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CREST: clinical bleeding and risk evaluation in hematology–oncology patients: a systematic review and meta-analysis of thromboelastography's role

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Thrombocytopenia and bleeding are common complications of hematologic malignancies. Often, prophylactic platelets are administered to minimize bleeding risk, based on total platelet count (TPC). However, TPC is a poor predictor, and does not provide rapid information. This review presents a novel prospective in the use of point-of-care viscoelastic studies to assess bleeding risk and guide transfusion therapy in a haematological oncological population, where its use can be extended to a ward level as a bedside test. Monitoring TEG maximum amplitude trends may be useful to guide transfusion protocols, especially for patients with total platelet counts ranging 30–100 × 10^9/l. Fibrinogen assessment in this group of patients may identify other blood components that require replacing to reduce bleeding risk. Normal maximum amplitude parameters for patients with low platelet counts can be a reassuring sign. This meta-analysis serves to remind the reader that absolute platelet quantity does not equate to the quality of clot formation. ***Blood Coagul Fibrinolysis*** **33:351–363 Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Thrombocytopenia and bleeding are common complications of hematologic malignancies. These result from the disease process or from treatment. To minimize the risk of bleeding, prophylactic platelet transfusions are often administered to these patients based on empiric total platelet counts (TPC). Currently, most guidelines recommend a transfusion for TPC below 10–20 × 10^9/l, depending on the patients' medical status [1–3].

Administering platelets is not without risk. Potential side effects include sepsis from bacterial contamination, febrile transfusion reactions, circulatory overload, and risk of thrombosis [1,4]. There are also cost and resource allocation constraints to consider. Overuse of platelets not only results in potential patient harm but such a practice leads to a waste of precious limited resources and adds financial costs to healthcare organizations and patients.

As a clinical tool, TPC has been shown to be a poor predictor of bleeding risk in thrombocytopenic patients [5]. Furthermore, conventional platelet testing is time-consuming and leads to delays in obtaining results. This causes an inability to provide timely patient care.

Newer point-of-care viscoelastic tests (VETs), such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) may help to overcome these problems. These tests provide global information on clot strength dynamics and the impact of the contributing factors; namely fibrin, platelets and coagulation factors, on in-vivo haemostasis [6]. Various studies have attempted to determine the correlation between TEG/ROTEM parameters. Although some have found that the TEG alpha angle was significantly related to WHO grade 2 bleeding [7], others report that maximum amplitude is a good predictor of clinical bleeding in patients with severe thrombocytopenia [8]. This article reviewed the current available evidence with a meta-analysis.

Methods

Criteria for considering studies for this review

Types of studies

All comparative studies investigating the relationship between TEG or ROTEM and bleeding in patients with hematologic malignancy.

Participants

All studies involving patients with hematologic malignancy who were expected to have low platelets and a potential risk of bleeding were included.

Index tests

This review focused on two global tests of haemostatic function: TEG (Thromboelastography, Haemonetics

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Corporation, Braintree, Massachusetts, USA) and ROTEM (Rotational Thromboelastometry, GmbH Leipzig, Sachsen, Germany).

Target conditions

The target condition was clinical bleeding amongst patients with hematologic malignancy.

Reference standards

This review used clinical standard for bleeding diagnosis as reference standards for comparison with TEG and ROTEM.

Search strategy

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a literature search of PubMed, EMBASE, the Cochrane Library, and CNKI was performed up to 31 August 2020 with no restriction on time and language. Search terms included 'hematologic malignancy', 'blood cancer/oncology', 'TEG', 'ROTEM', 'bleeding' and related synonyms. Searching included both free text and explored text terms. In addition, all reference listed in the included articles and relevant review articles were manually checked.

Selection of studies

Studies was selected based on predefined inclusion criteria. Included studies consisted of patients with haematological oncological conditions who were expected to have low total platelet counts. The patients were observed for bleeding tendencies and TEG/ROTEM was conducted at the point of clinical bleeding. Studies where patients were empirically subjected to transfusion without evidence of bleeding were excluded. The titles and abstracts of articles were independently assessed by two reviewers (C.K. and M.L.) and disagreements resolved through discussion. If disagreements cannot be resolved, the opinion of a third reviewer (H.H.I.) was sought. The enrolled articles were evaluated by reviewing the full text before eligible studies were selected. The PRISMA study flow diagram is shown below (Fig. 1).

Data extraction

For every included study, original data was retrieved and entered into predefined data extraction forms by two reviewers (G.L. and S.L.M.) independently. Extracted data included author information, year of publication, country, study design, inclusion and exclusion criteria, sample size, patient age, reference standard, index test, and outcome measures. Maximum amplitude (MA), clot formation time (K), reaction time (R), and alpha angle (α) from TEG were selected for analysis where data was available. EXTEM and INTEM MCF from ROTEM were selected for analysis because of their similarity with maximum amplitude in TEG. For studies with a larger variety in patient population, we extracted data pertaining to patients with hematologic malignancy.

To account for the differences in measurements for bleeding outcome, this review included TEG/ROTEM parameter readings, odds ratio (OR), incidence of bleeding, sensitivity, and specificity. 95% confidence intervals (CIs) for dichotomous data and standard deviation or range/interquartile range for continuous data were also retrieved for meta-analysis.

Dealing with missing data

Whenever necessary, the investigators and the authors of the included studies were contacted to retrieve missing or unreported data relevant to our study.

Assessment of methodological quality

Risk of bias assessment (RoB) was independently conducted by two reviewers (G.L. and S.L.M.) using the Quality Assessment of Diagnostic Test Accuracy Studies, Version 2 (QUADAS-2). It constitutes four key domains: patient selection, index test, reference standard, and flow and timing. Each domain was assessed for risk of bias, and the first three were also evaluated for applicability. RoB assessment for Diagnostic Test Accuracy was applied. One of the signalling questions ('If a threshold was used, was it prespecified?') was not applicable in this study and was removed from the signalling question list. Independently, the reviewers scored each item as 'yes', 'no' or 'unclear' as recommended by the *Cochrane Handbook for Diagnostic Test Accuracy Reviews*. A domain will be rated 'high risk of bias' if the response to a nested signalling question was 'No'. Any disagreement in quality assessment was resolved via consensus.

