


SUPPLEMENT ARTICLE

Platelet-to-red blood cell ratio and mortality in bleeding trauma patients: A systematic review and meta-analysis

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Abstract

Background: In traumatic bleeding, transfusion practice has shifted toward higher doses of platelets and plasma transfusion. The aim of this systematic review was to investigate whether a higher platelet-to-red blood cell (RBC) transfusion ratio improves mortality without worsening organ failure when compared with a lower ratio of platelet-to-RBC.

Methods: Pubmed, Medline, and Embase were screened for randomized controlled trials (RCTs) in bleeding trauma patients (age ≥ 16 years) receiving platelet transfusion between 1946 until October 2020. High platelet:RBC ratio was defined as being the highest ratio within an included study. Primary outcome was 24 hour mortality. Secondary outcomes were 30-day mortality, thromboembolic events, organ failure, and correction of coagulopathy.

Results: In total five RCTs ($n = 1757$ patients) were included. A high platelet:RBC compared with a low platelet:RBC ratio significantly improved 24 hour mortality (odds ratio [OR] 0.69 [0.53–0.89]) and 30-day mortality (OR 0.78 [0.63–0.98]). There was no difference between platelet:RBC ratio groups in thromboembolic events and organ failure. Correction of coagulopathy was reported in five studies, in which platelet dose had no impact on trauma-induced coagulopathy.

Conclusions: In traumatic bleeding, a high platelet:RBC improves mortality as compared to low platelet:RBC ratio. The high platelet:RBC ratio does not influence thromboembolic or organ failure event rates.

KEYWORDS

coagulopathy, organ failure, platelet, transfusion, trauma

Abbreviations: CCT, conventional coagulation test; ISS, injury severity score; MODS, multiple organ dysfunction syndrome; RBC, red blood cell; RCT, randomized controlled trial; TEE, thromboembolic events; TIC, trauma-induced coagulopathy; TXA, tranexamic acid; VHA, viscoelastic hemostatic assay.

1 | INTRODUCTION

Uncontrolled hemorrhage remains one of the major causes of preventable death after injury.¹ Trauma-induced

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coagulopathy (TIC) develops in 30%–40% of these patients.^{2,3} TIC is associated with both early and late mortality,^{2,4,5} with rates as high as 40%.^{6,7} Furthermore, TIC is associated with an increased incidence of acute lung injury, multiple organ failure, and infections.^{8–10}

Platelets play an important role in the pathophysiology of TIC.¹¹ Although platelet count typically does not decrease early after traumatic injury,^{12,13} several studies report severe platelet dysfunction after injury, associated with increased mortality.¹⁴ Interestingly, higher platelet counts later during intensive care stay are associated with improved survival,^{15–17} suggesting that maintaining high levels of platelets may prevent, at least partially, the loss of functionality. Alternatively, increasing platelet counts through platelet transfusion might contribute to earlier or improved hemostasis, possibly by limiting hyperfibrinolysis.¹⁸

Observational studies in civilian and military trauma patients suggest a survival benefit for patients receiving higher platelet ratios, which is underlined by results of a randomized controlled trial (RCT).^{8,19–21} Observational studies however, remain subject to bias. Also, it is unclear what the effect is of higher platelet ratios on organ failure and thromboembolic events. Therefore, the aim of this review was to investigate the effect of a high platelet:RBC ratio on mortality when compared with a lower platelet:RBC ratio as reported in RCTs. Furthermore, the effect of high platelet:RBC ratios on the correction of coagulopathy and on the development of thromboembolic events or organ failure was assessed. The hypothesis was that high platelet:RBC ratios are associated with lower early mortality when compared with lower platelet:RBC ratios, but have similar effects on the occurrence of organ failure and thrombosis.

2 | METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA).²²

Medline, PubMed, and Embase were searched with the assistance of a clinical librarian. The search strategy was initially developed for Medline and adapted for the other data sources (Appendix S1). In addition, we searched for ongoing trials on www.controlled-trials.com and www.clinicaltrials.gov. All articles until October 2020 were screened for inclusion.

2.1 | Study selection

All RCTs encompassing hemorrhaging trauma patients of at least 16 years old. Only English, German, and Dutch language articles were selected. Cohort studies, Case-control studies, reviews, correspondences, experimental studies, and

case reports/series were not eligible for inclusion. Studies were included if the dose of platelet transfusion was reported, as well as mortality rates or organ failure. Studies reporting on other patients than trauma were excluded.

