias was assessed using Funnel plots.

We performed the sensitivity analysis by removing the low-quality trials. We treated the trials with more than two

Table 1 Main characteristics of 27 studies selected for a meta-analysis

Article	Country	Population	Sample size	Age (I/C)	Male (%) (I/C)	Hypertension (%) (I/C)	Diabetes (%) (I/C)	Follow-up (months)	Intervention (I/C)	Higher Hb or Hct (mean±SD)	Lower Hb or Hct (mean±SD)
Cianciaruso *et al*[17] (2008)	Italian	CKD	95	58.5/56.5	56.5/67.3	NR	23.9/12.2	24	EPO/placebo	12.0–14.0	11.7±0.8
Drüeke *et al*[19] (2006)	22 countries	CKD	603	59.3/58.8	57.0/51.0	91/89	27/25	36	EPO/placebo	13.0–15.0	10.5–11.5
Gouva [13] (2004)	Greece	CKD	88	66.7/64.2	55.6/58.1	93/84	NR	22.5	EPO/placebo	12.9±0.4	10.3±1.0
Kuriyama[16] (1997)	Japan	CKD	108	63.8/59.2	55.0/52.0	78/76	55/58	9	EPO/placebo	Hct 35.5 (4.40)	25.3 (1.9)
Levin *et al*[21] (2005)	Canada	CKD	172	56.5/57.3	70.3/70.5	NR	41.0/35.1	24	EPO/placebo	12.0–14.0	9.0–10.5
Pfeffer *et al*[22] (2009)	24 countries	CKD	4038	68.0/68.0	41.5/44.0	NR	100/100	29.1	EPO/placebo	12.0–12.8	9.9–11.3
Rossert[23] (2006)	4 countries	CKD	390	58.5/57.8	58.0/61.0	72/70	34/35	36	EPO/EPO	13.0–15.0	11.0–12.0
Singh *et al*[20] (2006)	USA	CKD	1432	66.0/66.3	43.8/45.9	95.8/93.2	NR	16	EPO/EPO	13.5	11.3
Tsubakihara *et al*[15] (2012)	Japan	CKD	321	65.2/64.1	49.7/44.4	NR	NR	48	EPO/EPO	11.0–13.0	9.0–11.0
Villar *et al*[12] (2011)	France	CKD	89	68.5/65.2	60.9/65.1	97.8/100	100/100	24	EPO/EPO	13.0–14.9	11.0–12.9
Revicki *et al*[18] (1995)	Canada	CKD	83	56.5/58.4	35.0/30.0	NR	NR	12	EPO/EPO	Hct>36	<36
Roth *et al*[24] (1994)	USA	CKD	83	56.5/58.4	34.9/30.0	NR	NR	12	EPO/placebo	Hct>36	<36
Ritz *et al*[14] (2007)	USA	CKD	172	58/57	51.0/50.0	NR	100/100	15	EPO/EPO	13–15	10.5–11.5

CKD, chronic kidney disease; C, control; Hb, hemoglobin; HCT, hematocrit; I, intervention; NR, not reported.

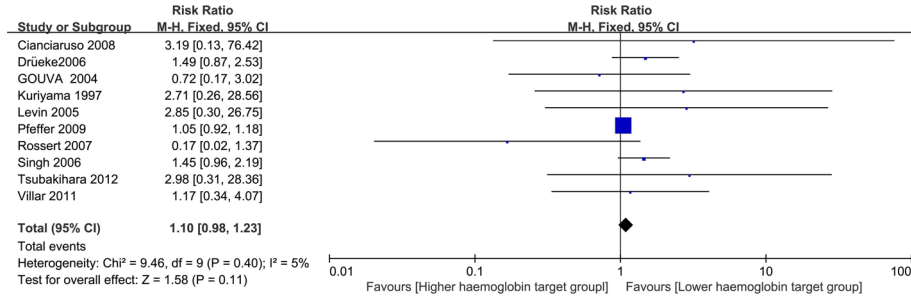

Figure 2 Metagraph of all-cause mortality.

'high risk' according to Review Manager 5.3 as low-quality trials.

RESULTS

Selection and characteristics of studies

Detailed characteristics and a summary of all studies are displayed in Table 1. Multiple publications were excluded from studies. Unique results were extracted and studies (as well as abstracts) containing unique results were also displayed. The average age of each group ranged from 56.5 to 68 years. The sample size of the studies varied from 83 to 4038. Duration of follow-up was from 9 months to 48 months.

Effects of higher or lower hemoglobin on all-cause mortality

In an analysis of 10 studies with 7270 participants reporting on all-cause mortality, no significant difference was found in all-cause mortality in the fixed effects model (RR 1.10, 95% CI 0.98 to 1.23; p=0.11) (figure 2).

Effects of higher or lower hemoglobin on stroke

Five studies with 6319 participants reported on stroke. No significant difference was found in stroke in the random effects model with heterogeneity between studies (RR 1.32, 95% CI 0.82 to 2.10; p=0.25) (figure 3).