Statistical analysis

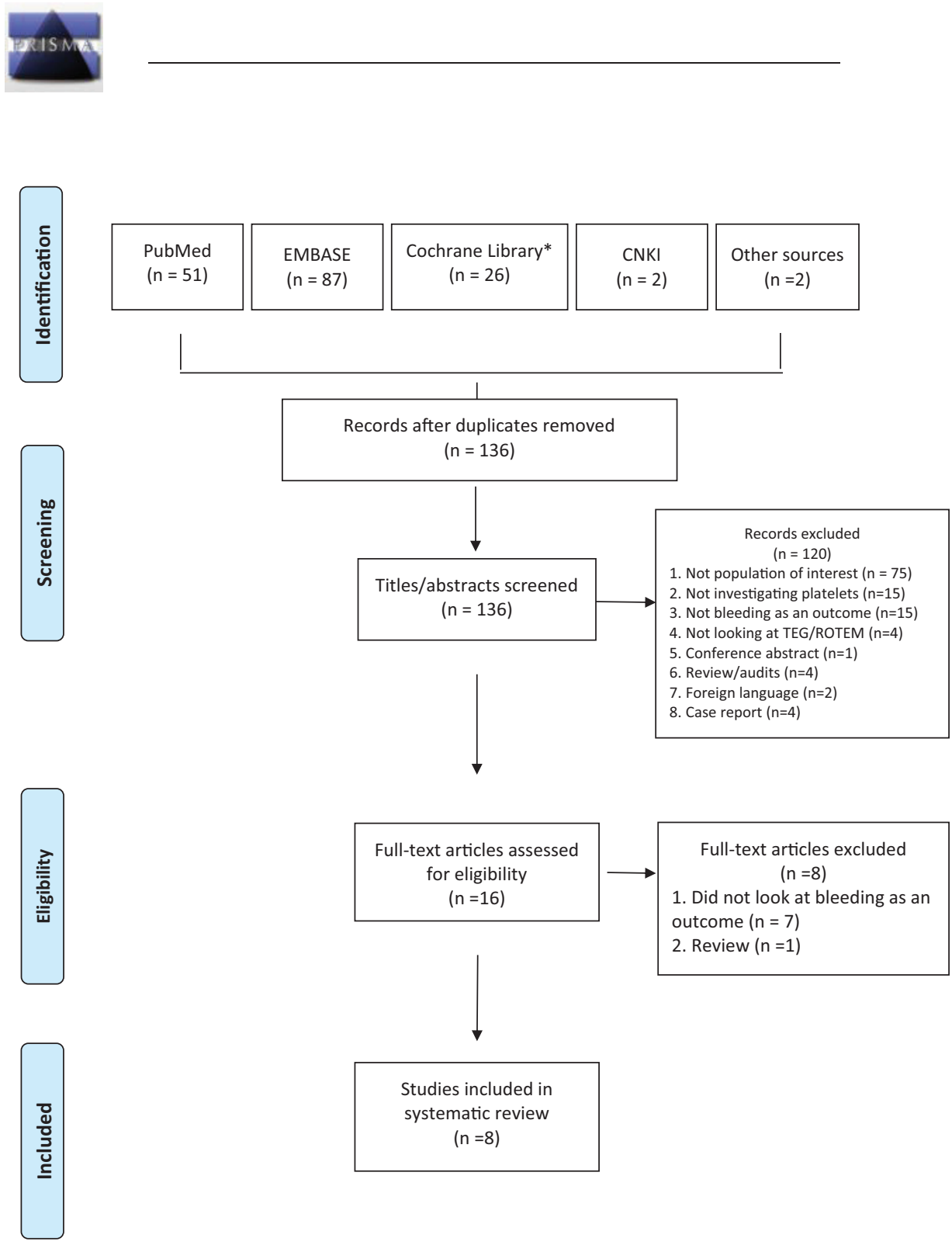
Data conversion

To handle the different outcome measures reported by the included studies, data conversion was conducted whenever necessary. If continuous data was reported by median, range and/or interquartile range, outcomes were converted into mean and standard deviation by taking reference from *Cochrane Handbook* [9] and established conversion methods before pooling [9,10]. For missing sensitivity and specificity data, the Calculator provided by RevMan5.3 was used for calculation by using reported prevalence and other diagnostic parameters, such as true-positive, false-positive, true-negative, false-negative rates, as well as positive-predictive values (PPVs) and negative-predictive values (NPVs) [9].

Data pooling

Outcomes were pooled for meta-analysis according to the reported measures and were classified into different study subgroups based on various classification levels of bleeding and cut-off values. In those instances, subtotals were reported. Continuous data was synthesized by

Fig. 1



PRISMA diagram.

mean, SD and sample size, and pooled mean difference was reported after meta-analysis. Incidence was synthesized as dichotomous data and reported as risk ratio with 95% confidence interval (CI). For studies that only reported ORs without group information, methods of GIV data were adopted for synthesis. Sensitivity, specificity, PPV and NPVs were extracted as diagnostic test accuracy data, if data were not reported in the study, calculation upon reported data would be presented. If outcomes had no comparison at the same level/cut-off among included studies, results from the individual study would be reported instead of the overall effects. Random effects model was adopted for meta-analysis.

All sources were managed by using RevMan5.3. Pooled estimates of sensitivity and specificity were produced from STATA 15. A P value less than 0.05 suggested statistical significance. For heterogeneity test, P less than 0.1 was considered as statistically significant.

Results

One hundred and sixty-eight citations were initially identified after the electronic and manual search. One hundred and thirty-six potentially eligible articles were screened by titles/abstracts after removing duplicates. Sixteen eligible full-text articles were then assessed after initial screening. Eight studies [4,7,8,11–15] were finally included for systematic review. Table 1 summarizes the characteristics of included studies. The studies came from four different countries. All studies were prospective cohort studies. In total, there were 2162 eligible patients included in our analysis, with mean age at 48.3 (range 12–93). In most of the studies, the reference standard for bleeding diagnosis was the WHO bleeding grade. In five of the studies [4,7,8,11,13], bleeding group was defined as WHO bleeding grade 2 and above whilst grades 1 and 0 were classified as nonbleeding group. Two studies [14,15] defined bleeding as WHO bleeding grade 1 and above. The last study [12] assessed bleeding by clinical data without specifying the criteria. For the index test, only one study [11] used ROTEM as the test of haemostatic function whereas the remaining seven studies used TEG

Quality assessment of included studies

The risk of bias and applicability concerns of included studies is shown in Fig. 2. Bao *et al.* and Kim *et al.* did not specify whether patient enrolment was consecutive or random sampling. He *et al.*, Kim *et al.*, and Xin *et al.* did not explain the exclusion of patients with certain clotting or haemostatic issues. Therefore the four studies mentioned above are labelled as unclear risk of bias in patient selection. With regards to the reference standard, He *et al.* did not clarify the criteria for diagnosing a bleed, thus the definition of disease was not clear. In the flow and timing domain, Estcourt *et al.* had one patient who withdrew from the study and the effect of the withdrawal is yet to be estimated. In addition, Kim *et al.* and Xin *et al.* reported results from patients with diseases other than hematologic oncology, therefore, a high risk of bias might be introduced in the patient flow domain.

In general, included studies performed well in the applicability concerns domain.

Outcome measurements

Thromboelastography

Parameter results Five studies [12,14–16] reported TEG parameters with actual values constituting maximum amplitude, R, K, and α. For better comparison, parameter readings of Kasivisvnathan *et al.* were selected from the first 24 h as there were more bleeding episodes compared with other periods in their study. Kim *et al.* and Kasivisvnathan *et al.* reported their results in median and range/IQR, which were then converted into mean and SD.

Overall, the bleeding group presented with significantly lower maximum amplitude, smaller alpha angle and longer K compared with the nonbleeding group (Fig. 3). The pooled estimate showed that maximum amplitude decreased 9.4 mm (95% CI: 4.76–14.05) amongst patients diagnosed with bleeding (WHO bleeding grade >=2). This trend was similar and significant compared with the other two subgroups [14.05 (95% CI: 11.78–16.32) and 16.61 (95% CI: 12.98–20.24), respectively].

K was prolonged 1.5 min (95% CI: 0.72–2.26) amongst WHO bleeding grade at least 2, 1.91 min (95% CI: 1.35–2.47) amongst the WHO bleeding grade at least one subgroup, and 2.13 min (95% CI: 1.31–2.95] in He *et al.* who assessed bleeding via clinical data.

Pooled data for alpha angle was found to be significantly reduced for the WHO grade at least one group [10.58° (95% CI: 8.18–12.98)] and 12.29° (95% CI: 8.37–16.21) in patients with clinical bleeding. This trend is seen in the WHO grade at least 2 group, where the decrease of alpha angle approached statistical significance.

