Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials.

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Summary box

What is already known about the subject?

- Acute upper gastrointestinal bleeding (AUGIB) is one of the leading indications for red blood cell (RBC) transfusion.
- Randomised controlled trials (RCTs) comparing liberal and restrictive RBC transfusion strategies for AUGIB have varying results.
- The overall risks and benefits are unclear, especially in clinically important subgroups such as those with cirrhosis, non-variceal upper gastrointestinal bleeding or with ischaemic heart disease

What are the new findings?

- In this meta-analysis of RCTs, restrictive RBC transfusion was associated with a significant overall reduction in mortality and rebleeding. The effect for rebleeding was consistent across subgroups.
- In patients with cirrhosis, the treatment effect for mortality was greatest with a 48% reduction in the risk of death with a restrictive RBC transfusion policy.
- No increased risk of ischaemic events was observed with restrictive RBC transfusion, although the number of studies recording this was small.

How might it impact on clinical practice in the foreseeable future?

- Restrictive transfusion thresholds (Hb 7-8 g/L) for AUGIB should be implemented across healthcare systems, apart from in those patients with exsanguinating bleeding.
- There is insufficient evidence to inform transfusion thresholds for patients with ischaemic heart disease and this is a key future area for research

ABSTRACT:

Objective To compare the benefit and harm of restrictive versus liberal red blood cell (RBC) transfusion in patients with acute upper gastrointestinal bleeding (AUGIB).

Design Systematic review with meta-analysis. MEDLINE, EMBASE, CENTRAL, CINAHL and the Transfusion Evidence Library were searched from inception to 20 October 2016 for randomised controlled trials (RCTs) comparing restrictive versus liberal RBC transfusion for AUGIB. Main outcomes were mortality, rebleeding, ischaemic events and mean RBC transfusion. The treatment effect was estimated for patient subgroups with cirrhosis, non-variceal upper gastrointestinal bleeding (NVUGIB) and ischaemic heart disease (IHD). Individual patient data from a cluster randomised trial was re-analysed.

Results Four published and one unpublished RCT totalling 1965 participants were included. The number of RBC units transfused were lower in the restrictive transfusion group (mean difference -1.90 units; 95% CI -2.26 to -1.53; $p<0.01$). Restrictive transfusion was associated with lower risk of mortality overall (RR 0.65, 95% CI: 0.44 to 0.97, $p=0.03$) and in the subgroup with cirrhosis (RR=0.52, 95% CI: 0.29 to 0.94, $p=0.03$), but not NVUGIB or IHD. Restrictive transfusion was associated with lower rebleeding risk overall (RR=0.53, 95% CI: 0.31 to 0.89, $p=0.02$), and for the subgroups with cirrhosis (RR=0.53, 95% CI: 0.30 to 0.94, $p=0.03$) and NVUGIB (RR=0.37, 95% CI: 0.15 to 0.92, $p=0.03$). No increased risk of ischaemic events was observed with restrictive transfusion.

Conclusions Compared to liberal transfusion, restrictive RBC transfusion was associated with a reduction in mortality, rebleeding and number of RBC units transfused, without apparent increase in ischaemic events.

INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) is a common medical emergency and important cause of morbidity and mortality worldwide [1]. Bleeding most frequently arises from non-variceal sources (non-variceal upper gastrointestinal bleeding; NVUGIB) or from variceal sources in patients with portal hypertension and liver cirrhosis. Whilst the general approach to management of these groups is similar, prognosis differs and is influenced by differing underlying mechanisms of bleeding and burden of comorbidity. Regardless, transfusion of red blood cells (RBCs) is integral to management and AUGIB is one of the leading single indications for RBC transfusion [2]. Large observational studies demonstrate considerable practice variation [3, 4] and current learned guidelines base recommendations regarding RBC transfusion thresholds for AUGIB on randomized controlled trials (RCTs) conducted in critically ill populations which excluded AUGIB or patients with significant haemorrhage [5, 6].

Given the rapid development of anaemia, hemodynamic compromise, high burden of co-morbidity and anticoagulant use associated with AUGIB, transfusion requirements may differ from other critically unwell populations. A Cochrane review of RCTs updated in 2010 comparing restrictive versus liberal RBC transfusion for AUGIB found no robustly conducted studies to inform this important clinical question [7]. Subsequently, two RCTs comparing transfusion thresholds for AUGIB have been published [8, 9]. In the first study, a single centre RCT of 921 patients with AUGIB, randomization to a restrictive strategy (transfusion when haemoglobin was below 70

g/L) was associated with a 45% lower risk of all-cause mortality and a 38% lower risk of rebleeding compared to a liberal transfusion strategy (transfusion when haemoglobin was below 90 g/L) [9]. However the treatment effect was only significant for patients with cirrhosis and variceal bleeding, with no difference observed in mortality or rebleeding rates in patients with peptic ulcer bleeding, the latter subgroup constituting the largest aetiology of AUGIB cases [9]. The second study, a cluster RCT comparing the feasibility of implementing restrictive (transfusion when haemoglobin was below 80 g/L) or liberal (transfusion when haemoglobin was below 90 g/L) transfusion policies in UK hospitals found no difference in any clinical outcomes for the overall cohort or subgroup analyses [8].