Burn victims were excluded, because transfusion practices are markedly different in this population.^{23,24} Bibliographies of systematic reviews and all included studies were screened for relevant publications. Selection of articles was performed by two reviewers (D.K. and R.v.A.). Discrepancies in the inclusion of articles were discussed and, if needed, a third independent reviewer was consulted.

2.2 | Data extraction

The design of the included studies was determined using the Cochrane group checklist.²⁵ The following patient characteristics were extracted from the studies: type of trauma (military or civilian), number of patients, sex, age, trauma mechanism (blunt or penetrating), and injury severity score. Furthermore, the total number of blood products administered to the patients was collected. Ratios of units of platelet:RBC and plasma:RBC were calculated using the means. If studies did not disclose means, they were estimated using the median and interquartile range.²⁶ The type of platelet product or the amount of patients receiving platelet transfusion was often not detailed. Thereby, a quantitative definition of a ratio was not possible. To enable performing our primary analysis, which is the comparison between high and low platelet:RBC ratios, the platelet dose was evaluated separately for every study, in which both pooled and apheresis platelet products were treated the same in the calculation of the platelet:RBC ratio in the study arms.²⁶ A high ratio was defined as being the highest comparator arm, whereas the low platelet:RBC ratio was defined as the lowest comparator arm. The platelet:RBC ratio for each study was calculated within 24 hours (h) after admission.

2.3 | Outcome measures

Primary outcome was mortality, defined as early mortality occurring within 24 h after admission to the hospital. Secondary outcomes were late mortality occurring within 30 days, thromboembolic events, organ failure, and correction of coagulopathy, defined as a normalization of coagulation test results within 24 h after transfusion.

2.4 | Quality assessment

A quality assessment of the RCTs included in this systematic review was performed using the Cochrane Collaboration tool for assessing risk of bias. The cohort was representative

when it consisted of a majority of blunt trauma for civilian studies and penetrating trauma for military studies. Comparability was defined adequate when there was a correction for injury severity scores and blunt trauma. The follow-up was defined as satisfactory when it was at least as long as hospital stay.

2.5 | Statistical analysis

Review Manager (RevMan 5, The Nordic Cochrane Centre, Copenhagen, Denmark) was used for the meta-analysis. Odds ratio (OR) with 95% confidence interval (CI) was used as a measure for dichotomous variables. Fixed-effects model was used for the analysis of RCTs because of the expected small number of studies and because only bleeding trauma patients in the civilian

setting were included and no other causes of blood loss. Thereby, it can be postulated that the effect size of platelet dose on TIC is similar between studies.²⁷ A *p* value of .05 was considered to be statistically significant.

3 | RESULTS

3.1 | Study selection and data extraction

After removal of duplicates, 2620 articles were screened. After title and abstract screening, 11 full texts were evaluated. From the 11 studies, 6 articles were excluded (Figure 1). Reasons for exclusions after full-text screening were as follows: no platelet transfusion given ($n = 4$), or reported ($n = 1$) and no outcome parameters ($n = 1$).