No significant differences in R were found for studies that looked at bleeding defined by WHO bleeding grade whereas He *et al.* reported slightly longer R [0.56 (95% CI: 0.04–1.08)] among bleeding patients.

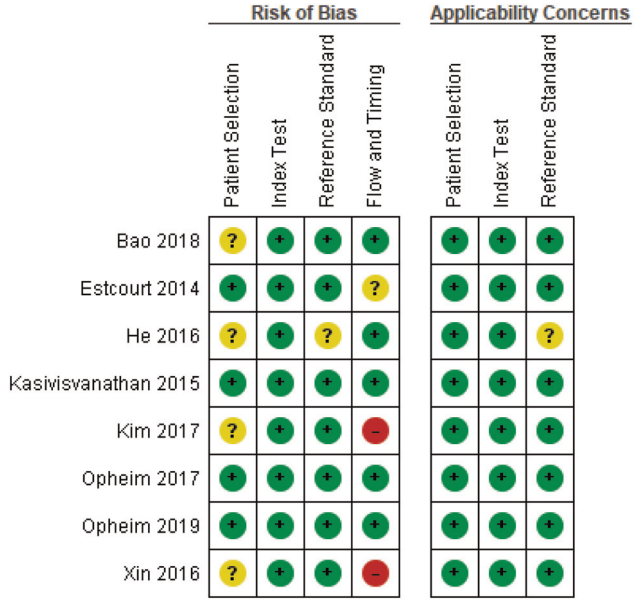
Odds ratio for bleeding prediction Four studies [8,13,14,15] reported adjusted odds ratios for bleeding prediction using TEG values (Fig. 4). When bleeding was stratified as WHO bleeding grade at least 2, Opheim *et al.* in 2019 found that the odds of bleeding were significantly lower when R time [OR = 0.72 (0.54, 0.96)], and alpha angle [OR = 0.88 (0.80, 0.97)] were increased.

Although no significant result was shown between bleeding and maximum amplitude amongst the pooled data,

Table 1 Characteristics of included studies

	Country	Study design	Inclusion criteria	Exclusion criteria	Sample size	Patient age, mean/median (SD/range) (years)	Reference standard	Plt count bleeding group	Plt count nonbleeding group	Index text	Parameters	Outcome measures	Results
Bao *et al.*, 2018	China	Prospective cohort	Patients with diagnosed with leukaemia	Preexisting bleeding tendencies, receiving anticoagulants or currently taking medication known to affect haemostasis, had active bleeding at the time of recruitment	226	44(12–72)	WHO bleeding grade at least 1	82.3 +/- 63.2	124.2 +/- 53.1	TEG	MA, *K*, *R*, α	Mean (SD), adjusted OR, diagnostic test accuracy	Relationship between *R* and MA in multivariate analysis
Estcourt *et al.*, 2014	UK	Prospective cohort	Patients at least 16 years with haematological malignancies and thrombocytopenic [total platelet count (TPC) $\leq 50 \times 10^9$/l] at admission, or expected to become thrombocytopenic for at least 5 days during inpatient treatment,	Inherited disorder of haemostasis, required antithrombotic medication during the period of thrombocytopenia or had a prior diagnosis of immune thrombocytopenia	50	50.1(20–70)	WHO bleeding grade	See inclusion criteria		ROTEM	EXTEM MCF, INTEM MCF	Adjusted OR	No statistically significant association between EXTEM/INTEM MCF after adjusting for total platelet count
He *et al.*, 2016	China	Prospective cohort	Patients with hematologic diseases	/	1073	45.7 (15–86)	Clinical data	72.0 +/- 143.774	189.14 +/- 186.79	TEG	MA	Incidence of bleeding, diagnostic test accuracy	Bleeding group had lower alpha angle and MA and prolonged *K*
Kasivisvanathan *et al.*, 2015	UK	Prospective cohort	Patients greater than 18 years with hematologic malignancy and initial TPC 30×10^9/l or less	Preexisting bleeding tendencies, receiving anticoagulants or currently taking medication known to affect haemostasis and/or were having active bleeding at the time of recruitment	30	51.8 (SD: 3.6)	WHO bleeding grade at least 2	Baseline 13 (12–16)	< 30	TEG	MA, *K*, *R*, α MA, *R*, α	Mean (SD) Median (range), diagnostic test accuracy	Statistically significant difference in MA, R, alpha angle and functional fibrinogen between bleeding and nonbleeding groups
Kim *et al.*, 2017	Korea	Prospective cohort	Patients with thrombocytopenia or hematologic malignancies	/	126	55 (15–93)	WHO bleeding grade at least 2	Grade 1: 42 (2–250) Grade 2: 18 (3–93)	Grade 0: 59 (4–345)	TEG	MA, *K* MA, *K*, *R*, α	Adjusted OR, diagnostic test accuracy Median (range)	No significant association of WHO >/= 2 and MA after adjustment for platelet count
Opheim *et al.*, 2017	Norway	Prospective cohort	Patients at least 18 years with haemato-oncologic disease and expected to need platelet transfusions	Known congenital clotting disorders, regular use of anticoagulants and immune thrombocytopenic purpura	13	46.6 (28–64)	WHO bleeding grade at least 2	15-30		TEG	α	Diagnostic test accuracy	Alpha angle smaller on days with WHO >/= 2 bleeding than days without
Opheim *et al.*, 2019	Norway	Prospective cohort	Patients >18 years with haematological malignancies who were expected to need at least one platelet transfusion	congenital clotting disorders, regular use of anticoagulants in the study observation period, and immune thrombocytopenic purpura	10	45.5 (28–64)	WHO bleeding grade at least 2	Platelets falling and approaching 50		TEG	MA, *R*, α	Adjusted OR	R and alpha angle significant from multiple logistic regression of significant bleeding
Xin *et al.*, 2015	China	Prospective cohort	Patients with hematologic diseases	Patients with no clear diagnosis at the end of the study or no diagnosis of hematologic disease on their last hemogram	634	48 (16–89)	WHO bleeding grade at least 1	72.18 +/- 148.05	189 +/- 188	TEG	MA, *K*, *R*, α	Mean (SD), adjusted OR, diagnostic test accuracy	MA associated with bleeding risk on multivariate analysis

Fig. 2



Risk of bias.

one study reported significant OR between bleeding and maximum amplitude when PLT 10×10^9/l or less [8].

Incidence of bleeding He *et al.* looked at the relationship between total platelet count (which is closely related to haemostasis) [17], and the incidence of bleeding events at different maximum amplitude levels (cut-off at 50 mmHg) (Fig. 5). Patients with haematological malignancy who had a total platelet count of $30–100 \times 10^9$/l and low maximum amplitude level (<50 mmHg) were four times more likely to have bleeding compared with patients with higher maximum amplitude level. No significant difference was found between different maximum amplitude levels if total platelet count was less than 30×10^9/l.

Diagnostic test accuracy Four studies [7,8,14,12] reported test accuracy data of TEG parameters (Table 2) on bleeding prediction. Due to different cut-offs of the parameters, the outcomes were reported individually. For maximum amplitude values, at cut-offs of 34.15, 34.4, and 40.8 mm, the sensitivity and specificity were 55 and 77%, 85 and 83%, 59 and 81%, respectively. The summary estimates of sensitivity and specificity of maximum amplitude were 69% (95% CI: 57–79%) and 77% (95% CI: 71–82%).

