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Impact of red blood cell transfusion on acute coronary syndrome: a meta-analysis

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Abstract The impact of red blood cell transfusion on outcomes in patients with acute coronary syndrome is controversial. Pubmed, EMBASE, and Cochrane Library were searched for studies of red blood cell transfusion and acute coronary syndrome that were published in any language, from January 1, 1966, to April 1, 2016. We analyzed 17 observational studies, of 2,525,550 subjects. We conducted a systematic review with meta-analysis of studies assessing the association between blood transfusion and the risk for all-cause mortality and reinfarction. The search yielded 17 observational studies, of 2,525,550 subjects, during a study follow-up period, ranging from 30 days to 5 years. Red blood cell transfusion compared with no blood transfusion is associated with higher short- and long-term all-cause mortality as well as reinfarction rates (adjusted RR 2.23; 95% CI 1.47–3.39; HR 1.93; 95% CI 1.12–3.34; RR 2.61; 95% CI 2.17–3.14, respectively). In hemoglobin-stratified analyses, a graded association between red blood cell transfusion and mortality was observed, transfusion and risk of all-cause mortality was borderline significant at hemoglobin levels below 8.0 g/dL (RR 0.52; 95% CI 0.25–1.06), and was associated with an increased risk of mortality at a hemoglobin above 10 g/dL (RR 3.34; 95% CI 2.25–4.97). Red blood cell transfusion was associated with an increased risk of short- and long-term mortality as well as myocardial reinfarction. However, transfusion appeared to have beneficial or neutral effects on mortality at hemoglobin levels below 8.0 g/dL, and harmful effects above 10 g/dL. A large definitive randomized controlled trial addressing this issue is urgently required.

Keywords Red blood cell transfusion · Acute coronary syndrome · Meta-analysis

Introduction

Anemia is common among patients hospitalized with acute coronary syndrome (ACS), and is associated with poor outcomes [1–3]. However, the risk–benefit of transfusion is poorly understood, and the specific indications for transfusion in this population remain ill-defined [4]. The latest guidelines from the American College of Cardiology/American Heart Association for the management of patients with non-ST-elevation ACS demonstrated that there is no benefit of routine red blood cell transfusion in MI patients with hemoglobin levels >8 g/dL [5]. The American Association of Blood Banks (AABB) recommends a restrictive transfusion strategy (7–8 g/dL) in hospitalized, stable patients, however, provides no recommendation either for or against transfusion in patients with ACS [6]. A small randomized pilot study that randomized 45 ACS patients suggested a benefit to a more restrictive transfusion strategy [7]. A previous meta-analysis concluded that red blood cell transfusion or a liberal blood transfusion strategy is associated with higher all-cause mortality rates compared with no blood transfusion or a restricted transfusion strategy, with significant heterogeneity observed among the outcomes [8]. As the results of

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several recently published studies are available, we conducted a meta-analysis of observational studies assessing the impact of red blood cell transfusion on the risk of mortality and reinfarction in ACS patients.

Methods

Search strategy

This meta-analysis was conducted according to the recommendations of the meta-analysis of observational studies in epidemiology (MOOSE) [9]. To search for relevant studies that identified the impact of red blood cell transfusion on clinical outcomes in acute coronary syndromes, we performed an electronic search of Pubmed, EMBASE, and Cochrane Library from January 1966 to April 2016. Key words and/or MeSH terms searched were as follows: (transfusion OR blood transfusion OR red blood cell transfusion) AND (acute coronary syndrome OR myocardial infarction OR unstable angina). No restrictions were applied. Moreover, the reference lists of retrieved articles were scanned to locate additional publications.

Study selection

Studies were included if they met the following criteria: (1) all patients suffered from acute coronary syndrome; (2) there is a transfused group compared with a non-transfused group; (3) there is an evaluation of the association between red blood cell transfusions and clinical outcomes in patients with ACS; (4) there is provided the odds ratios (OR) or relative risk (RR), or hazard risk with its 95% confidence intervals (CI), for transfused group versus non-transfused group. Excluded from this analysis were studies that evaluated liberal transfusion versus restrictive transfusion in patients with ACS. In our protocol, anemia referred to anemia on admission and/or anemia developing during their hospitalization.

Data extraction

All data were extracted independently by two investigators (Y.W., X.S.) according to the prespecified selection criteria using a standardized data form. The following data from each publication were extracted: the last name of the first author, year of publication, study design, study population, results of studies (study-specific adjusted RRs or ORs with their corresponding 95% CIs), confounding factors adjusted for in the analysis, types of ACS, patients' age and gender at baseline, and baseline and nadir hemoglobin levels. We extracted the maximally adjusted effect estimates (ORs and HRs). Some studies separated risk estimates according to the different follow-up periods, including short term (in-hospital, 1, and 6 months) and long term (1, 5 year). In this situation, we extracted the results reported at the longest available follow-up duration. Any disagreement was resolved by consensus.