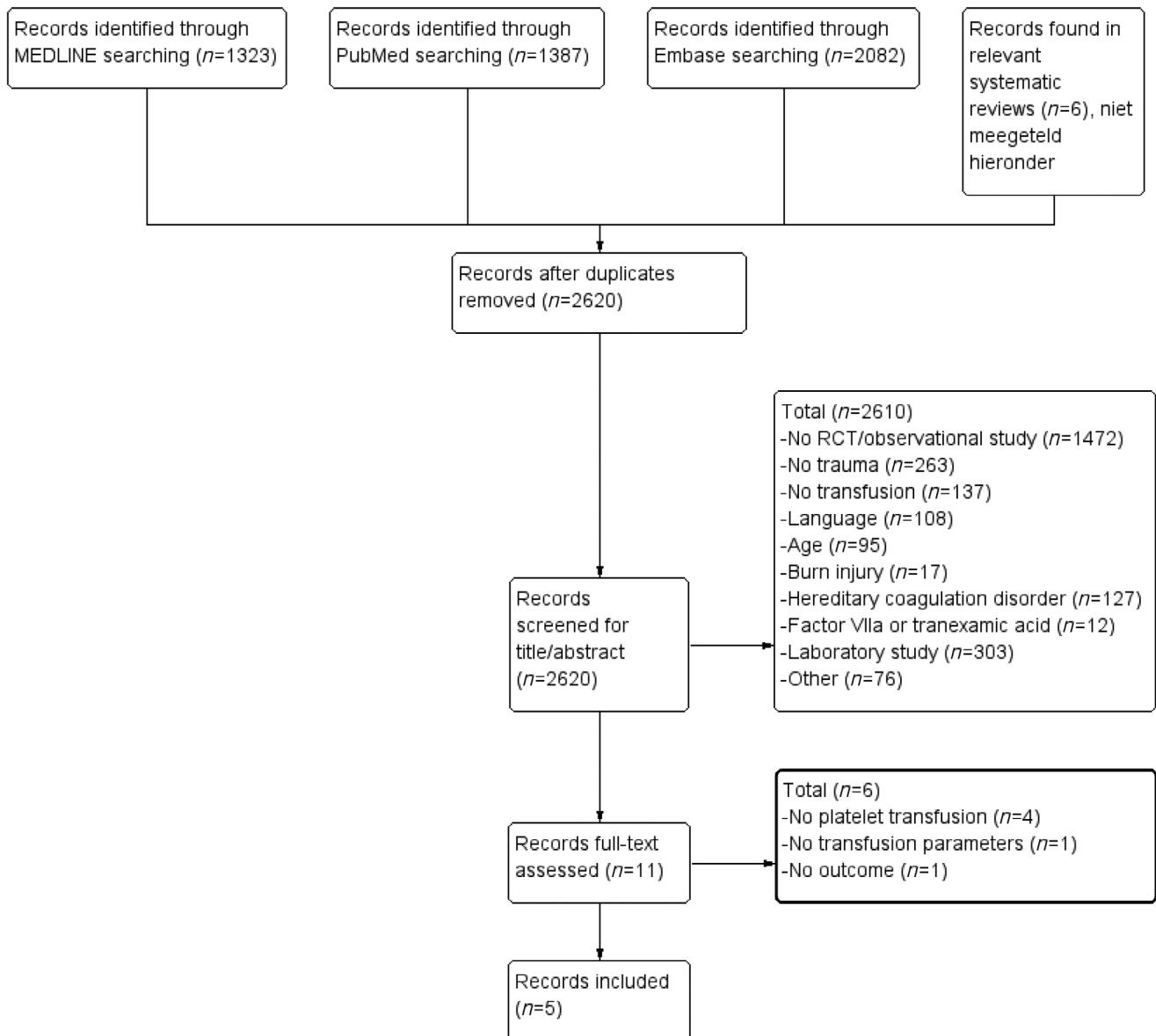


FIGURE 1 Flowchart of selection process

In total, this review included five studies,^{21,28-31} encompassing 1757 patients. The baseline characteristics of the patients in the RCTs are shown in Table 1. The calculated differences of platelet:RBC ratios are shown in Table 2.

The five RCTs consisted of 856 patients transfused with a high platelet:RBC ratio and 901 patients with a low platelet:RBC ratio. Injury severity scores were similar in both groups. The majority of the patients were male and had sustained a blunt trauma.

3.2 | Quality assessments

The overall quality of the studies was moderate, as shown in Figure 2. All but one RCT scored high risk of bias, due to the impossibility of blinding of personnel to the allocation of treatment strategy.

3.3 | The effect of PLT:RBC ratio on mortality

Transfusion of a high platelet:RBC ratio was associated with lower 24-h mortality compared with a low platelet:RBC ratio (Figure 2, OR 0.69 [95% CI: 0.53–0.89]). Furthermore, a high platelet:RBC ratio was associated with lower 30-day mortality compared with a low platelet:RBC ratio (OR 0.78 [95% CI: 0.63–0.98]). To determine whether these results were influenced by a concomitant higher dose of plasma transfusions, additional analyses were performed by comparing high plasma:RBC ratio versus low plasma:RBC ratio and high platelet:plasma ratio versus low platelet:plasma ratio (Figure 3A–D). A high platelet:plasma ratio remained associated with a lower mortality compared with a low platelet:plasma ratio (Figure 3A,B). Contrastingly, a high plasma:RBC ratio was not associated with improvements in 24-h mortality and 30-day mortality compared with a low plasma:RBC ratio in these included studies (Figure 3C, D). This suggests that the observed benefit of a high platelet:RBC ratio in this analysis is independent of the amount of plasma transfusions employed.