Xin *et al.* did not report their cut-offs but reported maximum amplitude sensitivity and specificity as 74 and 72%, respectively. However, sensitivity and specificity of diagnostic test accuracy increased slightly to 78 and 77% after combining maximum amplitude values with PLT for distinguishing bleeding. After narrowing down patients with PLT below 20×10^9/l, maximum amplitude alone presented extremely high specificity of nearly 100%, and maximum amplitude + PLT together had a higher sensitivity.

For *K*, with a cut-off value of greater than 2.5 min, the sensitivity and specificity were 78 and 54% for predicting WHO bleeding grade 2 and above.

The test accuracy for α in the Opheim *et al.* 2017 study was based on bleeding events among observation days ($N = 204$). α was found to be significantly smaller on days with WHO grade 2 bleeding than on days without bleeding. Sensitivity and specificity were 56 and 84%, respectively, at a cut-off value of α less than 32.15°.

PPV and NPV were also reported in Table 2. For maximum amplitude, PPV ranged from 39 to 58%, whereas NPV were consistently high, ranged from 82 to 95%. Pooled estimates of PPV and NPV were 45% (95% CI: 37–53%) and 90% (95% CI: 86–94%). Same pattern was found in *K*. Overall, maximum amplitude and *K* had a much higher NPV than PPV, indicating that if patients had higher maximum amplitude or lower *K* (compared with reported cut-off), there was high probability of nonbleeding according to WHO bleeding grade.

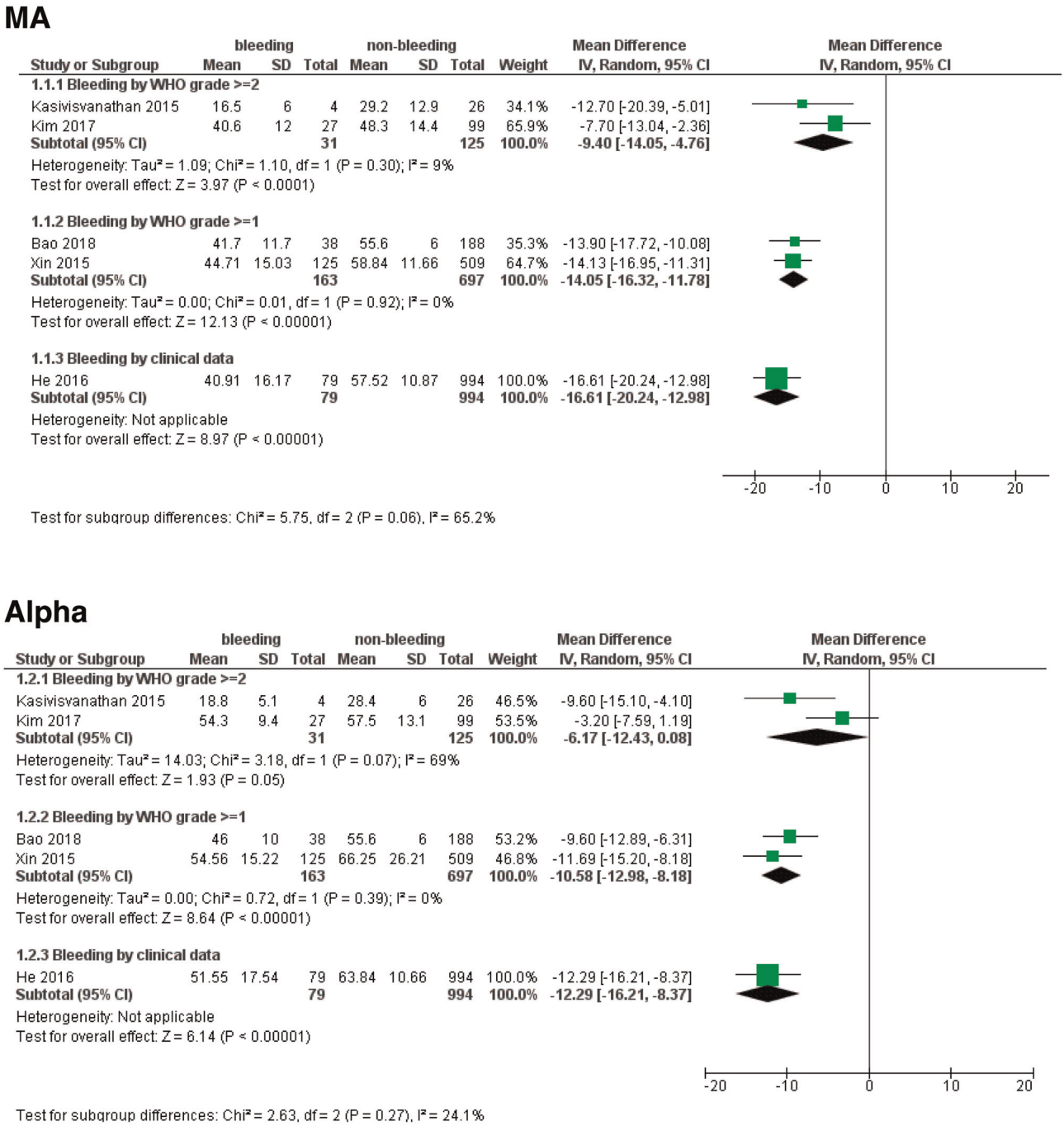
Four studies [12,14,15,16] reported area under ROC curve (AUC) of maximum amplitude and maximum amplitude combined with PLT (Supplementary Figure 1, http://links.lww.com/BCF/A131). In general, maximum amplitude combined with PLT had a higher AUC than maximum amplitude alone. This relationship is true for all patient populations analysed and in patients with lower level of PLT (20 or less, or 30 $\times$ 10^9/l), regardless of the definition of bleeding (either by WHO grade $\geq$1 or by clinical data).

Rotational thromboelastometry The most commonly used parameters for ROTEM were the EXTEM and INTEM MCF. However, no significant difference was found in the odds of bleeding between the bleeding and nonbleeding groups (Fig. 6).

Discussion

Our comprehensive literature search of several databases identified only eight eligible studies, with five reporting raw parameters showing association of maximum amplitude, *K* and α angle parameters with bleeding tendency. Pooled data from two studies suggested that a decrease in maximum amplitude by 9.4 mm, and a decrease in alpha angle by 6.17° was associated with a higher risk of bleeding (WHO bleeding grade $\geq$ 2, platelet range $12–130 \times 10^9$). These trends are similar in the other subgroup results (bleeding defined by WHO grade at least 1 and bleeding by clinical data). Additionally, this meta-analysis found that a prolonged *K* is associated with