In order to adequately assess the efficacy and safety of restrictive versus liberal transfusion strategies for AUGIB, it is important to pool the results across studies. Accordingly, we conducted a systematic review and meta-analysis of randomized controlled trials comparing restrictive and liberal RBC transfusion thresholds in adults with AUGIB to determine the impact upon the clinical outcomes of RBC transfusion, mortality, rebleeding and ischaemic events. In addition, we examined treatment effects for mortality and rebleeding in three important pre-specified subgroups: (a) patients with liver cirrhosis and; (b) patients with NVUGIB; (c) patients with baseline ischaemic heart disease (IHD).

METHODS

This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

Data Sources, Searches and Study Selection

We conducted a systematic search of MEDLINE (1946 to 20 October 2016), EMBASE (1974 to 20 October 2016), CENTRAL (The Cochrane Library 2016, Issue 9), CINAHL (1982 to 20 October 2016), the Transfusion Evidence Library (1950 to 20 October 2016) and ongoing trial databases (searched 20 October 2016). We included RCTs that studied participants aged 16 years and older with AUGIB and compared the following interventions: (1) RBC transfusion and standard care versus other intravenous fluid and standard care; (2) initial RBC transfusion to a maximum of two units versus initial RBC transfusion with no upper limit (and more than two units); (3) RBC transfusion trigger of less than 80 g/L versus red blood cell transfusion trigger of more than 80 g/L, but less than 110 g/L for women and less than 130 g/L for men. Potentially eligible studies were also required to report at least one of the following outcomes: mortality, re-bleeding, number of RBC units transfused or an ischemic event (any of acute myocardial infarction, stroke, or acute kidney injury). We included studies irrespective of language, sample size or length of follow up. Two reviewers (AO, MD) independently assessed eligibility of articles identified in the search strategy for inclusion in the review and discussed those deemed potentially eligible (Figure 1).

Data Extraction and Quality Assessment

Two reviewers (AO and MD) independently extracted data using standardized data collection forms. Information was extracted on general study characteristics (author, year of publication, sample size, length of study follow up) and participant

characteristics (age, sex, mean Rockall score [11], number of participants with variceal or NVUGIB and number of participants with liver cirrhosis or IHD). For the clinical outcomes of interest, effect estimates and associated 95% confidence intervals (CI) and p-values were extracted. Where reported, effect size estimates were also recorded for patients with a non-variceal source of bleeding, liver cirrhosis and for patients with underlying IHD. Where available, hazard ratios were extracted. If no effect estimates were provided, odds-ratios were calculated and Peto's method was used when there were no events in any study group. Standard errors were estimated based on reported p-values.

The cluster randomized trial by Jairath et al. reported results as mean differences [8]. Since we had access to the individual patient data from this study, we re-analysed the individual patient data from the trial to calculate hazard ratios in order to facilitate meta-analysis. This was performed through multilevel modelling of time-to-event data with treatment as a fixed effect and study site as a random effect. The study by Villanueva et al [9] reported results for adults with bleeding from peptic ulcers but this data was not reported in the original publication by Jairath et al [8] In order to allow for meta-analysis, we used the individual patient data from the study by Jairath et al [8] to obtain estimates for adults with NVUGIB. We otherwise adhered to the pre-specified analyses that were described in the published statistical analysis plan for the trial [12]. A risk of bias assessment was performed using the Cochrane Risk of Bias tool [13].

Data Synthesis and Analysis

Summary estimates for each outcome were computed by random effects meta-analysis using the generic inverse variance method [14]. Heterogeneity was assessed using the I^2 statistic. The p-value for the I^2 statistic was also assessed to determine the strength of evidence for heterogeneity. We anticipated that few eligible studies would be identified, with varying levels of detail regarding baseline characteristics of participants. Therefore, we planned a conservative approach to exploring heterogeneity using sensitivity analyses in relation to study design (parallel versus cluster). In accordance with Cochrane guidance, we refrained from conducting an analysis for publication bias because our meta-analysis identified fewer than 10 studies [15].

The absolute risk reduction (ARR) was calculated for significant outcomes using the formula ARR = (1- relative risk) (assumed control risk) [14]. The assumed control risk was calculated using the pooled event rate (in events per patient month of follow up) in the control group of the two trials that reported length of follow up [8, 9]. Results were expressed as percentages. The number needed to treat (NNT) was calculated as 1/ARR.

All analyses were performed using RevMan (version 5.3.5), Stata 14 (StataCorp, College Station, TX) and R Statistical Software (Version 3.2.0). A p-value of less than 0.05 was considered statistically significant.

RESULTS

In total, 2849 abstracts were reviewed and 2824 excluded based on screening of the title and abstract. Twenty-five full-text articles were reviewed and 20 articles were excluded because the studies were non-randomized or review articles, the intervention of interest was not used or no relevant outcomes were reported (Figure 1). Accordingly, five studies, involving 1965 participants (917 assigned to a restrictive transfusion strategy and 1064 assigned to a liberal transfusion strategy) were included in the meta-analysis (Table 1) [8, 9, 16-18]. The study by Lee et al [17] was reported as on-going with interim results reported from a conference abstract.