3.4 | The effect of PLT:RBC ratio on thromboembolic events and organ failure

Three out of five RCTs described thromboembolic events (Figure 4A). No difference in thromboembolic events was observed in high compared with low platelet:RBC ratio groups (OR 0.91 [95% CI: 0.64–1.31]). All RCTs reported organ failure outcomes (Figure 4B). No difference in

TABLE 1 Characteristics of trauma patients included in randomized controlled trials

Study	Year	Randomization	Group (n)	Male (%)	Blunt (%)	Lactate (mmol/L)	Base excess (mEq/L)	ISS	RBC (units)	Plasma (units)	PLT (units)	PLT product	Cryoprecipitate (units)	PLT:RBC	Plasma:RBC	TXA (%)	MODS (%)	TEE (%)	ICU free days	24 h mortality (%)	30 days mortality (%)
Baksaas-Aasen et al. ³¹	2020	VHA	201	73.2	67.2	5.0*	-8.4*	27*	6.3*	6.3*	8*	P	N.R.	1.27:1	1:1	93.5	86.0	8.5	12*	14	25
Sperry et al. ³⁰	2018	Standard care	271	73.8	83.4	3.9*	N.R.	21*	6.5*	1*	0.3*	^a A/P	N.R.	0.04:1	0.15:1	N.R.	57.6	N.R.	N.R.	22	33
		Prehospital plasma	230	71.3	81.3	3.5*	N.R.	23*	4*	0.8*	0.3*	^a A/P	N.R.	0.06:1	0.19:1	N.R.	63	N.R.	N.R.	14	22
Gonzalez et al. ²⁹	2016	CCT	55	74.5	65.5	5.7*	-13.6*	34*	11*	8*	1*	A	1*	0.09:1	0.73:1	16.4	5.5	10.9	9*	22	15
		VHA	56	66.0	69.6	6.3*	-11.8*	31*	10*	5.5*	1*	A	0.5*	0.10:1	0.55:1	7.1	3.6	16.1	14*	7	13
Holcomb et al. ²¹	2015	1:1:1	338	77.8	54.7	N.R.	-8.1*	28*	9.5*	7.5*	12*	P	0*	1.26:1	0.79:1	18.9	5.9	11.5	5*	13	22
		1:1:2	342	82.7	50.6	N.R.	-8.6*	27*	10*	5.5*	6*	P	2.3*	0.60:1	0.55:1	19.9	4.4	10.8	5*	17	26
Nascimento et al. ²⁸	2013	Fixed ratio	37	64.9	64.9	N.R.	N.R.	35	7.5*	6*	7*	P	0*	0.93:1	0.80:1	13.5	2.7	N.R.	21*	22	30
		Lab guided ratio	32	71.9	59.4	N.R.	N.R.	35	8.5*	4.8*	4*	P	2.5*	0.47:1	0.56:1	18.7	0	N.R.	17*	9	9

Note: Baseline characteristics of included randomized controlled trials. All units are reported in mean or *calculated mean. All ratios are calculated with the mean. 1:1:1 = ratio platelets:plasma:red blood cell. Standard care in Sperry et al. 2018 received both prehospital red blood cells and crystalloids.

Abbreviations: A, apheresis platelet product; CCT, conventional coagulation test; ISS, injury severity score; MODS, multiple organ dysfunction syndrome; N, number of patients; N.R., not reported; P, pooled platelet product; PLT, platelet; RBC, red blood cell; TEE, thromboembolic events; TXA, tranexamic acid; VHA, viscoelastic hemostatic assay.

^aPersonal communication with Prof. dr. J. Sperry: site dependent use of pooled or apheresis platelet product.

TABLE 2 Calculated transfusion ratios for all meta-analyses

Outcome	Mean (SD) ratio in high group	Mean (SD) ratio in low group	Median (IQR) ratio in high group	Median (IQR) ratio in low group
24 h and 30 day mortality Platelet:RBC ratio	0.85 (0.56)	0.40 (0.27)	1.26 (0.06–1.26)	0.60 (0.04–0.60)
24 h and 30 day mortality Platelet:plasma ratio	1.08 (0.56)	0.65 (0.38)	1.28 (0.33–1.60)	0.55 (0.25–1.09)
24 h and 30 day mortality Plasma:RBC ratio	0.70 (0.34)	0.53 (0.30)	0.79 (0.19–0.80)	0.55 (0.15–0.56)
TEE Platelet:RBC ratio	1.15 (0.34)	0.56 (0.15)	1.26 (1.26–1.27)	0.60 (0.60–0.62)
MODS Platelet:RBC ratio	0.83 (0.56)	0.39 (0.27)	1.26 (0.06–1.26)	0.60 (0.04–0.60)

Note: Mean and median ratios of blood products with either SD or interquartile range (IQR), respectively. Groups in studies are divided into having a low or high blood product ratio and based on the units of transfusion products used in that specific study. Abbreviations: TEE, thromboembolic events; MODS, multiple organ dysfunction syndrome.