Fig. 3

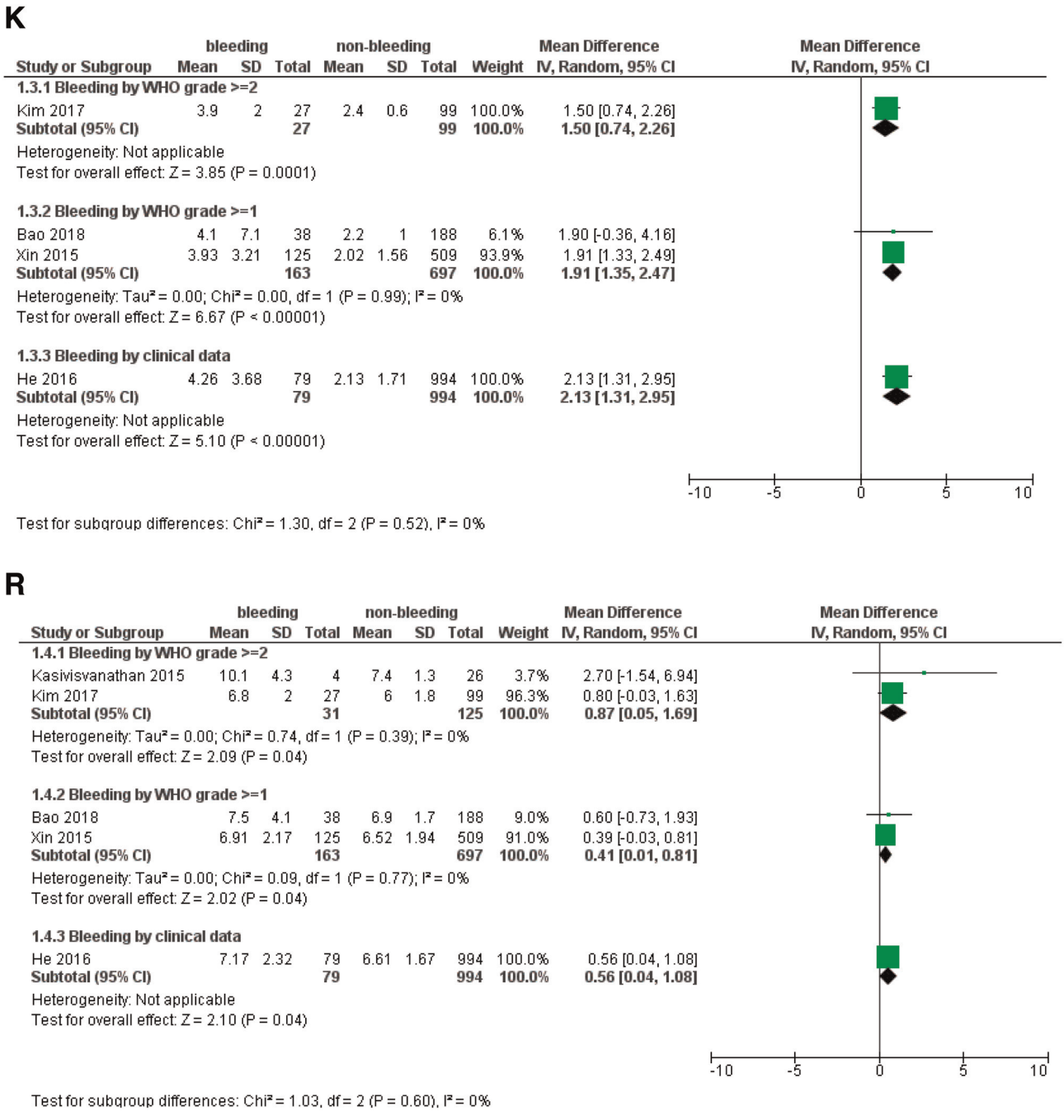


Parameter results with respect to bleeding.

increased bleeding tendency whereas there was no association between the *R* parameter and bleeding tendency in this population of patients.

However, when adjusted odds ratios were compared, there was no observed differences in the odds of bleeding between groups despite the difference in maximum amplitude values. This suggests that a decrease in trend of maximum amplitude is potentially more informative than interpreting an absolute maximum amplitude value [18]. Although no differences in the odds of bleeding were found with respect to the parameter *K*, Opheim *et al.* found that the odds of bleeding were significantly lower when the alpha angle was increased. This finding reflects

Fig. 3



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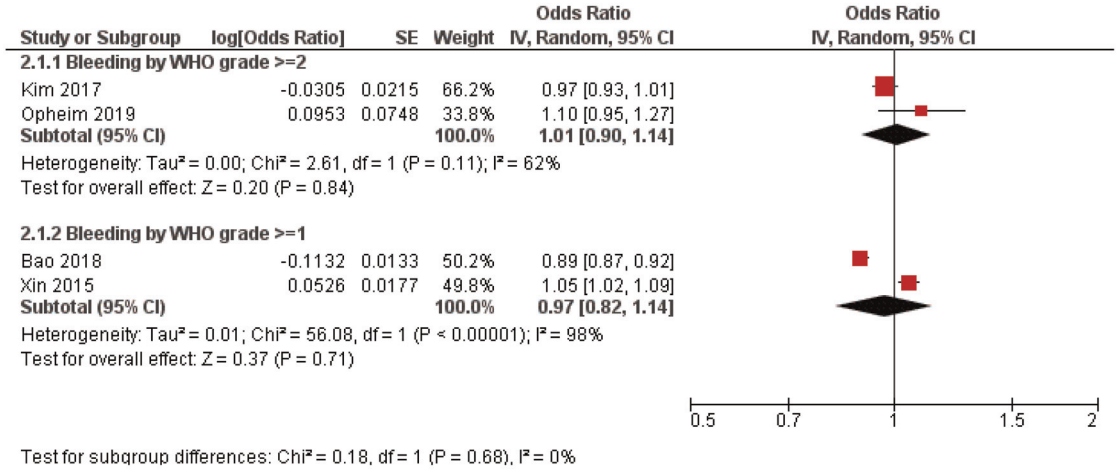
the predictive value of TEG parameters [7,13] in odds of bleeding and the significant role played by fibrinogen in the clotting status [19] of patients with hematologic oncology.

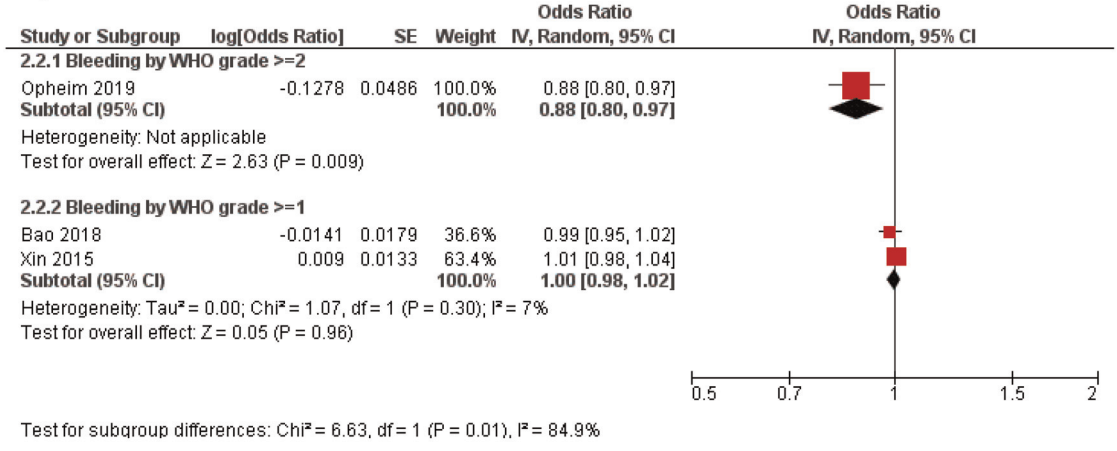
To our knowledge, this is the first meta-analysis of studies evaluating the usefulness of TEG/ROTEM in predicting bleeding for haematological oncological patients with low platelets. Thromboelastography was first described in 1948 [20] and since then, its use has been popular in cardiac surgery, and liver transplant surgery [21]. The use of thomboelastography has also been translated into trauma care [22]. In these settings, it has proven to be useful in decreasing the need for allogenic transfusions, and potentially morbidity and mortality-related outcomes [23,24]. In fact, point-of-care