To assess the study quality, a nine-star system based on the Newcastle–Ottawa Scale [10] was applied in which a study was judged on two broad perspectives. The high-quality study was defined as a study with $\geq$6 awarded stars. We provide details on the study quality assessment in the Supplementary results of the Online Appendix. For the consistency of evaluation in our meta-analysis, all the hematocrit values reported in the studies were converted to hemoglobin ones using a standard published equation [Hb (g/dL) = Hct (%)/3] [11, 12].

Statistical analysis

To compute a pooled estimate with 95% CI, we used the adjusted RRs, ORs, or hazard risks and their 95% CIs of red blood cell transfusion compared with no blood transfusion. Possible heterogeneity was tested in results across studies using Cochran's Q and I^2 statistics [13]. The null hypothesis, that the studies are homogeneous, would be rejected if P value is less than 0.05 or I^2 was >50%. The fixed effect model (Mantel–Haenszel) was used to calculate pooled RR among studies, when minimal heterogeneity exists. When substantial heterogeneity existed, the random-effect model (DerSimonian and Laird) was preferred [14]. Subgroup analysis is carried out by study design (secondary analysis of RCTs vs. cohort/case–control vs. principal component analysis), nadir hemoglobin (Hb $\leq$ 8 g/dL vs. Hb > 8 g/dL), follow-up duration (short-term vs. long-term) in the analysis. To observe the influence of the individual data set on the pooled result, we conducted a sensitivity analysis by excluding each study one by one and recalculating the combined estimates on remaining studies. A P value <0.05 was considered statistically significant. The possibility of publication bias was assessed by Begg test and visual inspection of a funnel plot [15, 16]. $P < 0.05$ for Begg's test was considered to be representative of a significant statistical publication bias. All data analyses were performed with Stata (version 11.0; StataCorp, College Station, TX, USA).

Results

Literature search

The search algorithm yielded 941 records; of them, 117 records were excluded due to overlapping data with already included studies. Another 728 were excluded as irrelevant on

the basis of title and abstract. The full text article of the remaining 96 studies was reviewed and assessed for satisfaction of the eligibility criteria. Seventeen studies that met all criteria were included in this analysis (Fig. 1) [17–33].

Study characteristics and quality assessment

A total of 17 studies that included 2,525,550 subjects, published from 2001 through 2015, were identified in this meta-analysis. Of the 17 studies, 4 were secondary analysis of RCTs studies [18, 24–26], 12 were cohort studies [17, 19–23, 28–33] and 1 was a case–control [27] study (Table 1). Sample sizes ranged from 370 to 2,258,711, and the number of transfused patients varied from 68 to 48,430. Salisbury et al. have d non-overlapping propensity scores for red blood cell transfusion, the investigators used a well-described, although infrequently used technique, called principal component analysis (PCA), which creates a set of artificial variables (principal components) based on correlations from a much larger dataset [34]. Sherwood et al. study was the largest study with a total of 2,258,711 patients, and the overall rate of transfusion was 2.14% [32]. Four studies [25, 26, 30, 33] separated the risk estimates according to the different follow-up durations. Most individual studies were adjusted for a wide range of potential confounders, including patient baseline characteristics, transfusion propensity, baseline hemoglobin, nadir hemoglobin, and major bleeding.

Study-specific quality scores are summarized in Tables 2 and 3 in the Online Appendix. The scores of all cohort studies were 9, and the score of one case–control study was 7. All of the studies included in our meta-analysis were of high-quality (had ≥6 awarded stars).