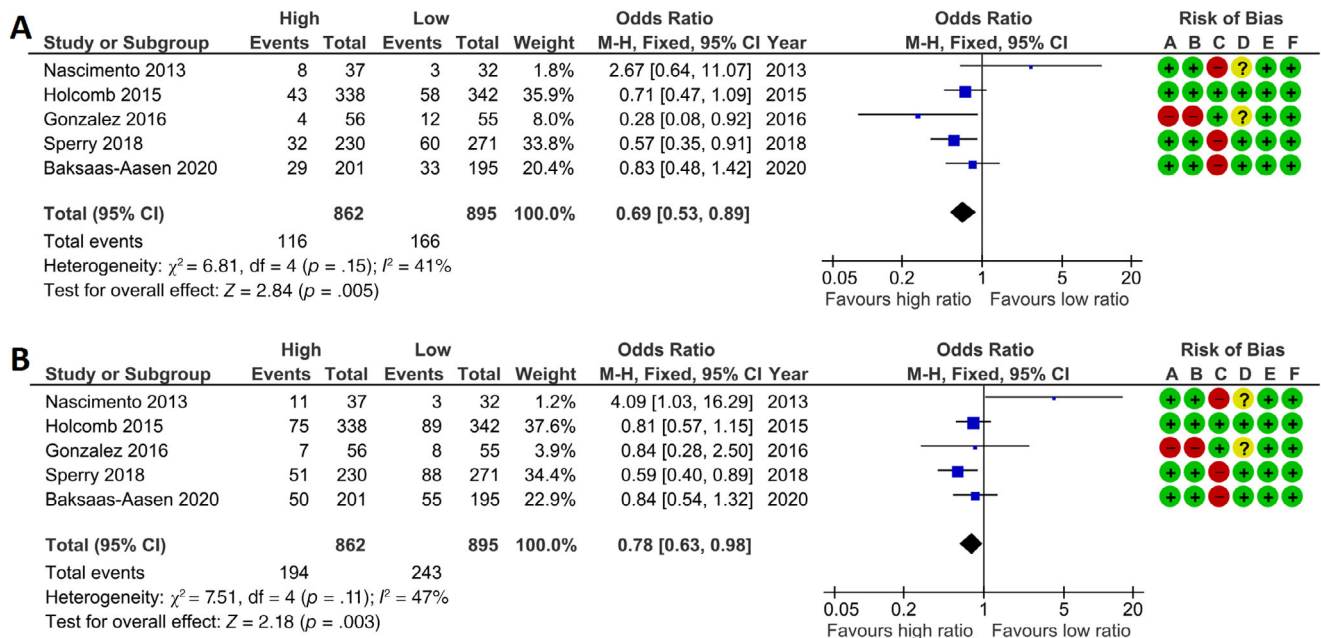


FIGURE 2 High platelet:RBC ratio improves 24-h and 30-day mortality in randomized controlled trials compared with low platelet:RBC ratio. Meta-analyses of (A) 24-h and (B) 30-day mortality represented in a forest plot. Weighted mean platelet:red blood cell ratio in the high ratio group was 0.85 (SD 0.56) and in the low platelet dose group 0.40 (0.27). Events = number of deceased, total = total number of patients, high = group with highest platelet:RBC ratio, low = group with lowest platelet:RBC ratio, M-H = Mantel-Haenszel. Risk of bias was assessed for (A) random sequence generation, (B) allocation concealment, (C) blinding of participants and personnel, (D) blinding of outcome assessment, (E) incomplete outcome data, (F) selective reporting. + = low risk, - = high risk, ? = unknown risk