Fig. 4

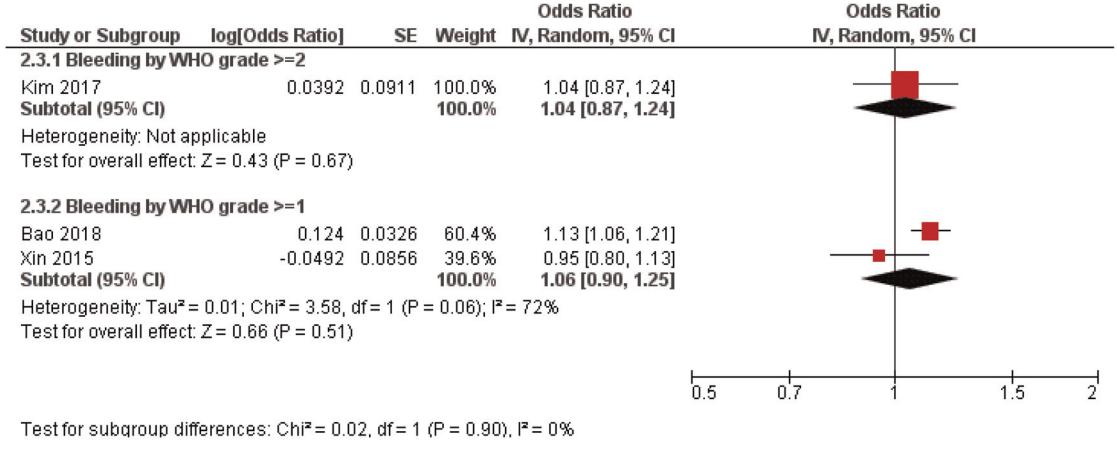
MA



Alpha



K



Odds ratio of thromboelastography parameters for bleeding prediction.

Fig. 4

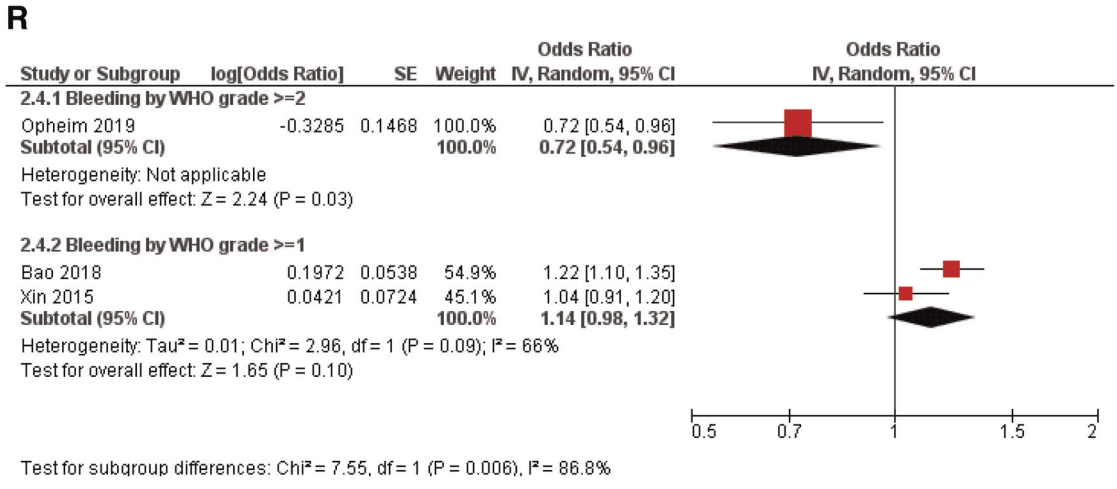


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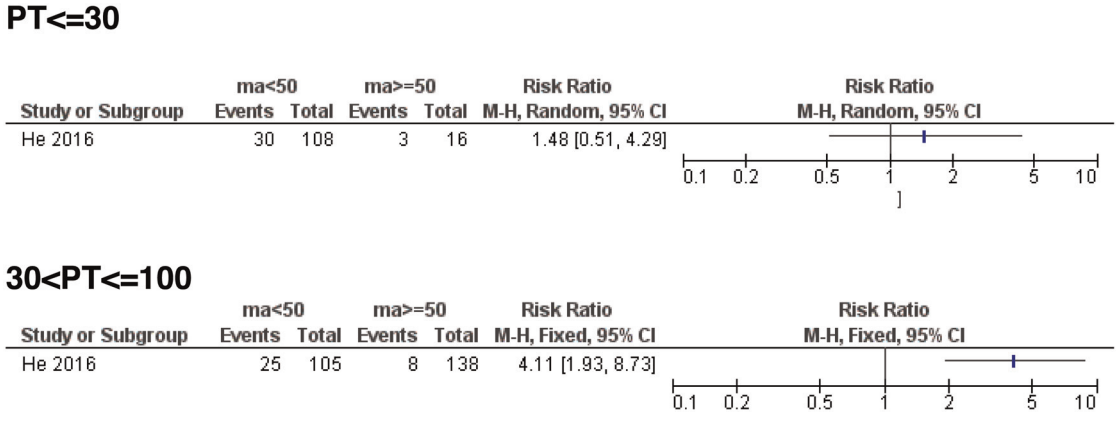
Fig. 5



Risk ratio of bleeding at different maximum amplitude levels.

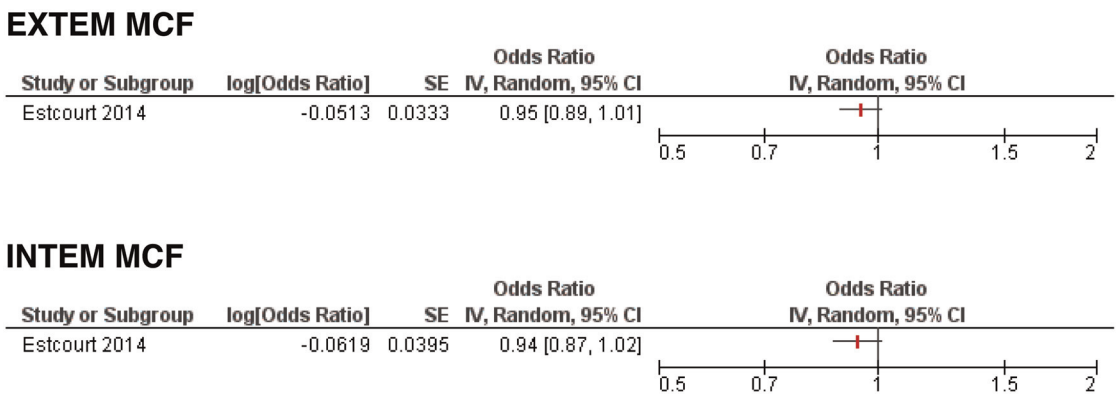
VET testing has been recognized by NICE to be useful to help determine if the cause of bleeding results from a clotting defect or a surgical bleed. Both ROTEM and TEG systems have been recommended by NICE to help monitor blood clotting during and after cardiac surgery [25]. Maximum amplitude is influenced by platelets and fibrinogen [26,27], *K* and α are influenced by fibrinogen, whereas *R* reflects factor activation [27]. Changes in