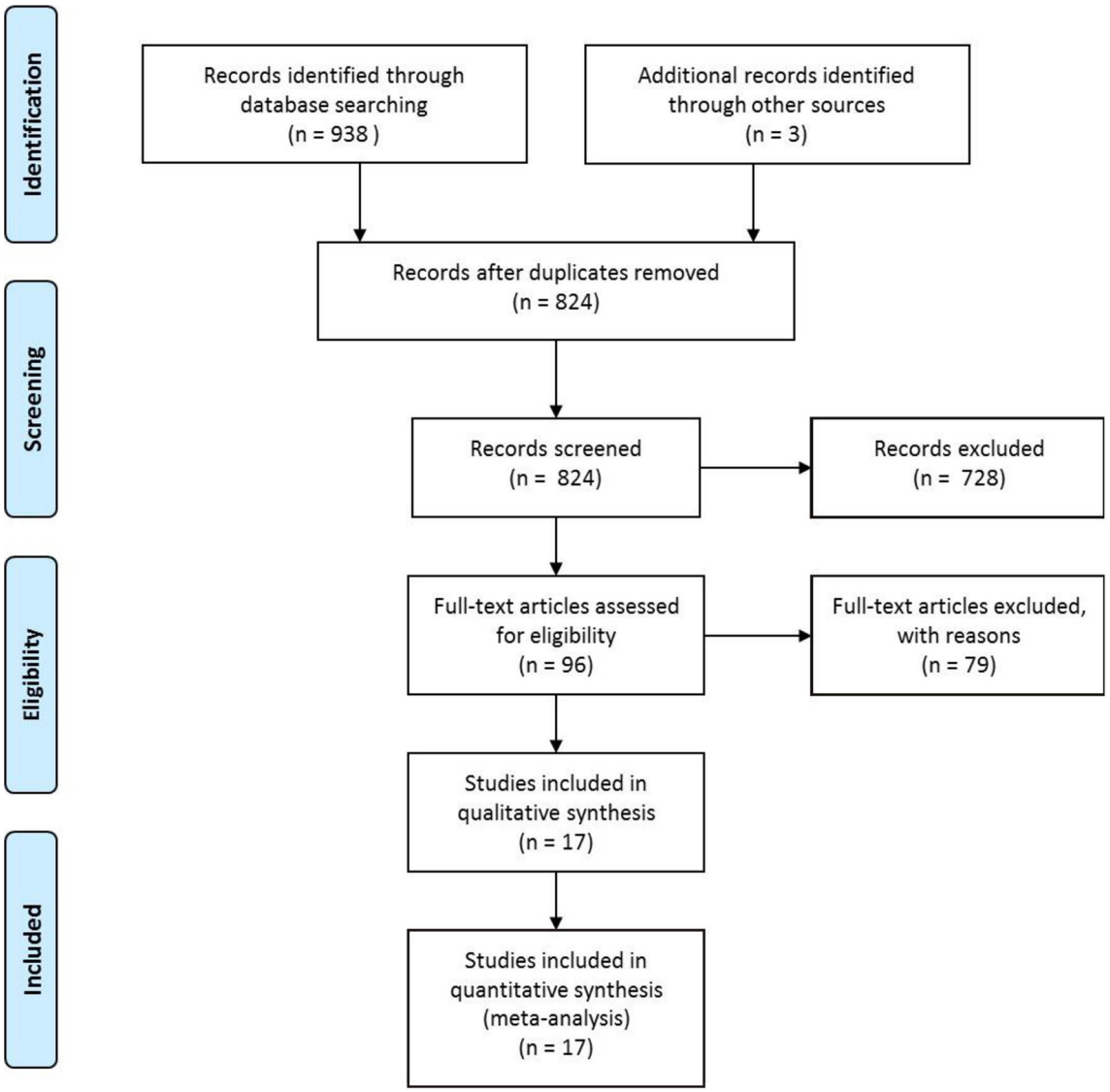

Fig. 1 Flow chart of study selection

Table 1 Key characteristics of the 17 studies included in the meta-analysis

Sources	Study Design	Transfused/total patients (*n*)	Adjusted OR/ HR (95% CI)	Adjustments	Types of ACS	Median age, year		Male %		Nadir Hb, g/dL		Baseline Hb, g/dL	
						T	NT	T	NT	T	NT	T	NT
Wu et al. [17]	Multicenter cohort	3680/78,974	–	Clinical factors, medication use, predictors of transfusion	STEMI, non-STEMI	–	–	–	–	–	–	–	–
Rao et al. [18]	Secondary analysis of three RCTs (GUSTO IIb, PURSUIT, PARAGON B)	2401/24,112	30 days: 3.94 (3.26–4.75)	Baseline characteristics, bleeding and transfusion propensity and nadir hematocrit	Non-STEMI, unstable angina	69	64	59	66	9.7	12.5	13.3	13.9
Yang et al. [19]	Multicenter cohort	12,724/85,111	In hospital: 1.67 (1.48–1.88)	Clinical factors associated with blood transfusion	Non-STEMI	73	67	53	61	8.7	11.7	11.7	13.7
Jani et al. [20]	Multicenter cohort	1033/4623	In hospital: 2.02 (1.47–2.79)	Co-morbidities, in-hospital characteristics, propensity score for transfusion	STEMI, non-STEMI	70	67	47	61	–	–	10.5	11.4
Singla et al. [21]	Single-center cohort	110/370	–	Significant univariate predictors: hypotension on presentation, pulmonary edema, increased troponin-I levels	Non-STEMI	70	70	99	97	–	–	8.9	9.8
Alexander et al. [22]	Multicenter cohort	4610/44,242	–	Clinical factors, baseline hematocrit, transfusion by nadir hematocrit interaction	Non-STEMI	–	–	–	–	–	–	–	–
Aronson et al. [23]	Single-center cohort	192/2326	6 months: 1.9 (1.3–2.9)	Baseline characteristics, transfusion propensity, nadir hemoglobin	STEMI, non-STEMI	69	61	57	79	8.8	12.8	11.8	14.3
Jolicoeur et al. [24]	Secondary analysis of RCT (APEX AMI)	213/5532	90 days: 2.16 (1.20–3.88)	Baseline characteristics, in-hospital co-interventions, transfusion propensity	STEMI	71	61	47	78	8.7	12.9	12.9	14.8
Nikolsky et al. [25]	Secondary analysis of RCT (CADILLAC)	82/2060	30 days: 4.71 (1.97–11.26) 1 year: 3.16 (1.66–6.03)	Potential confounders including baseline anemia and transfusion propensity	STEMI, non-STEMI	68	59	48	74	10	–	13.1	14.7
Shishehbor et al. [26]	Secondary analysis of RCT (GUSTO IIb)	307/3575	6 months: 4.81 (3.00–7.71) 1 year: 3.03 (2.25–4.08)	Baseline characteristics, transfusion propensity, nadir hemoglobin, co-morbidities, in-hospital treatments	STEMI	67	62	59	78	8.6	12.6	13.9	14.7
Aggarwal et al. [27]	Single-center case–control	206/3190	In hospital: 1.8 (0.6–5.1)	Baseline factors and confounders	STEMI, non-STEMI	71	71	50	45	8.7	9.2	10.7	10.4
Ergelen et al. [28]	Single-center cohort	88/2537	–	Potential confounders	STEMI	64	56	55	84	8.4	12.1	11	13.4
Valente et al. [29]	Single-center cohort	68/1123	In hospital: 1.29 (0.49–3.40)	Transfusion propensity, baseline characteristics, nadir hemoglobin, major bleeding	STEMI	–	–	–	–	–	–	–	–
Tajstra et al. [30]	Single-center cohort	82/2415	30 days: 3.1 (1.41–6.8) 5 year: 1.45 (1.0–2.1)	Baseline characteristics	STEMI	67	59	39	74	–	–	13	14.2