General characteristics of included studies

General characteristics of the five trials are reported in Table 1. The trials from Villanueva et al [9] and Jairath et al [8] contributed 1825/1965 (93%) of the total study participants. Four trials randomised participants to two differing RBC transfusion strategies (three using haemoglobin thresholds [8, 9, 17] and one using haematocrit thresholds [18]) and one trial randomised participants to transfusion *vs.* no transfusion [16]. One trial was conducted before the routine use of endoscopic therapy and high dose proton pump inhibition, although this trial only included 50 participants [16]. The two largest studies [8, 9] enrolled unselected patients and thus enrolled participants with NVUGIB as well as patients with liver cirrhosis and variceal bleeding. Only one trial included all presentations with AUGIB, regardless of

age or co-morbidity and thus was the only trial to include patients with IHD at baseline [8].

Length of follow up was reported in two of the five studies and ranged from 28 days to 45 days (Table 2). Two studies included adults with cirrhosis and variceal bleeding [8, 9] whereas three studies included adults with NVUGIB only [16-18]. Only one study included adults with baseline IHD [8].

RBC Transfusions

Four studies reported the mean number of transfusions received by adults in each study group (Figure 2). The pooled mean difference was -1.90 units (95% confidence interval (CI): -2.26 to -1.53, p<0.00001) in favour of the restrictive transfusion strategy. Moderate heterogeneity was noted (I^2=64%, p=0.04). To explore sources of heterogeneity further, we excluded the study by Jairath et al [8], because this study used a cluster randomized design whereas other studies were parallel group by design. With this exclusion, the effect estimate increased slightly (mean difference=-2.05, 95% CI: -2.30 to -1.79, p<0.00001) and heterogeneity was reduced (I^2=39%, p=0.19).

All-Cause Mortality

Four studies reported all-cause mortality as an outcome. The pooled relative risk of all-cause mortality overall was 35% lower in patients managed with a restrictive transfusion strategy compared to those managed with a liberal transfusion strategy (Relative risk (RR)= 0.65, 95% CI: 0.44 to 0.97, p=0.03) (Figure 3). There

was minimal evidence of heterogeneity (I^2=1%, p=0.37). The pooled relative risk of all-cause mortality in patients with cirrhosis was 48% lower in patients managed with a restrictive transfusion strategy compared to those managed with a liberal transfusion strategy (Figure 3, RR=0.52, 95% CI: 0.29 to 0.94, p=0.03). No difference for all-cause mortality was observed between restrictive and liberal transfusion strategies in patients with a NVUGIB (RR=0.78, 95% CI: 0.47 to 1.29, p=0.33) (Figure 3) or amongst patients with baseline IHD (RR=4.38, 95% CI: 0.86 to 22.31, p=0.08). The corresponding ARR was 2.22% (0.32%-3.55%) for all-cause mortality overall and 6.5% (0.83%-9.68%) for mortality in the cirrhosis subgroup (Table 4). The NNT to prevent one death using a restrictive transfusion strategy was 45 (28 to 315) overall, and 15 (10 to 121) in the subgroup of patients with cirrhosis (Table 4).

Rebleeding

All studies reported rebleeding as an outcome. The pooled relative risk of rebleeding was 47% lower in adults managed with a restrictive transfusion strategy compared to adults managed with a liberal transfusion strategy (RR=0.53, 95% CI: 0.31 to 0.89, p=0.02) (Figure 4). There was little heterogeneity (I^2=39%, p=0.328) and results did not change excluding the interim results from Lee *et al* [17].

Treatment effects were similar across subgroups. In patients with cirrhosis, the pooled relative risk of rebleeding was also 47% lower in the restrictive transfusion group compared to the liberal transfusion group (RR=0.53, 95% CI: 0.30 to 0.94, p=0.03) (Figure 4). In patients with a NVUGIB the relative risk of rebleeding

was 63% lower in the restrictive transfusion group compared to the liberal transfusion group (Figure 4, RR=0.37, 95% CI: 0.15 to 0.92, p=0.03). Finally, no difference was observed between the two transfusions strategies in the relative risk of rebleeding among patients with baseline IHD (RR=0.71, 95% CI: 0.13 to 3.88, p=0.69). The corresponding ARR was 4.21% (1.44%-6.03%) for overall rebleeding, 5.87% (0.75%-8.74%) for rebleeding in the cirrhosis group and 6.10% (0.9%-8.4%) for rebleeding in the NVUGIB (Table 4). The NNT to prevent one rebleeding event using a restrictive transfusion strategy was 24 (17 to 70) in the group overall, 17 (11 to 134) in the subgroup with cirrhosis and 16 (12 to 111) in the subgroup with NVUGIB (Table 4).

Ischaemic events

Three trials reported data for acute myocardial infarction [8, 9, 18], two trials for stroke [9, 18] and two trials for acute kidney injury [8, 9]. No difference was observed between restrictive and liberal transfusion strategies for acute myocardial infarction (RR=0.73, 95% CI: 0.38 to 1.43, p=0.36), ischaemic stroke (RR=0.49, 95% CI: 0.02 to 12.01, p=0.66) or acute kidney injury (RR=0.77, 95% CI: 0.56 to 1.04, p=0.09) (Figure 5).