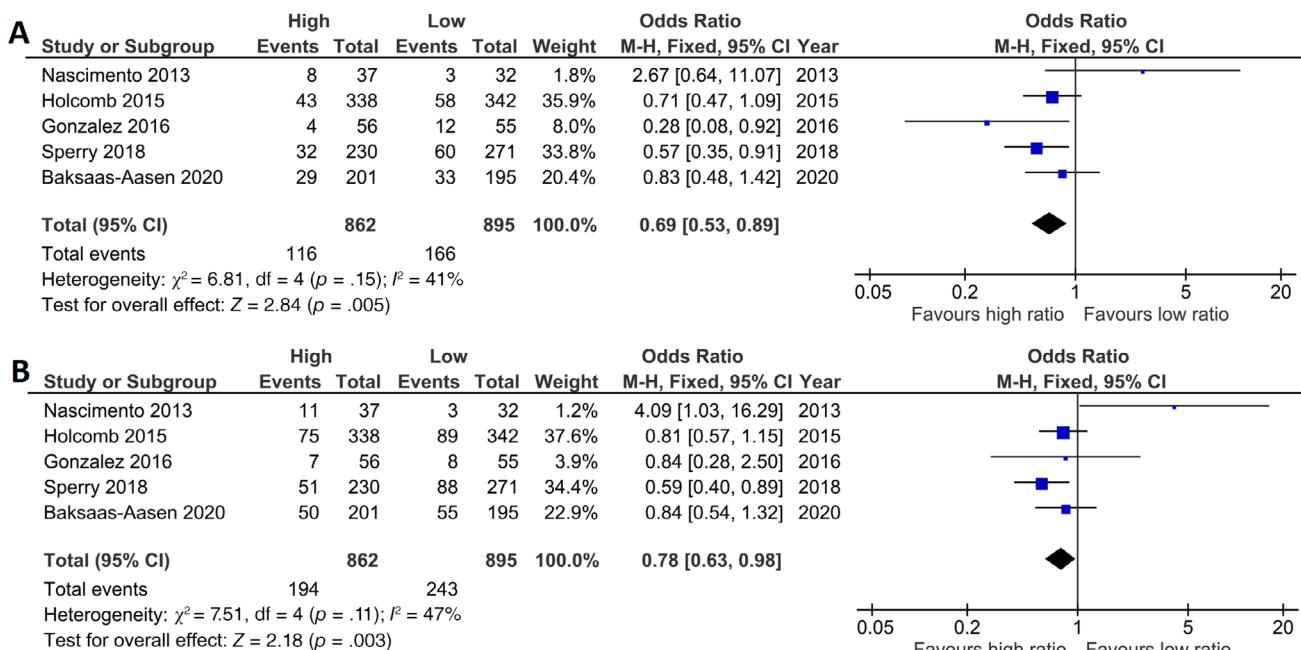
organ failure was seen in high compared with low platelet:RBC ratio (OR 1.24 [95% CI: 0.94–1.64]).

3.5 | The effect of PLT:RBC ratio on correction of coagulopathy

Correction of coagulopathy after transfusion was reported in four studies.^{21,28,29,31} In these studies, no significant differences were observed among patients

transfused with high or low platelet:RBC ratios in terms of correction of deranged international normalized ratio, platelet counts, and fibrinogen levels within 24 h posttransfusion.^{28, 29, 32} For example, in the high ratio group, platelet count dropped from 215 [165–279] × 10⁹/L to 97 [72–128] × 10⁹/L, and in the low ratio group, platelet count dropped from 144 [117–157] × 10⁹/L to 109 [91–130] × 10⁹/L in the first 24 h.²⁹ However, there were no different effects of high and low platelet dose on platelet counts.²⁹ In

High platelet:plasma ratio compared to low platelet:plasma ratio on A. early and B. late mortality



High plasma:RBC ratio compared to low plasma:RBC ratio on C. early and D. late mortality