Table 1 continued

Sources	Study Design	Transfused/total patients (*n*)	Adjusted OR/HR (95% CI)	Adjustments	Types of ACS	Median age, year		Male %		Nadir Hb, g/dL		Baseline Hb, g/dL	
						T	NT	T	NT	T	NT	T	NT
Salisbury et al. [31]	Multicenter cohort	1121/3108	In hospital: 0.73 (0.58–0.92)	Site and patient characteristics	STEMI, non-STEMI	76	76	43	43	–	–	–	–
Sherwood et al. [32]	Cohort from the CathPCI registry	48,430/2,258,711	In hospital: 4.63 (4.57–4.69)	Patient risk factors	STEMI, non-STEMI, unstable angina	66	65	60	67	–	–	11	13.6
Ducrocq et al. [33]	Cohort from FAST-MI registry	151/3541	In hospital: 1.4 (0.7–2.8) 5 year: 1.1 (0.8–1.5)	Baseline characteristics	STEMI, non-STEMI	–	–	–	–	–	–	–	–

ACS acute coronary syndrome, *STEMI* ST elevated myocardial infarction, *T* transfusion, *NT* no transfusion, *Hb* hemoglobin, *HR* hazard ratio, *OR* odds ratio, *RCT* randomized clinical trials

Short-term all-cause mortality

Among the 17 selected studies, 13 studies provided adjusted risks of all-cause mortality expressed as ORs, hazard ratios. Red blood cell transfusion compared with no blood transfusion is associated with higher short-term all-cause mortality rates, with a pooled RR of 2.23 (95% CI 1.47–3.39). There was evidence of statistical heterogeneity of RRs across studies ($I^2 = 75.5\%$; $P < 0.001$). A sensitivity analysis showed that one study [32] with the largest overall number of participants had great influence on the model's result. After excluding this study, subgroup analysis according to study design (secondary analysis of RCTs vs. cohort/case–control vs. principal component analysis) significantly lowered the study heterogeneity (Fig. 2). The finding of increased all-cause mortality in red blood cell transfusion was consistently found in the subgroups but by the principal component analysis study.

Long-term all-cause mortality

Four studies [25, 26, 30, 33] reported additional long-term (1-, 5-year) hazard ratios, showing that the estimate of the association between red blood cell transfusion and all-cause mortality was significant (HR 1.93; 95% CI 1.12–3.34; Fig. 3). Statistically significant heterogeneity was observed among these studies ($I^2 = 88.2\%$; $P < 0.001$). In subgroup analysis by follow-up periods, the summary HR was 3.05 (95% CI 1.26–1.51) for the two studies with data on 1-year mortality. The association between red blood cell transfusion and 5-year mortality was borderline significant (HR 1.24; 95% CI 0.95–1.62). There was little evidence of heterogeneity for both 1-year mortality ($I^2 = 0\%$; $P = 0.908$) and 5-year mortality ($I^2 = 19.4\%$; $P = 0.265$).

Hemoglobin-stratified analyses

To further explore the association between red blood cell transfusion and risk of all-cause mortality, we performed stratified analyses with five studies [17, 18, 22, 23, 25, 31] reporting of the pre-transfusion nadir hemoglobin strata. A graded association between red blood cell transfusion and all-cause mortality was observed (Fig. 4). The association between red blood cell transfusion and risk of mortality was borderline significant at hemoglobin levels ≤8.0 g/dL (RR 0.52; 95% CI 0.25–1.06; $I^2 = 84\%$). Red blood cell transfusion was neither associated with mortality with hemoglobin between 8 and 9 g/dL (RR 0.81; 95% CI 0.48–1.37; $I^2 = 84.8\%$) nor between 9 and 10 g/dL (RR 0.84, 95% CI 0.43–1.63, $I^2 = 93.3\%$). Red blood cell transfusion at a hemoglobin above 10 g/dL was associated with an increased risk of mortality (RR 3.34; 95% CI