Risk of Bias

Two studies were at low risk of bias for all categories [8, 9] and the remaining three studies were at unclear risk of bias for most categories, except the study by Villarejo et al [18], which was at high risk of bias for attrition (Table 3).

DISCUSSION

This study is the most up-to-date systematic review and meta-analysis of randomized trials comparing restrictive and liberal transfusion strategies among adults with AUGIB, including re-analysis of individual participant data from a cluster-randomised trial [8]. We identified data from five RCTs enrolling 1965 participants with AUGIB and were able to examine treatment effects in clinically important subgroups, including patients with liver cirrhosis, NVUGIB and those with IHD. A restrictive transfusion threshold was associated with a mean two-unit reduction in the number of RBCs transfused. Given that AUGIB is reported to be the single leading indication for RBCs transfusion in England [2, 4], implementation of restrictive practice is likely to have considerable resource and financial implications for blood transfusion services worldwide. It was recently estimated that even a moderate 13% absolute reduction in RBCs for AUGIB, a modest treatment effect observed in one of the trials included in this review, could lead to over £3 million saving for the UK National Health Service [8, 19].

For all cause AUGIB, the pooled results demonstrate that restrictive RBC transfusion was associated with a 35% relative reduction in mortality (risk difference 2.2%, number needed to treat with restrictive transfusion to prevent one death = 45), supporting the results observed in the trial by Villanueva at al [9]. The mechanism by which liberal RBC transfusion leads to increased mortality is unclear, although several hypotheses exist. First, transfusion is associated with immunomodulatory effects, which are considered to predispose to increased risk of hospital acquired infections [4, 20, 21]. Second, liberal transfusion is also associated with circulatory

overload, which may lead to harmful effects both in older patients with IHD, as well as in patients with cirrhosis through worsening of portal hypertension. Third, the increased mortality may be mediated through increased rebleeding, given the known excess mortality in patients who experience rebleeding compared to those who do not [1]. It is notable in subgroups that the excess risk of death was only observed in patients with liver cirrhosis and not in patients with NVUGIB. This may be related to decompensation of underlying end stage liver disease [22], but also that patients with cirrhosis generally present with more severe bleeding compared to patients with NVUGIB [23].

We found that restrictive transfusion was associated with a lower risk of rebleeding for all cause AUGIB, but also had a consistent and similar magnitude of treatment effects across patients with cirrhosis as well as NVUGIB (NNT 24). This has important implications for clinical practice, since strategies to prevent rebleeding have been highlighted as a key treatment target in the management of AUGIB [1]. For patients with liver cirrhosis, a liberal approach to transfusion has been shown to increase portal pressures which is likely to directly mediate rebleeding [24]. In patients with a non-variceal source, mechanisms are incompletely understood, but are postulated to be related to impaired clot formation and stability, since transfusion is considered to counteract the splanchnic vasoconstrictive response to hypovolaemia, as well as to impair coagulation [21].

A key area of uncertainty is whether patients with IHD can be safely managed with a restrictive transfusion practice. This is particularly relevant to patients with NVUGIB

where there is a large burden of comorbidity, where almost 40% of patients have co-existent IHD [3, 25, 26]. In a meta-analysis of transfusion strategies in over 40 RCTs across various therapeutic areas (medical and surgical), a restrictive transfusion strategy (in most cases threshold of 80 g/l) was associated with a 78% increased risk of a new acute coronary syndrome compared to a liberal transfusion strategy (in most cases threshold of 80 g/l) which was statistically significant (absolute risk 2.7% liberal transfusion vs. 4.6% restrictive transfusion), but no increased risk of mortality [27]. Whilst in this meta-analysis of AUGIB we observed no increased risk of acute coronary syndrome, these data should be interpreted with caution, since the largest trial by Villanueva et al excluded patients with a recent history of an ischaemic event at trial entry [9]. Thus improving the evidence base for safe transfusion threshold in patients with IHD is a key research priority, until which time default recommendations of restrictive transfusion practice should not apply to this group of patients [28].

There are some limitations to this review. First, differing transfusion thresholds were used in the trials which may reduce the validity of pooling data since exposure to anaemia would be longer with lower values, although in the majority (3 of 5 trials) an Hb of 80 g/L was set as the restrictive policy. Second, the vast majority of data arose from two RCTs, nonetheless these were trials published within the last 3 years using modern day approaches to the management of AUGIB. It should be noted that the trial from Villanueva et al was an efficacy trial, conducted under strict protocols of care in a specialist institution with access to endoscopy within 6 hours to all patients; therefore these results should be interpreted in the context of each

institution's access to endoscopic therapy, since this in itself may influence thresholds for transfusion [4, 21]. Finally, we were unable to obtain further data from the abstract presentation by Lee et al, which is reported as on-going [17].

In conclusion, the results of this meta-analysis suggest that for patients with AUGIB the use of a restrictive transfusion strategy (haemoglobin level 70-80 g/l) is associated with a reduction in mortality and rebleeding, with the strongest treatment effect observed in patients with liver cirrhosis. These results may not apply to patients with IHD or severe haemorrhage, where decisions for transfusion should be based upon clinical judgement and individualised risk.