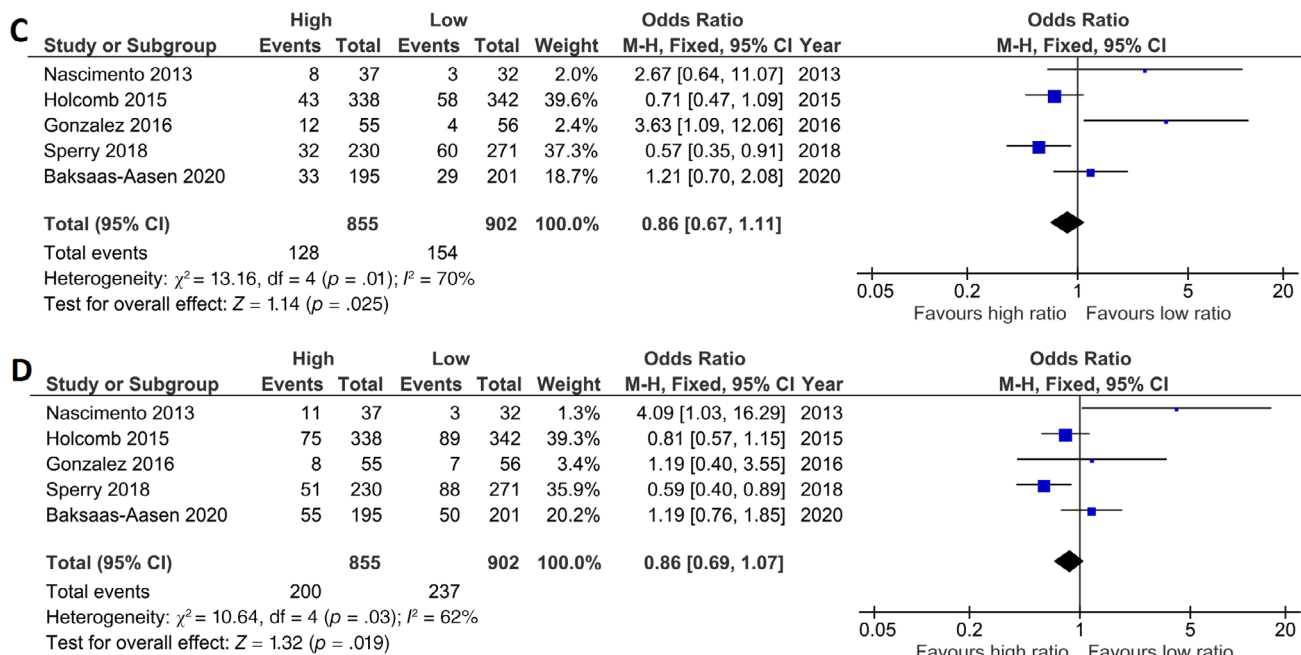


FIGURE 3 High platelet:plasma, but not high plasma:RBC ratio, improves 24-h mortality and 30-day mortality in randomized controlled trials. Meta-analyses of high and low platelet:plasma ratio on (A) 24-h and (B) 30-day mortality and high and low plasma:RBC ratio on (C) 24-h and (D) 30-day mortality represented in a forest plot. Weighted mean platelet:plasma ratio in the high ratio group was 1.08 (SD 0.56) and in the low ratio group 0.65 (0.38). Weighted mean plasma:RBC ratio in the high ratio group was 0.70 (0.34) and in the low ratio group 0.53 (0.30). Events = number of deceased, total = total number of patients, high = group with highest platelet:plasma or plasma:RBC ratio, low = group with lowest platelet:plasma or plasma:RBC ratio, M-H = Mantel-Haenszel

the most recent RCT, the percentage of patients with a prothrombin time ratio more than 1.2 at time of hemostasis was similar.³¹ Thromboelastography

results 24 h after resuscitation were reported in another study, and no significant differences in these values were observed between both groups.²⁹