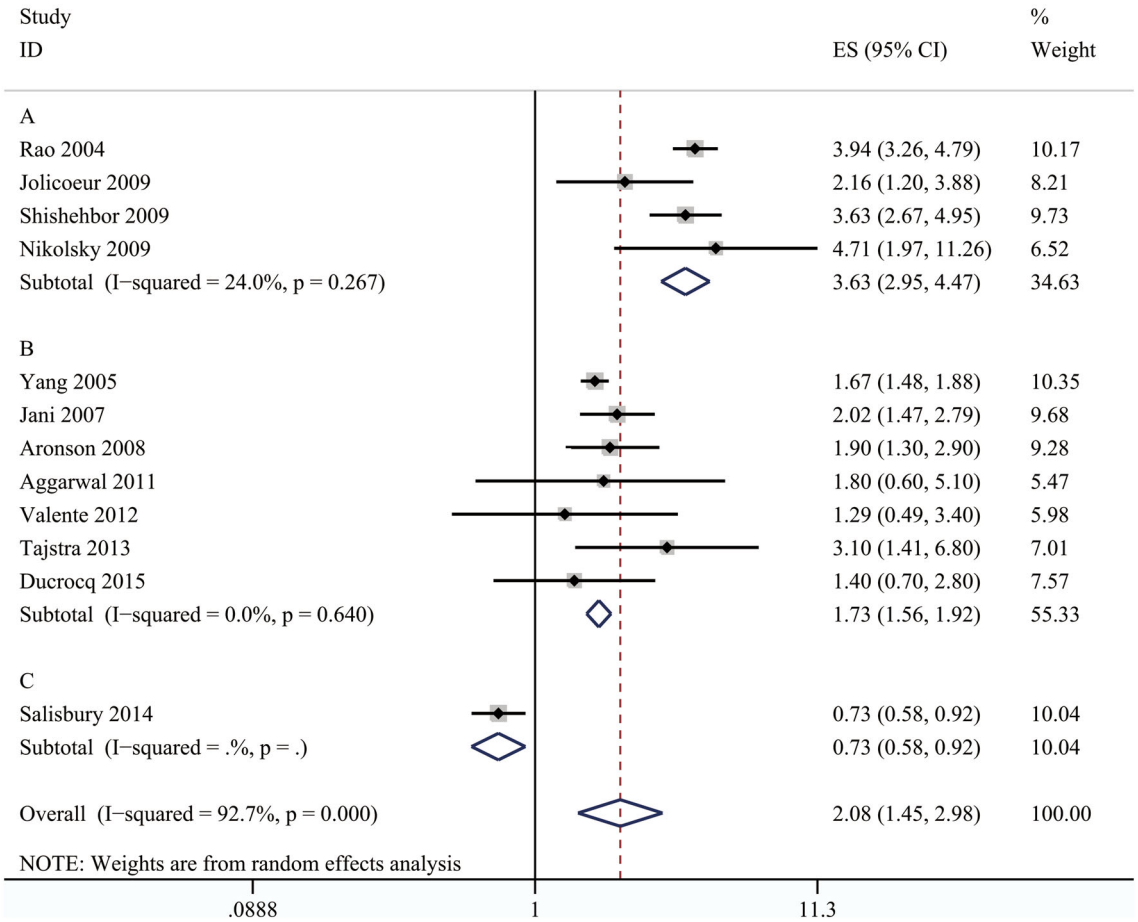

Fig. 2 Blood transfusion and short-term all-cause mortality. *A* Secondary analysis of RCTs, *B* cohort/case–control, *C* principal component analysis

2.25–4.97; $I^2 = 0\%$). Statistically significant heterogeneity was observed among these studies.

Myocardial infarction

Red blood cell transfusion was also significantly associated with a higher risk for subsequent myocardial infarction (RR 2.61; 95% CI 2.17–3.14; Fig. 5). Substantial heterogeneity was seen among these studies ($P = 0.000$; $I^2 = 79.2\%$). The pooled estimates of the RRs were consistently greater than 2 after separating from the study Sherwood et al. [32] with the largest number of participants, and study subgroup was more homogeneous ($P = 0.087$; $I^2 = 48\%$).

Publication bias

Visual inspection of the Begg funnel plot for both risk of all-cause mortality and myocardial reinfarction does not reveal the asymmetry typically associated with publication bias. Evidence of publication bias was also not seen with the Begg test (Begg $P = 1.00$ and 0.88 for mortality and reinfarction, respectively).

Discusssion

This meta-analysis of observational studies indicated that red blood cell transfusion was associated with short and long-term mortality risk in ACS patients with hemoglobin of above 8 g/dL. However, in the stratified analysis according to nadir hemoglobin, the impact of red blood cell transfusion on mortality varied at different hemoglobin targets. Red blood cell transfusion at hemoglobin below 8 g/dL appeared to decrease the risk of mortality, and its use at hemoglobin between 8 and 10 g/dL remained inconclusive. This result supported a generally more restrictive red blood cell transfusion strategy. The association persisted and remained statistically significant in the subgroup analysis of short- and long-term mortality. A previous review published by Garfinkle suggested that red blood cell transfusion in patients, post-ACS, undertaken at hemoglobin levels below