Author contributions

AO, MJRD and VJ wrote the manuscript. VJ conceived the idea for the review. AO and MD screening the trials and extracted data. AO and MD performed the analysis with guidance from MT and GSCfrom GSC and MT. CD devised the search strategy. SB and SH provided methodological expertise. AJS, BCK, RFAL, CV, MFM and VJ provided original data from their studies and contributed clinical expertise. All authors critically reviewed the manuscript.

Conflicts of interest

AO, MJRD, MT, CD, GSC, SH, SB and ANB have no conflicts of interest to declare. AJS, BK, RFAL, CV, MFM and VJ were original authors of trials included in this review.

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Figures

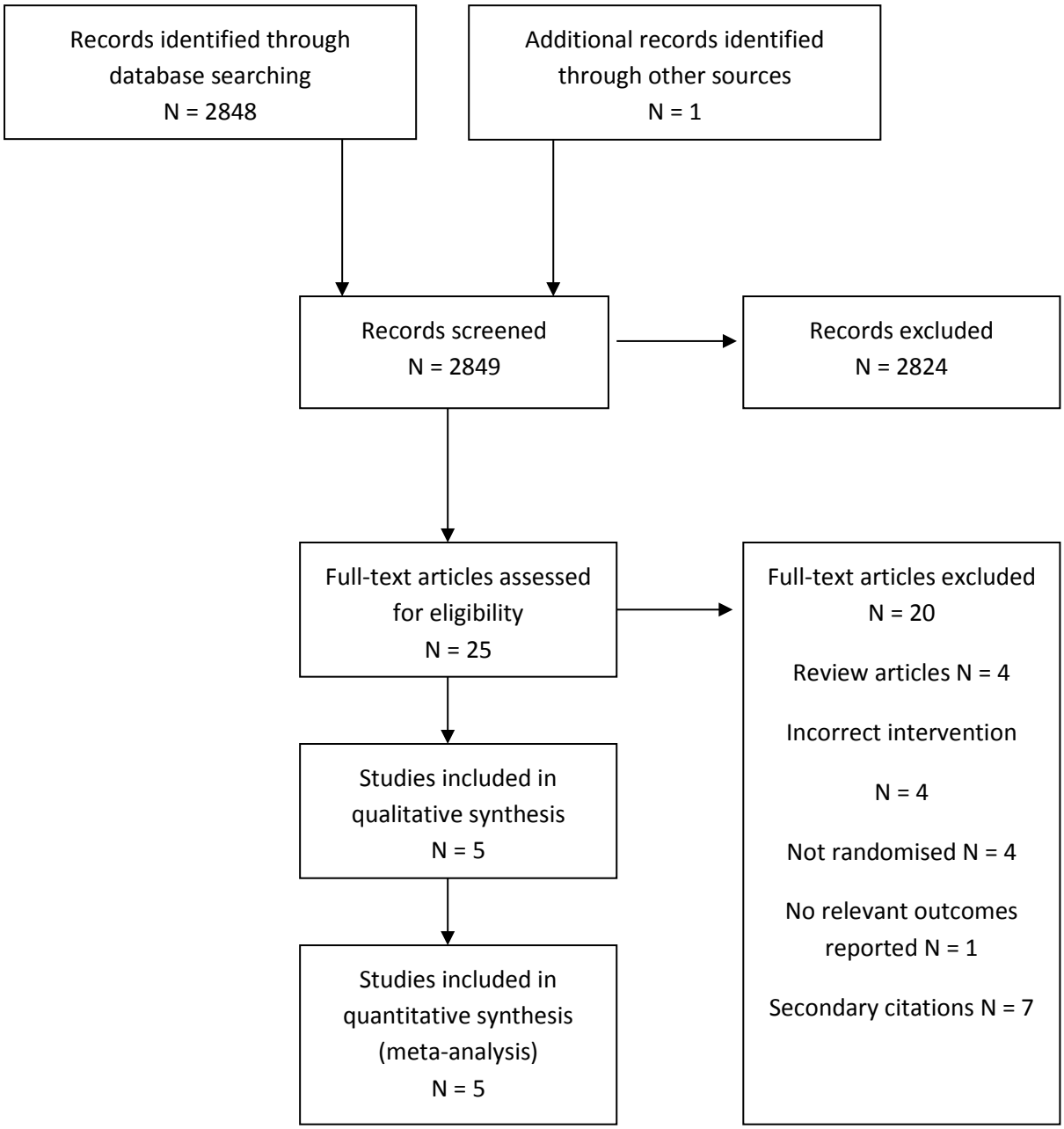


Figure 1: Identification of Eligible Studies

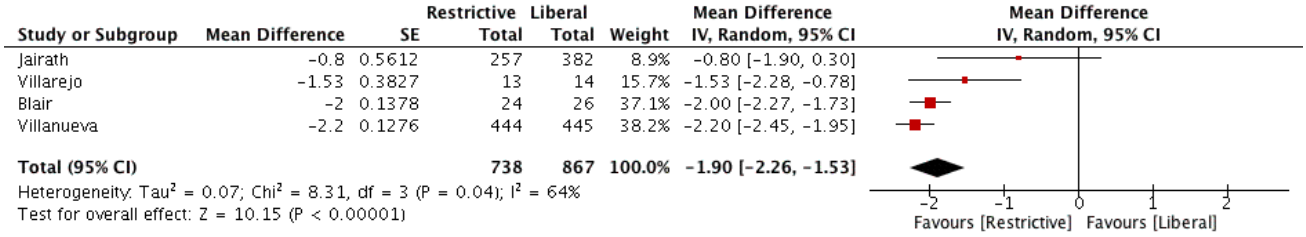
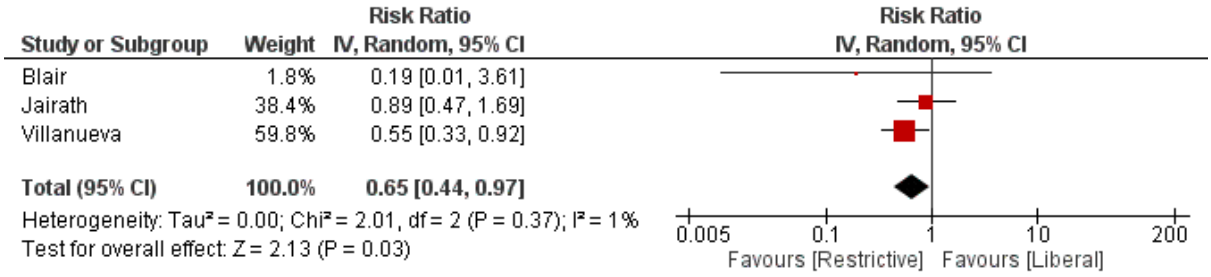


Figure 2: Pooled mean difference for number of transfusions in restrictive versus liberal transfusion groups. CI – confidence interval, IV – inverse variance, SE – standard error

3a



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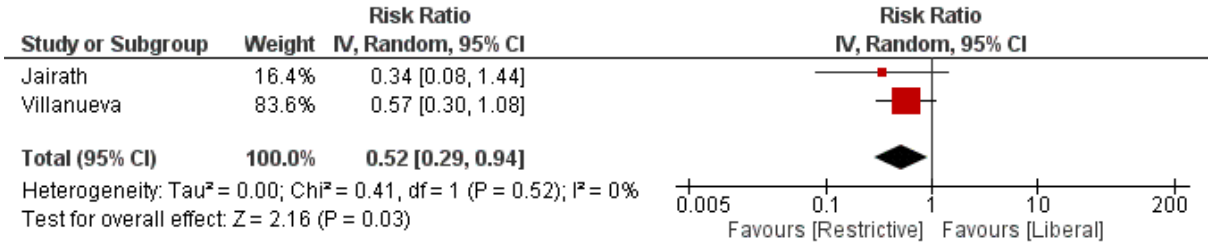


3c

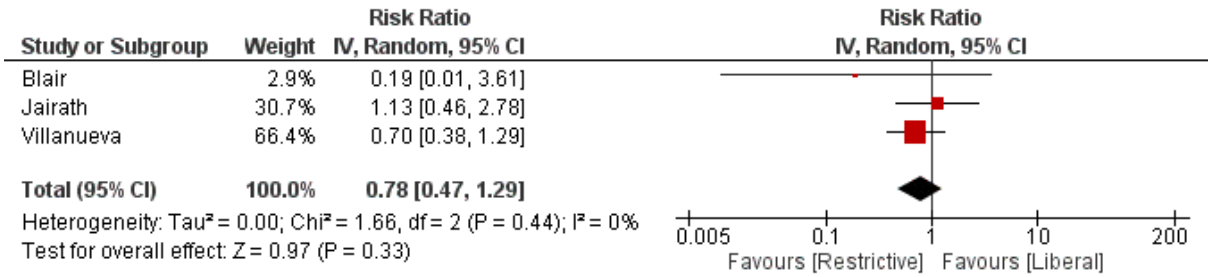
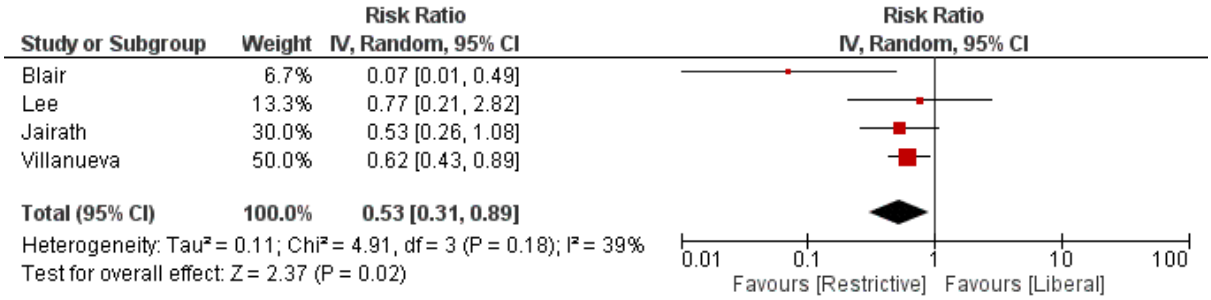
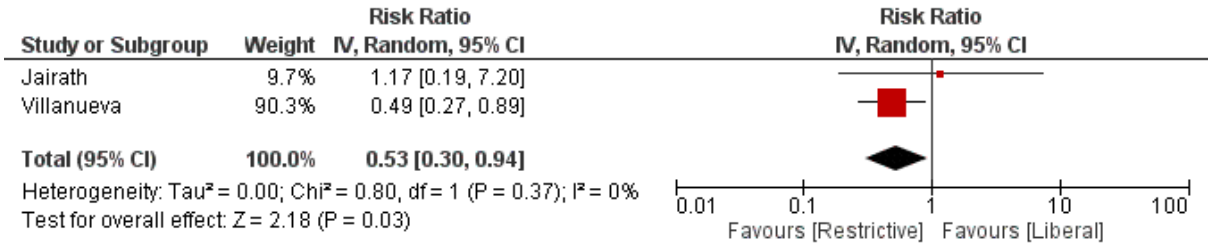