Table 2 Diagnostic test accuracy of thromboelastography parameters

Study	Parameters	Cut-off	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV
He, 2016	MA	<=34.15 mm	18	21	15	70	0.55 [0.36, 0.72]	0.77 [0.67, 0.85]	0.46 [0.30, 0.63]	0.82 [0.73, 0.90]
Kim, 2017	MA	<=34.4 mm	23	17	4	82	0.85 [0.66, 0.96]	0.83 [0.74, 0.90]	0.58 [0.41, 0.73]	0.95 [0.89, 0.99]
Kim, 2017	MA	<=40.8 mm	16	19	11	80	0.59 [0.39, 0.78]	0.81 [0.72, 0.88]	0.46 [0.29, 0.63]	0.88 [0.79, 0.94]
Xin, 2016	MA	Unknown	93	143	32	366	0.74 [0.66, 0.82]	0.72 [0.68, 0.76]	0.39 [0.33, 0.46]	0.92 [0.89, 0.94]
Kim, 2017	*K*	>2.5 min	21	46	6	53	0.78 [0.58, 0.91]	0.54 [0.43, 0.64]	0.31 [0.21, 0.44]	0.90 [0.79, 0.96]
Opheim, 2017	α	<32.15°	54	17	42	91	0.56 [0.46, 0.66]	0.84 [0.76, 0.91]	0.76 [0.64, 0.85]	0.68 [0.60, 0.76]
Conditional estimates										
Xin, 2016	MA + PLT	Unknown	97	117	28	392	0.78 [0.69, 0.85]	0.77 [0.73, 0.81]	0.45 [0.39, 0.52]	0.93 [0.91, 0.96]
Xin, 2016	MA (PLT<=20)	Unknown	15	0	41	26	0.27 [0.16, 0.40]	1.00 [0.87, 1.00]	1 [0.78, 1]	0.39 [0.27, 0.51]
Xin, 2016	MA + PLT (PLT<=20)	Unknown	47	10	9	16	0.84 [0.72, 0.92]	0.62 [0.41, 0.80]	0.82 [0.70, 0.91]	0.64 [0.43, 0.82]

MA, maximum amplitude; NPV, negative-predictive value; PPV, positive-predictive value.

Fig. 6



Odds ratio of rotational thromboelastometry parameters for bleeding prediction.

maximum amplitude have also been demonstrated to indicate platelet dysfunction in trauma-induced coagulopathy [22,28]. These various parameters in VET measure various components of the clotting process in the haematological oncological state – where platelets, and potentially fibrinogen, are major players. It has also been shown that in different states of health, there is a shift in the contributory roles of the clotting components to clot strength [26]. Monitoring TEG trends for a patient may, therefore, serve as a beneficial guide in bleeding prediction, whether during the perioperative period or during routine clinical patient care.

Although TPC has traditionally been used to guide platelet transfusion, correlation with bleeding is poor [5]. This may be explained by the complex mechanism of coagulation in haematological malignancies where other factors, such as intrinsic platelet dysfunction, changing levels of fibrinogen with malignancy and its interaction with clotting factors may play a role [29,30]. As disease progresses, many patients with haematological malignancies may need to undergo various invasive procedures and may require prophylactic platelet transfusion. These procedures include lumbar puncture, bone marrow biopsy, endoscopy (bronchoscopy, gastroscopy, colonoscopy) and insertion of indwelling venous catheters and central lines. A quick, reliable test of coagulation, included as part of an algorithm to guide well tolerated transfusion of blood products, would be useful to reduce risk of bleeding. This will be especially helpful in the setting of urgent invasive procedures with an imminent risk of bleeding amongst hematologic oncology patients. Both TEG and ROTEM have the potential to assess global coagulation and facilitate rapid decision-making in blood transfusion. This prevents unnecessary transfusions, conserve resources and improve morbidity outcomes. As such, its use may be expanded beyond trauma and surgeries to other disciplines of medicine that would benefit from rapid point-of-care-testing in coagulation diagnosis. However, the use of TEG/ROTEM is still uncommon and not well established in haematological oncological practice with few studies attempting to establish the VET profile in this population [29].

In He's study [12], patients were stratified according to platelet counts. He found that patients with TPC in the range of $30–100 \times 10^9$/l, with low maximum amplitude levels of less than 50 mm were four times more likely to experience bleeding. This observation is of particular interest in the background of ongoing clinical debate and controversy as to whether a prophylactic platelet transfusion is beneficial (when platelet count is $30–100 \times 10^9$/l) in reducing bleeding prior to invasive procedures, such as central line placement, lumbar puncture, and bone marrow biopsy [31–33]. This finding further supports inclusion of TEG evaluation in a clinical support algorithm that determines the need for prophylactic platelet transfusion. Additionally, maximum amplitude appears to have a high NPV, which is consistent across several studies (Table 2). A higher maximum amplitude, despite a reduced platelet count, is reassuring where bleeding risk is concerned. Although He's study was labelled as high risk of bias because of its retrospective nature, it included a large number of patients (1073 patients with haematological malignancies) and did not report any missing data. In addition, it is very reflective of the typical clinical scenario clinicians face in day-to-day practice when making transfusion decisions for such patients.

This study is limited by the available evidence. All studies classified bleeding by WHO grades, except He *et al.* [12], who grouped patients largely into a bleeding versus nonbleeding group. Due to the different cut-offs used as clinically significant bleeding in clinical practice, this meta-analysis was conducted on studies using WHO

bleeding grade as the clinical outcome. There were eight studies found – the small number of publications could be related to the fact that viscoelastic testing is relatively new. Two foreign language articles were excluded. All available studies were prospective cohort studies, and four out of eight had a small sample size (50 patients or less). One article (Escourt *et al.*), used ROTEM (sample size 50 patients), whereas the rest used TEG. There was also heterogeneity in classification of bleeding, although most studies used the WHO classification grade. In the Opheim 2019 *et al.*, TEG parameter outcomes was a secondary outcome, although the study was small (10 patients). Of note, the larger studies included patients frequently classified as paediatric population (12–18 years). Although that adds to heterogeneity of the study population, it may strengthen the external validity of our findings.

Only one study, Estcourt *et al.* [11], investigated the relationship between ROTEM, coagulation and platelet parameters. However, the study concluded that there was no relationship between ROTEM MCF (INTEM and EXTEM) and bleeding, after adjusting for total platelet count. ROTEM MCF is closely related to TEG maximum amplitude and is influenced similarly by platelets and fibrinogen [34]. As such, it was unanticipated to see that the ROTEM MCF did not have a relation to the incidence of bleeding. Although it was a well conducted study, the sample size was small (50 patients) and that might have contributed to the insignificant results.

Despite these limitations, this is the first article attempting to align all the available evidence regarding this topic and serves to highlight that more information is required in this area. As a diagnostic test, TEG parameters, such as maximum amplitude appears to have a consistently reasonable specificity, this is especially so when the platelets are low [14]. Therefore, we postulate that it is reassuring when patients with low platelets have normal maximum amplitude parameters.

Conclusion

This review presents a novel prospective in the use of point-of-care viscoelastic studies to assess bleeding risk and guide transfusion therapy in a haematological oncological population. The studies are few, reflecting the need for renewed interest in a rapid and reliable point-of-care test to resolve a very real and common dilemma when dealing with such patients. VET parameters that are of interest differs between perioperative, trauma and oncological scenarios as the underlying mechanism causing the coagulopathy differs. This makes it difficult to extrapolate VET data across clinical scenarios. Further research to study the co-relation between the maximum amplitude parameter range and bleeding outcome in the presence of thrombocytopenia would be useful to predict cases with low risk of bleeding. This will reduce the practice of prophylactic platelet transfusion based solely on low TPC.

The availability of reliable point-of-care testing is especially pertinent in justifying the need for prophylactic platelet transfusion for invasive procedures. Monitoring TEG maximum amplitude trends may be useful to guide transfusion protocols. This recommendation is especially true for patients with total platelet counts ranging 30–100×10^9/l. Additional fibrinogen assessment in this group of patients may identify other blood components that require replacing to reduce the risk of bleeding. Normal maximum amplitude parameters for patients with low platelet counts can be a reassuring sign.