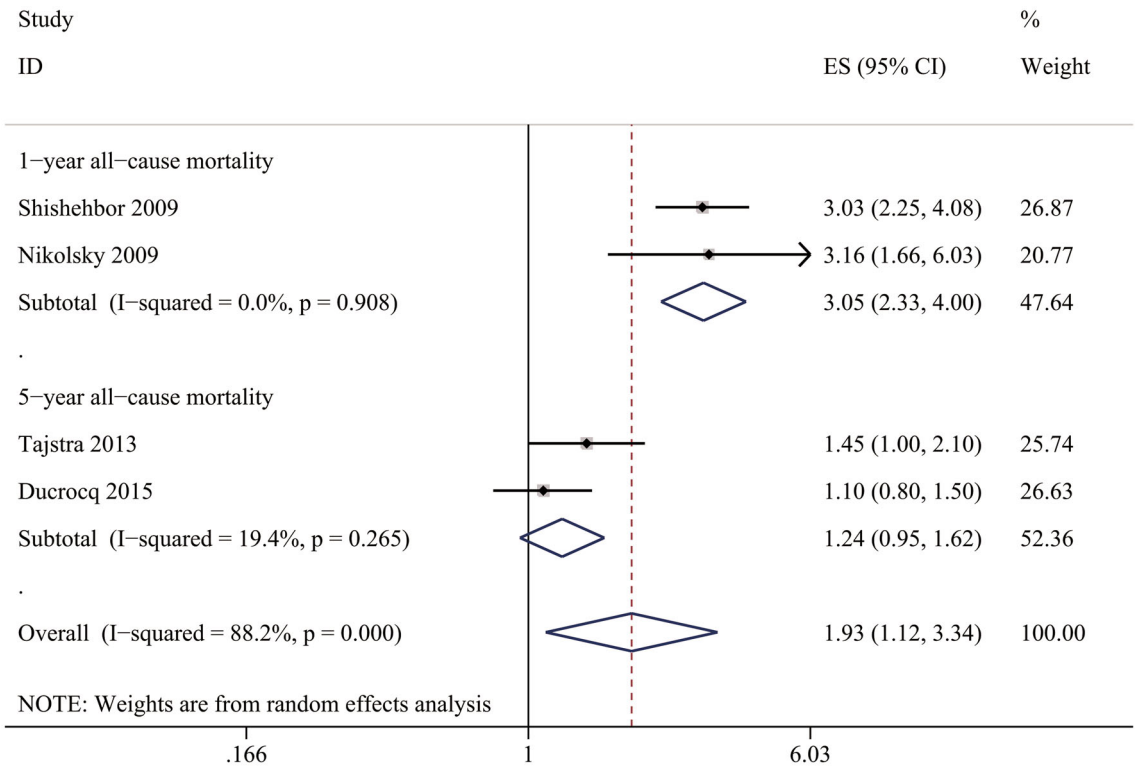

Fig. 3 Blood transfusion and long-term all-cause mortality

8.0 g/dL, was found to be beneficial, at worst, or neutral. Conversely, there is a suggestion of harm when transfusion was undertaken at hemoglobin levels above 11.0 g/dL, supporting a more conservative transfusion strategy [35]. Of note, although one study included in our meta-analysis suggested that red blood cell transfusion was associated with lower in-hospital mortality after propensity matching those with overlapping scores, a marked variation was noted in the association between transfusion and mortality stratified according to nadir hemoglobin, and transfusion was associated with lower risk of mortality among those with nadir hemoglobin values <7 g/dL [31].

A pervious meta-analysis conducted by Chatterjee [9] in 2012 assessed the effect of blood transfusion versus no transfusion and of restrictive versus liberal, together. The effect of the former would tend to mask the real effects of the latter; hence the two different issues, we believe, should be considered separately. To our knowledge, the current study is the first to focus on evaluating the effect of red blood cell transfusion versus no transfusion in patients suffering from ACS. Statistically substantial heterogeneity can be seen in some results of our meta-analysis, likely related to observational study design heterogeneity in the patient population, and variability in the reporting of hemoglobin strata. Subgroup analysis according to study design and follow-up duration significantly reduced the heterogeneity observed in the mortality results.

Another finding emerging from our meta-analysis was that red blood cell transfusion was significantly associated with an increased risk of reinfarction. The mechanism by which transfusion had increased risk for myocardial reinfarction might be explained by recent findings of increased platelet reactivity rather than inflammatory and thrombotic biomarkers resulting from red blood cell transfusion [36]. This finding was in agreement with results from meta-analysis by Chatterjee [9]. Nonetheless, as mentioned before, they put the effect of transfusion versus no transfusion and of restrictive versus liberal together, with significant heterogeneity observed. Further adequately powered randomized trial is needed to confirm this finding and affirm the potential protective effect of red blood cell transfusion on mortality in ACS patients with the use of a restrictive transfusion policy.