Figure 3: Pooled relative risk of mortality in restrictive versus liberal transfusion groups. Figure 3a Overall mortality. **Figure 3b** Mortality in cirrhosis subgroup. **Figure 3c** Mortality in non-variceal bleed subgroup. No deaths occurred in either arm of one trial and consequently it is not represented in the forest plots for overall mortality or in the non-variceal bleeding subgroup [18]. CI – confidence interval, IV – inverse variance.

4a



4b



4c

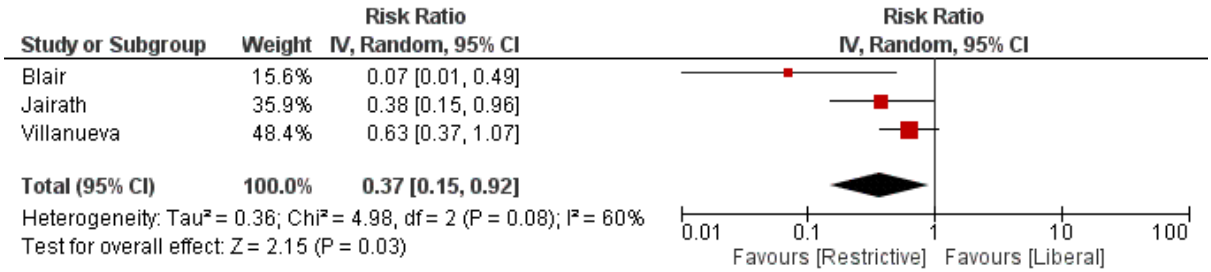
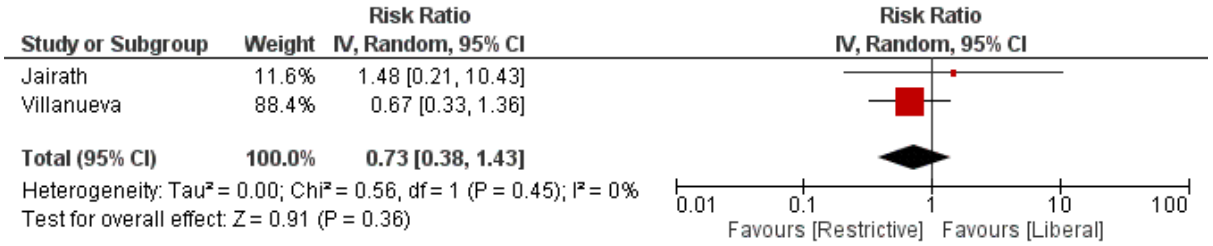
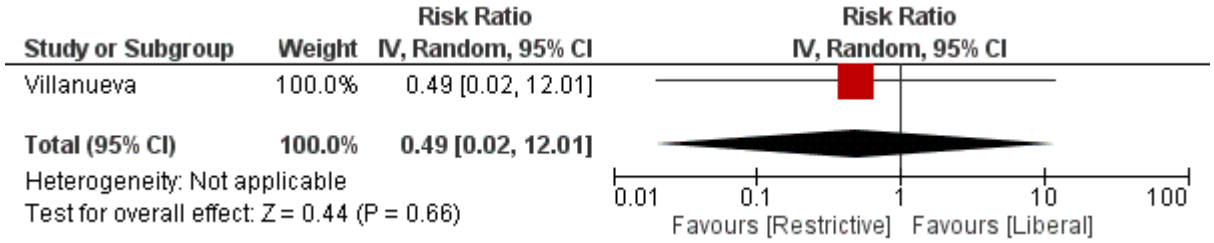


Figure 4: Pooled relative risk of rebleeding in restrictive versus liberal transfusion groups. Figure 4a Overall rebleeding. **Figure 4b** Rebleeding in cirrhosis subgroup. **Figure 4c** Rebleeding in non-variceal bleed subgroup. No rebleeding occurred in either arm of one trial and consequently it is not represented in the forest plots for overall rebleeding or in the non-variceal bleeding subgroup [18]. CI – confidence interval, IV – inverse variance.