Effects of higher or lower hemoglobin on treatment of renal replacement

In an analysis of 12 studies with 7523 participants reporting on treatment of renal replacement including hemodialysis, peritoneal dialysis, or renal transplant, no significant difference was found in any treatment of renal replacement in the fixed effects model (RR 1.08, 95% CI 0.95 to 1.22; p=0.23) (figure 4).

Effects of higher or lower hemoglobin targets on transfusion

Three studies with 4194 participants reported on transfusion. A significant decrease in the risk of transfusion was found in the higher Hb target group by 41% in the fixed effects model without heterogeneity between studies (RR 0.59, 95% CI 0.52 to 0.67; p<0.00001) (figure 5).

Sensitivity analysis and publication bias

Pfeffer *et al* (2009)[22] provided well-designed RCTs that have the biggest sample size and may impact on clinical outcome mainly, such as transfusion and stroke.

Figure 6 shows a funnel plot of the studies. All studies lie inside the 95% CIs, with an even distribution around the vertical, indicating no obvious publication bias.

DISCUSSION

This meta-analysis evaluated current evidence from RCTs comparing different hemoglobin targets in predialysis patients. The result suggested that compared with lower hemoglobin, higher hemoglobin target significantly reduced the risk of transfusion. Meanwhile, no significant difference in all-cause mortality, stroke, and any treatment of renal replacement was observed between two groups.

The impact of maintaining different hemoglobin targets on survival of predialysis patients was investigated previously in observational studies and RCTs, showing inconsistent results. The former suggested that higher hematocrits (33%–36%) reduced risk for death by 7%.[25] However, recent meta-analyses of only RCTs with samples varying from 464 to 7902 participants indicated no reduction of all-cause mortality and even higher risk of death in patients with CKD with higher Hb target than those with lower ones.[10 26 27] The articles that studied renal replacement therapy patients such as hemodialysis, peritoneal dialysis, and kidney transplant were not involved in the analysis of results. In light of the deficit in the ability of observational

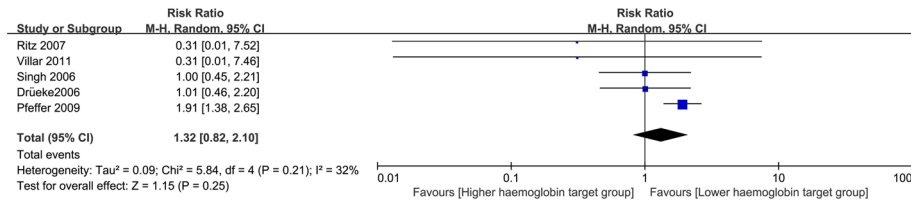

Figure 3 Metagraph of stroke.

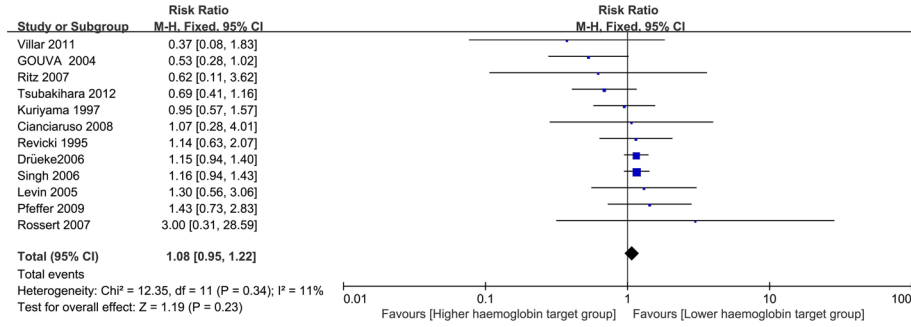

Figure 4 Metagraph of treatment of renal replacement.

studies to discover causality between intervention and clinical outcome, the present evidence seemed to suggest no favorable association between higher hemoglobin and survival advantage in CKD populations.

Importantly, no significant difference was found in stroke between two groups, not in line with a recent meta-analysis investigating different dose of erythropoiesis-stimulating agents in patients with CKD.[10] It is reported that the higher hemoglobin was associated with increased risk of stroke. The underlying mechanism might partly be the facilitation of spontaneous platelet aggregation by EPO used to treat anemia and its interaction with blood coagulation factors, both leading to tendency of thrombosis.[28 29] According to our result, the higher hemoglobin target did not put patients with CKD at increased risk of stroke. However, trial reports did not specify whether stroke events were fatal or not.

Benefit of the higher hemoglobin target was the reduction of transfusion rate. The discretionary and abused use of blood products may have negative consequences including immune disorders, pulmonary complications, increased the chance of infection, longer intensive care unit stay, RBC alloimmunization, and increased overall mortality.[30–33] In addition to the health risks associated with transfusions, blood products are an increasingly hospitalization expense. It is reported that medical institutions in the USA pay approximately US$225 per unit of RBCs, let alone but the triple cost of the administrative and labor costs associated with receipt, storage, transportation, and transfusion of the blood products.[34] As such, reducing the unnecessary use of blood products has the potential to control hospital costs associated with blood products and reduce transfusion-related morbidities. But we failed to conduct the risk benefit analysis or cost of ESA use. In detail, we cannot assess number needed to treat, differing risk populations, or whether trials of short duration in healthier patients can really assess the thrombotic or stroke risk of ESAs.