The study by Docherty et al. supported the use of a more liberal transfusion threshold (>80 g/L) compared with restrictive transfusion [37]. The patients included in his study with acute and chronic cardiovascular disease (non-cardiac surgery) varied from known coronary artery disease (ACS, chronic ischaemic heart disease) to other cardiovascular disease such as cerebrovascular accident and peripheral vascular disease). Our study compared transfusion strategy with no transfusion specifically in patents with ACS, and we showed a restrictive transfusion policy seems to have beneficial or neutral effects on mortality. In

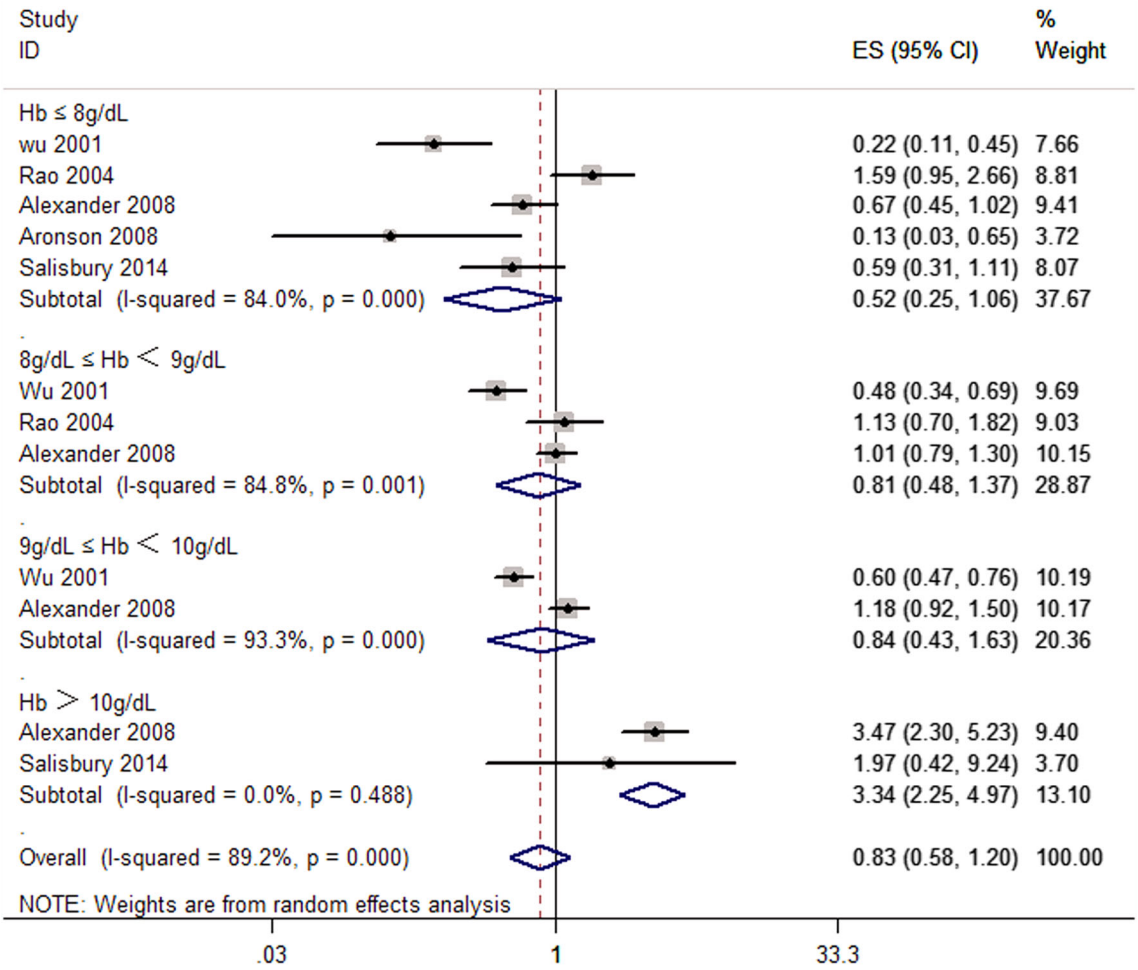

Fig. 4 Blood transfusion and all-cause mortality in hemoglobin-stratified analyses

patients with ACS, anemia was associated with hemodynamic instability such as hypotension and tachycardia) [1]. RBC transfusion is the only effective approach to rapidly increase hemoglobin levels in anemic patients with ACS. In our meta-analysis, some studies administered a blood transfusion when the hemoglobin reached <8.0 g/dL, or in the presence of a reduction in Hb concentration associated with hemodynamic instability [18, 29]. Some studies suggested that the RBC transfusion may have deleterious effects on outcome, and should be considered individually but withheld in hemodynamically stable patients [17, 23], and others failed to adequately capture the hemodynamic status at the moment of transfusion. Due to the infection or further ischemic events that may have resulted from blood transfusion, it is now advocated to limit transfusion to patients in gravely unstable hemodynamic situations; and especially in the setting of acute cardiac care, it is now increasingly recommended to consider transfusion in hemodynamically stable patients only for baseline hemoglobin values <7 g/dL [38]. In addition, the impact of blood transfusion on outcome is related to causes of anemia (i.e., renal insufficiency or cardiogenic shock) as well as previous co-morbidities. Therefore, the issue of whether hemodynamically unstable patients require aggressive transfusion deserves further scrutiny.