This meta-analysis serves to remind the reader that absolute platelet quantity does not equate to the quality of clot formation. Future studies should focus on this questionable platelet range where prophylactic transfusion limits are still subject to debate.

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H.I.H. participated in the literature search, synthesis of results and writing of manuscript.

Conflicts of interest

There are no conflicts of interest.

References

1 ClinicalTransfusionPracticeGuidelinesforMedicalInternsBangladesh.pdf [Internet]. [cited 2020 Jul 4]. Available at: https://www.who.int/bloodsafety/transfusion_services/ClinicalTransfusionPracticeGuidelinesforMedicalInternsBangladesh.pdf?%20ua=1.

2 companion-25-pbm-guidelines.pdf [Internet]. [cited 2020 Jul 4]. Available at: https://www.blood.gov.au/system/files/documents/companion-25-pbm-guidelines.pdf.

3 Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, *et al.* Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med* 2015; **162**:205–213.

4 Kasivisvanathan R, Koutra M, Rooms M, Black E, Desai L, Mallett SV, *et al.* Thromboelastography (TEG®) compared with total platelet count in thrombocytopenia haematological malignancy patients with bleeding: a pilot observational study. *Transfus Med* 2015; **25**:307–312.

5 Friedmann AM, Sengul H, Lehmann H, Schwartz C, Goodman S. Do basic laboratory tests or clinical observations predict bleeding in thrombocytopenic oncology patients? A reevaluation of prophylactic platelet transfusions. *Transfus Med Rev* 2002; **16**:34–45.

6 Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. *Am J Hematol* 2014; **89**:228–232.

7 Opheim EN, Apelseth TO, Stanworth SJ, Eide GE, Hervig T. Thromboelastography may predict risk of grade 2 bleeding in thrombocytopenic patients. *Vox Sang* 2017; **112**:578–585.
8 Kim SY, Gu JY, Yoo HJ, Kim JE, Jang S, Choe S, *et al.* Benefits of Thromboelastography and Thrombin Generation Assay for Bleeding Prediction in Patients With Thrombocytopenia or Hematologic Malignancies. *Ann Lab Med* 2017; **37**:484–493.
9 Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [cited 25 August 2020]. Available at: handbook/current.
10 Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018; **27**:1785–1805.
11 Estcourt LJ, Stanworth SJ, Harrison P, Powter G, McClure M, Murphy MF, *et al.* Prospective observational cohort study of the association between thromboelastometry, coagulation and platelet parameters and bleeding in patients with haematological malignancies- the ATHENA study. *Br J Haematol* 2014; **166**:581–591.
12 He Y, Xin X, Geng Y, Tang N, Zhou J, Li D. The value of thromboelastography for bleeding risk prediction in hematologic diseases. *Am J Med Sci* 2016; **352**:502–506.
13 Opheim EN, Apelseth TO, Stanworth SJ, Eide GE, Hervig T. Multiple electrode aggregometry and thromboelastography in thrombocytopenic patients with haematological malignancies. *Blood Transfus Trasfus Sangue* 2019; **17**:181–190.
14 Xin X, Liu Z, Jian C, Tian M, Fang J, Sun H, *et al.* The role of thromboelastography in predicting bleeding risk and guiding the administration of platelet transfusions in hematological patients: a cohort study. *Ann Hematol* 2016; **95**:1163–1168.
15 Bao H-X, Du J, Chen B-Y, Wang Y. The role of thromboelastography in predicting hemorrhage risk in patients with leukemia. *Medicine (Baltimore)* 2018; **97**:e0137.
16 Kasivisvanathan R, Koutra M, Rooms M, Black E, Desai L, Mallett SV, *et al.* Thromboelastography (TEG®) compared with total platelet count in thrombocytopenia haematological malignancy patients with bleeding: a pilot observational study. *Transfus Med Oxf Engl* 2015; **25**:307–312.
17 Versteeg HH, Heemskerk JWM, Levi M, Reitsma PH. New fundamentals in hemostasis. *Physiol Rev* 2013; **93**:327–358.
18 Arora S, Singh PM, Goudra BG, Sinha AC. Changing trends of hemodynamic monitoring in ICU - from invasive to noninvasive methods: Are we there yet? *Int J Crit Illn Inj Sci* 2014; **4**:168–177.
19 Harr JN, Moore EE, Chin TL, Ghasabyan A, Gonzalez E, Wohlauer MV, *et al.* Platelets are dominant contributors to hypercoagulability after injury. *J Trauma Acute Care Surg* 2013; **74**:756–762; discussion 762-765.
20 Hartert H. Blood clotting studies with Thrombus stressography; a new investigation procedure. *Klin Wochenschr* 1948; **26 (37–38)**:577–583.
21 Hans GA, Besser MW. The place of viscoelastic testing in clinical practice. *Br J Haematol* 2016; **173**:37–48.
22 Wirtz MR, Baumann HM, Klinkspoor JH, Goslings JC, Juffermans NP. Viscoelastic testing in trauma. *Semin Thromb Hemost* 2017; **43**:375–385.
23 Deppe A-C, Weber C, Zimmermann J, Kuhn EW, Slottosch I, Liakopoulos OJ, *et al.* Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: a meta-analysis of 8332 patients. *J Surg Res* 2016; **203**:424–433.
24 Fahrendorff M, Oliveri RS, Johansson PI. The use of viscoelastic haemostatic assays in goal-directing treatment with allogeneic blood products - a systematic review and meta-analysis. *Scand J Trauma Resusc Emerg Med* 2017; **25**:39.
25 Overview | Detecting, managing and monitoring haemostasis: viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems) | Guidance | NICE [Internet]. NICE; [cited 15 January 2021]. Available at: https://www.nice.org.uk/guidance/dg13.
26 Harr JN, Moore EE, Chin TL, Ghasabyan A, Gonzalez E, Wohlauer MV, *et al.* Platelets are dominant contributors to hypercoagulability after injury. *J Trauma Acute Care Surg* 2013; **74**:756–765.
27 Shaydakov ME, Sigmon DF, Blebea J. Thromboelastography (TEG). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 29 August 2020]. Available at: http://www.ncbi.nlm.nih.gov/books/NBK537061/
28 Wohlauer MV, Moore EE, Thomas S, Sauaia A, Evans E, Harr J, *et al.* Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. *J Am Coll Surg* 2012; **214**:739–746.
29 Walsh M, Moore EE, Moore H, Thomas S, Lune SV, Zimmer D, *et al.* Use of viscoelastography in malignancy-associated coagulopathy and thrombosis: a review. *Semin Thromb Hemost* 2019; **45**:354–372.
30 Moscardó A, Latorre A, Santos MT, Bonanad S, Vallés J. Platelet function in malignant hematological disorders. *Curr Opin Oncol* 2015; **27**:522–531.
31 Sharma S, Sharma P, Tyler LN. Transfusion of blood and blood products: indications and complications. *Am Fam Phys* 2011; **83**:719–724.
32 Squires JE. Indications for platelet transfusion in patients with thrombocytopenia. *Blood Transfus* 2015; **13**:221–226.
33 Szczepiorkowski ZM, Dunbar NM. Transfusion guidelines: when to transfuse. *Hematology* 2013; **2013**:638–644.
34 Sankarankutty A, Nascimento B, Teodoro da Luz L, Rizoli S. TEG and ROTEM® in trauma: similar test but different results? *World J Emerg Surg WJES* 2012; **7 (Suppl 1)**:S3.