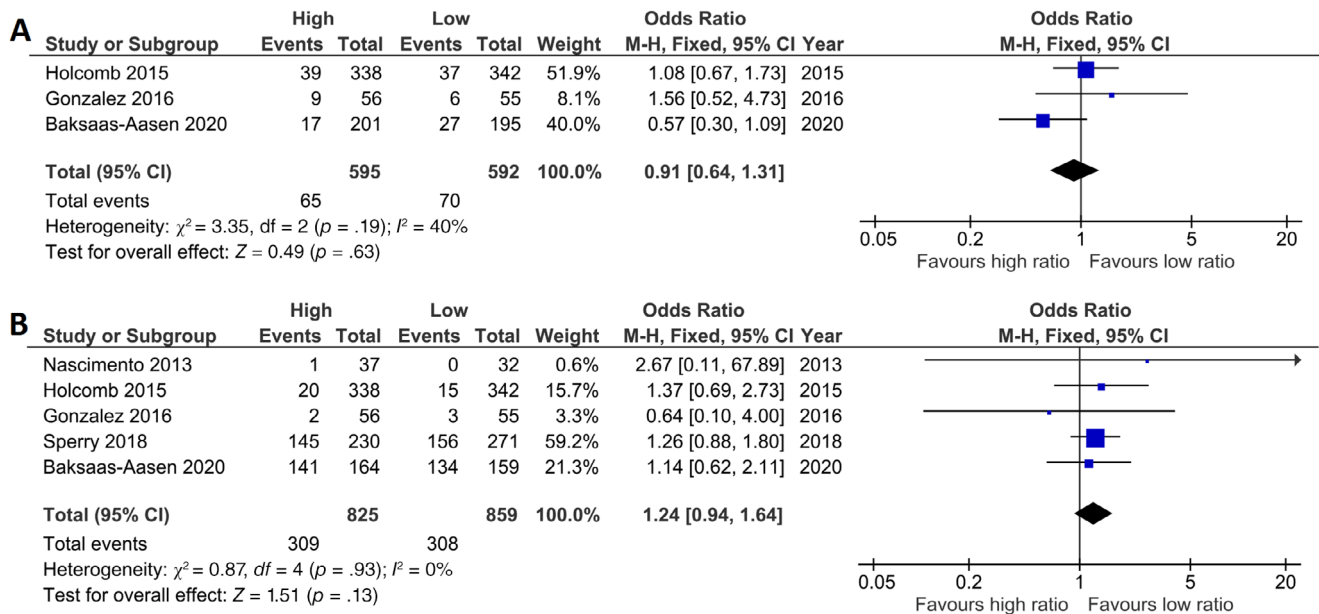


FIGURE 4 High platelet:red blood cell ratio has no effect on thromboembolic events or organ failure in trauma patients included in randomized controlled trials. Meta-analyses of high and low platelet:RBC ratio on (A) thromboembolic events (TEE) and (B) multiple organ dysfunction syndrome (MODS) represented in a forest plot. Weighted mean platelet:RBC ratio in the high ratio group was 1.15 (SD 0.34) and in the low ratio group 0.56 (0.15) for TEE and 0.83 (0.56) and 0.39 (0.27) for MODS. Events = number of patients affected, total = total number of patients, high = group with highest platelet:RBC ratio, low = group with lowest platelet:RBC ratio, M-H = Mantel-Haenszel

4 | DISCUSSION

In this systematic review of RCTs on the impact of platelet dose on outcome of bleeding trauma patients, a high compared to a low platelet:RBC ratio was associated with improved early and late mortality. With regard to thromboembolic events and organ failure, no difference was found between platelet:RBC dose groups. Also, no differences were observed on correction of coagulopathy, although most studies only reported conventional coagulation test results.

Patients receiving higher platelet:RBC ratios had lower mortality rates than patients receiving a lower ratio of platelet:RBC. As patients who received a high platelet dose concomitantly received a high dose of plasma, additional analyses were done by comparing a high plasma:platelet or plasma:RBC to a low plasma:platelet or plasma:RBC ratio, respectively. In these analyses, no differences were observed between high and low plasma:RBC ratios. This suggests that the effect on mortality in these analyses could, at least in part, be attributed to platelet dose.³³

The effect of a high platelet dose was greater for 24-h mortality than for 30-day mortality. This may not be surprising, as the high platelet dose may improve TIC and thereby prevent death due to exsanguination. However,

correction of TIC was not different between groups, although often not assessed with viscoelastic tests. Thereby, conclusions as to how platelet transfusion would improve TIC cannot be drawn. Observational data suggest that replenishment of platelets may improve platelet function as well as mitigating hyperfibrinolysis, possibly due to the release of platelet plasminogen activator inhibitor-1 or antiplasmin.^{18,34} The optimal dose of platelets remains to be determined. Preclinical data from our research group suggest that a platelet:RBC ratio of 2:1 resulted in improved correction of coagulopathy as determined by viscoelastic tests, without the occurrence of thrombi in organs.³⁵ In future trials, besides platelet count, evaluation of platelet function in the trauma population after resuscitation therapies is crucial as it may reveal new therapeutic targets to enhance platelet function early in trauma.

No differences in thromboembolic events and organ failure scores were observed in RCTs comparing high and low platelet:RBC ratios, underlining that a high platelet:RBC ratio was also associated with lower 30 thin;days mortality.

Taken together, the implications of this review may be that a median platelet:RBC ratio of higher than 0.6 should be targeted in clinical practice, however the exact ratio remains to be determined.

There are several limitations in this systematic review. The approach of calculating platelet:RBC ratio resulted in possible overlap in transfusion ratio for high and low ratio groups, which could have influenced the analyses. However, in determining ratios, not all studies reported on the type of platelet product (apheresis or pooled buffy coat platelets) and the amount of patients receiving platelet transfusions, rendering it impossible to calculate the absolute platelet:RBC ratio. Furthermore, if overlap in transfusion ratios is present, the effect of a high platelet dose on mortality could potentially be even larger.

5 | CONCLUSION

Resuscitation with a high compared to low platelet:RBC ratio improves early and late mortality in patients with traumatic bleeding. The high platelet:RBC ratio did not influence the occurrence of organ failure. The optimal ratio for platelet:RBC and its effect on platelet function in traumatic bleeding remains to be determined.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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