This study has several limitations. First, although we focused on adjusted effect estimates to minimize the effect of confounding, unmeasured confounding could still remain. All of the studies that assessed the association between red blood cell transfusion and mortality were observational studies, and thus may be affected by confounding by indication and other inherent bias. There was a possibility that bleeding leads to both mortality and the need for transfusion. Also, transfused patients tended to be older, and likely have a worse clinical prognosis than non-transfused patients. It reinforces the need for future studies evaluating the association between red blood cell transfusion and mortality focus on plausible causal mechanisms or mediating factors, such as major bleeding, anemia, and nadir hemoglobin levels. This may distort the true relationship between red blood cell transfusion and clinical outcomes of ACS patients, if these factors are not taken

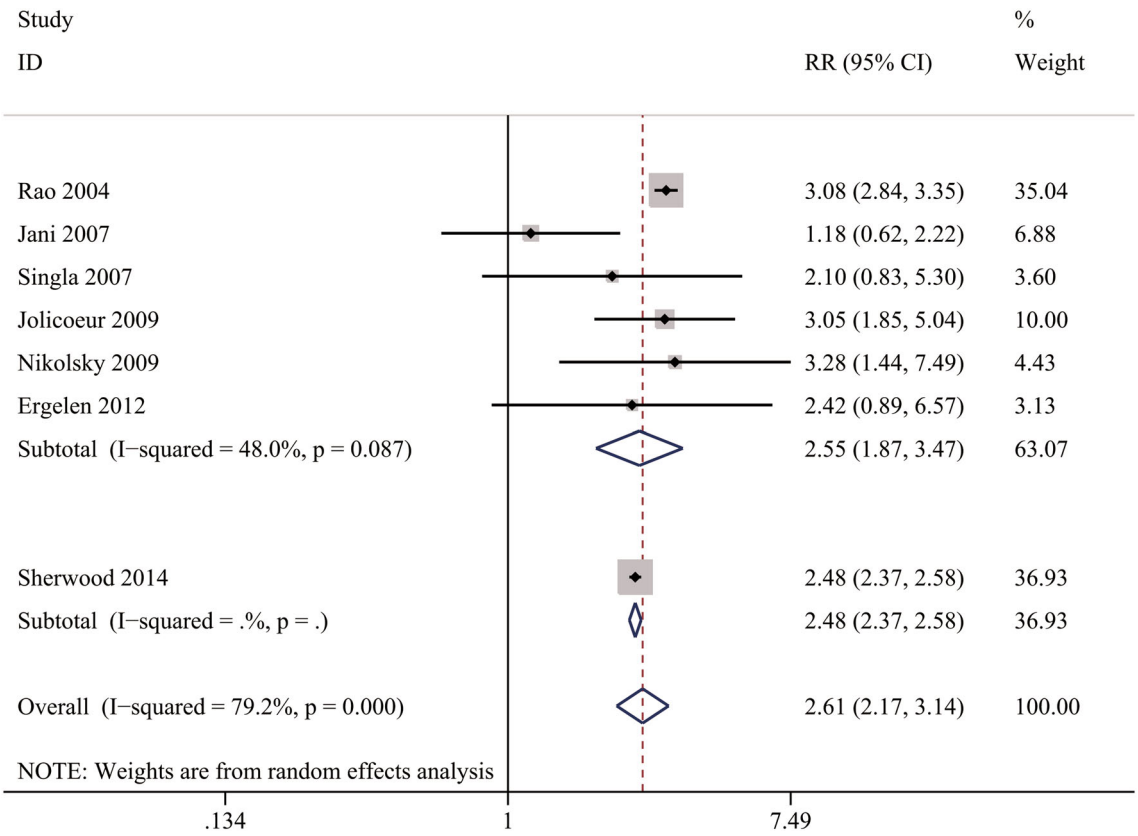

Fig. 5 Blood transfusion and myocardial reinfarction

into account. Second, a limited numbers of studies were involved in hemoglobin-stratificatied analysis, and statistical heterogeneity was observed in several of our analyses. This was not surprising due to the variations in method of statistical methods (e.g., type of RR estimate) case number, types of study design, spectrum of ACS, nadir hemoglobin levels, and adjustments across studies. However, subgroup analyses showed pooled estimates consistently greater than 1 across a number of clinical factors.

Despite these limitations, our meta-analysis provided evidence that red blood cell transfusion was associated with all-cause mortality and subsequent infarction. Also, a graded association between transfusion and mortality was observed, suggesting the utility of more restrictive transfusion strategy. However, because of potential confounding, this result should be considered with some caution.

Conclusion

Red blood cell transfusion was associated with an increased risk of short- and long-term mortality as well as myocardial reinfarction. However, transfusion appeared to have beneficial or neutral effects on mortality at hemoglobin levels below 8.0 g/dL, and harmful effects above 10 g/dL. While waiting for more definitive evidence from prospective randomized controlled studies, these findings offer possible interim guidance for physicians on transfusing patients with acute coronary syndrome.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent All of the eligible articles included in the meta-analysis stated that they had obtained informed consent from participants.

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