5a



5b



5c

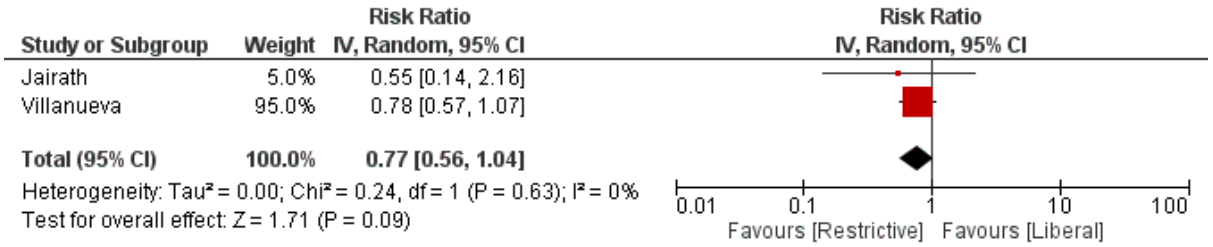


Figure 5: Pooled relative risk of vascular outcomes in restrictive versus liberal transfusion groups. Figure 5a Myocardial infarction. **Figure 5b** Ischaemic stroke. **Figure 5c** Acute kidney injury. CI – confidence interval, IV – inverse variance.

Tables

Author [Country]	Design	Intervention haemoglobin threshold	Follow-up	Outcomes reported
Blair et al, 1986 [16] [United Kingdom]	Single Centre, Parallel Group	Restrictive: 80 g/L Liberal: no threshold (all received 2 units red cells)	Not Stated	• Mortality • Rebleeding • Red cell transfusions
Lee et al, 2014 [17] [South Korea]	Single Centre, Parallel Group	Restrictive: 80 g/L Liberal: 100 g/L	Not Stated	• Rebleeding
Jairath et al, 2015 [8] [United Kingdom]	Multicentre, Cluster Randomized	Restrictive: 80 g/L Liberal: 100 g/L	28 days	• Mortality • Rebleeding • Acute myocardial infarction • Stroke • Transfusion reactions • Acute kidney injury • Bacterial infection • Red cell transfusions • Duration of hospitalization
Villanueva et al, 2013 [9] [Spain]	Single Centre, Parallel Group	Restrictive: 70 g/L Liberal: 90 g/L	45 days	• Mortality • Rebleeding • Acute myocardial infarction • Stroke • Transfusion reactions • Acute kidney injury • Bacterial infection • Red cell transfusions • Duration of hospitalization
Villarejo et al, 1999 [18] [Argentina]	Single Centre, Parallel Group	Restrictive: Haematocrit 21% Liberal: Haematocrit 28%	Not Stated	• Mortality • Rebleeding • Acute myocardial infarction • Stroke • Duration of hospitalization

Table 1: Characteristics of included studies

Study Name	Study Group	Number of participants	Mean Age (years)	Male n (%)	Cirrhosis n (%)	Variceal Bleed n (%)	Non-Variceal Bleed n (%)	Cardiac Disease n (%)
Blair et al, 1986 [16]	Restrictive	26	60	34 (68)	0	0	26 (100)	0
	Liberal	24	64		0	0	24 (100)	0
Lee et al, 2014 [17]*	Restrictive	32	-	-	-	-	-	-
	Liberal	31	-	-	-	-	-	-
Jairath et al, 2015 [8]**	Restrictive	403	58	244 (61)	45 (11)	25 (6)	261 (65)	61 (15)
	Liberal	533	60	322 (60)	91 (17)	56 (11)	331 (62)	76 (14)
Villanueva et al, 2013 [9]	Restrictive	444	64	314 (71)	139 (31)	101 (23)	343 (77)	0
	Liberal	445	66	291 (65)	138 (31)	109 (24)	336 (76)	0
Villarejo et al, 1999 [18]	Restrictive	14	-	-	0	-	-	0
	Liberal	13	-	-	0	-	-	0

Table 2: Baseline characteristics of participants in included studies. *The study by Lee et al [17] was on-going and results were obtained from an abstract. **Endoscopy was not performed for 117 adults in the restrictive group and 146 adults in the liberal group and therefore source of bleeding could not be identified for cases.

Study	Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Investigators	Blinding of Outcome Assessors	Attrition	Selective Outcome Reporting	Other Bias
Blair et al, 1986 [16]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Lee et al, 2014 [17]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Jairath et al, 2015 [8]	Low	Low	Low	Low	Low	Low	Low	Low
Villanueva et al, 2013 [9]	Low	Low	Low	Low	Low	Low	Low	Low
Villarejo et al, 1999 [18]	Low	Low	Low	Low	Low	High	Unclear	Unclear

Table 3: Risk of bias

Outcome	Absolute Risk Reduction (%)	Number Needed to Treat
Mortality – overall	2.22 (0.32-3.55)	45 (28 to 315)
Mortality – cirrhosis	6.50 (0.83-9.68)	15 (10 to 121)
Rebleeding – overall	4.21 (1.44-6.03)	24 (17 to 70)
Rebleeding – cirrhosis	5.87 (0.75-8.74)	17 (11 to 134)
Rebleeding – non-variceal bleeding	6.1 (0.9-8.4)	16 (12 to 111)

Table 4: Absolute risk reduction and number needed to treat for restrictive versus liberal transfusion groups. The number needed to treat was only calculated where a statistically significant treatment effect was obtained.