The effect of the hemoglobin target on renal function still remains uncertain. No protection effect of the higher hemoglobin target on outcome of renal replacement therapy was found in the current study or in a previous meta-analysis.[10] Although Strippoli *et al* reported a lower end-point serum creatine clearance in the lower hemoglobin group, the risk of end-stage renal disease did not decrease accordingly.[26]

The KDIGO guideline suggested HB≤11.5 g/L for patients with CKD according to the upper HB boundary of the lower Hb level group in major ESA RCTs, and uncertainty still existed on the effect of Hb concentration between 11.5 and 13.0 g/L.[35] In addition, emphasis was put on individual treatment balancing the pros and cons of ESA therapy and blood transfusion.[35] In the current study, the Hb concentrations in two groups were approximately 120–140 g/L and 90–110 g/L. On the basis of current clinical data, a higher hemoglobin target was recommended for patients with CKD. Importantly, in cases that tended to develop anemia-related symptom such as fatigue and decreased physical function, and those required higher hemoglobin target to avoid episode of cardiovascular disease like heart failure, coronary artery disease, maintaining a higher Hb concentration might be beneficial. As we know, the standards for blood transfusions vary from patient to country. In the USA, most institutions do not transfuse for hemoglobin's 8 or higher in the absence of symptomatology. In China, patients with absence of symptomatology, generally Hb less than 7 g/L, may be considered blood transfusions. If this practice is in place elsewhere, it may make the finding of fewer transfusions in the higher target range more of an artifact of regulation rather than a biological phenomenon.

In this meta-analysis, there were several limitations that must be taken into consideration. First, we cannot specify the proper hemoglobin or hematocrit level in predialysis patients. In detail, over all studies, the lower Hb boundary of the high Hb group overlapped the upper boundary of the low Hb group when compared among studies. In at least three studies, the upper and lower limits come very close such as Pfeffer (2009),[22] Rossert (2007), Villar (2011),[12]

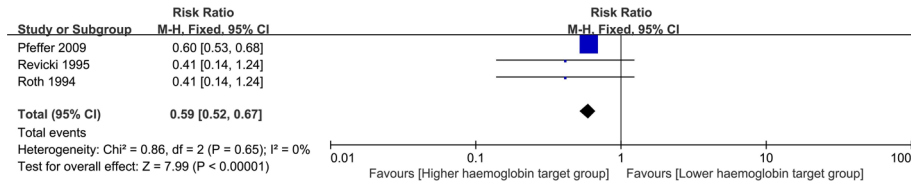

Figure 5 Metagraph of transfusion.

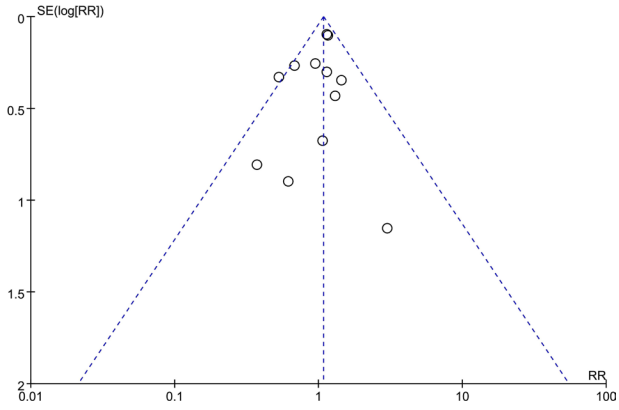

Figure 6 The funnel plot of this study.

and Cianciaruso (2008).[17] But the level of the Hb or Hct interval can also be distinguished. We reanalyzed the data excluding above studies, but the results for all-cause mortality, stroke, transfusion, and renal replacement therapy were unchanged (see online supplementary files S3-S6). Several studies included concentration on the clinical outcome of different Hct levels and cannot explain the corresponding Hb levels. The missing element is the dose of ESA used in some studies. Second, for the characteristics of studies, such as the sample, the follow-up periods are hugely different, which might increase heterogeneity and bias the results. Third, unpublished reports could not be identified, which might have biased our results. Finally, due to lack of relative articles of studying higher Hb (such as>150 g/L), we cannot summarize and give the answer of upper limit of Hb concentration.

CONCLUSION

In this meta-analysis pooling, available RCTs suggested that targeting the higher hemoglobin target when treating predialysis patients decreases risk of transfusion and had no significant effect on increased risk of death, risk of stroke, and any treatment of renal replacement. Overall, our studies favor the higher hemoglobin target in predialysis patients.

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Correction notice This article has been corrected since it was published Online First. The affiliations for Rongqian Yang, Zhesi Zhang, Hongquan Peng and Yanbing Chen have been corrected.

Contributors Conceived and designed the experiments: XL, HL, YY. Performed the experiments: YZ, SL, HP. Analyzed the data: WH, RY, YC. Contributed reagents/materials/analysis tools: ZZ, LL, YC. Wrote the paper: YY, SL, XL.

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