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Use of viscoelastic tests to predict clinical thromboembolic events: a systematic review and meta-analysis

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Abstract

We aimed to assess whether whole-blood viscoelastic tests are useful to identify patients who are hypercoagulable and at increased risk of thromboembolism. Two investigators independently analyzed studies in the MEDLINE, EMBASE, and Cochrane controlled trial register databases to determine the ability of viscoelastic tests to identify a hypercoagulable state that is predictive of objectively proven thromboembolic events. Thirty-eight eligible studies, including 8748 patients, were identified and subject to meta-analysis. The majority of the studies (n=33, 87%) used the maximum clot strength to identify a hypercoagulable state which had a moderate ability to differentiate between patients who developed thromboembolic events and those who did not (area under the summary receiver-operating-characteristic [sROC] curve =0.71, 95% confidence interval [CI]: 0.65-0.76). The pooled sensitivity, specificity, and diagnostic odds ratio to predict thromboembolism were 55% (95%CI: 42-67), 78% (95%CI: 68-85), and 3.7 (95%CI: 2.6-5.3), respectively. The predictive performance did not vary substantially between patient populations, and publication bias was not observed. Current evidence suggests that whole-blood viscoelastic tests have a moderate ability to identify a variety of patient populations with an increased risk of thromboembolic events, and can be considered as a useful adjunct to clinical judgement to stratify a patient's risk of developing thromboembolism.

Introduction

Both arterial and venous thromboembolic events are important preventable causes of morbidity and mortality[1]. According to the latest Centers for Disease Control and Prevention analysis, about 547,596 hospitalizations were complicated by venous thromboembolism each year for those aged ≥18 years in the United States[2]. About 100,000 patients died each year as a result of venous thromboembolism[2,3].

Anticoagulation is the current gold standard in preventing both arterial and venous thromboembolism. However, omission or a delay in initiating appropriate anticoagulant therapy or prophylaxis remains common often due to clinicians' concerns about risk of bleeding[4], especially in patients who have deranged coagulation parameters (e.g. cirrhotic patients) or those after major surgery or severe trauma[5,6]. It would be ideal if we can individualize anticoagulation for patients with different risks of thromboembolism, and differentiate between patients who are hypercoagulable and those who are at increased risk of bleeding[7,8].

Although numerous clinical thromboembolic prediction scores have been developed, their reliability and applicability in different patient populations remains uncertain[9-11]. An alternative approach is to use biomarkers or coagulation blood tests to identify individuals who have a hypercoagulable state. Many novel coagulation biomarkers have been discovered, but most of these biomarkers are expensive, not widely available, and consequently, far from useful as a practical thromboembolic-risk stratifying tool[12,13].

In-vitro whole-blood viscoelastic tests – including thromboelastography (TEG®) or rotational thromboelastometry (ROTEM®) – are widely used in many institutions to identify the mechanisms of bleeding in order to guide blood product transfusion for patients with active bleeding[13]. Emerging evidence suggests that an increase in in-vitro clot strength, demonstrated on a viscoelastic test, reflects a hypercoagulable state, and may be useful to identify patients who are at increased risk of thromboembolism[14,15].

We hypothesized that whole-blood viscoelastic tests can differentiate between patients who are hypercoagulable with an increased risk of thromboembolism and those who are not[16,17]. In this meta-analysis, we critically analyzed the literature to determine the ability of viscoelastic tests in identifying a hypercoagulable state that is predictive of objectively proven thromboembolic events. Specifically, we also assessed whether the commonly available viscoelastic tests have different abilities to predict arterial and venous thromboembolic events.

Materials and Methods

Search Strategy and Selection Criteria

This meta-analysis was conducted according to the PRISMA and STARD guidelines (**Appendices I and II**). Two investigators independently searched the EMBASE (January 1980 to September 2016), MEDLINE (1966 to September 2016), and Cochrane Controlled Trial Register (CENTRAL) (2016, issue 9) databases using the following exploded Medical Subject Heading (MeSH) terms: "viscoelastic point-of-care", "thromboelastography", "thromboelastometry", "rotational thromboelastometry", "TEG", or "ROTEM" with "thrombosis", "venous thrombosis",

"venous thromboembolism", "deep vein thrombosis", "pulmonary embolism", "prothrombotic", or "thrombotic". In this meta-analysis, only human studies, without any language restrictions, were included. The reference lists of related editorials, reviews and original articles identified were searched for relevant studies, and the web sites of the International Network of Agencies of Health Technology Assessment in Health Care were also searched to ensure all suitable studies were included. The literature search was further updated in October 2017.

Although many viscoelastic tests are available, thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) tests are by far most widely available and used. As such, we have restricted our analysis to studies that used either of these two tests in this meta-analysis and compared their ability in predicting thromboembolic events.

Data Extraction and Quality Assessment

Two investigators independently examined the abstracts of the identified studies, followed by detail data extraction from the full texts if they were deemed eligible for this meta-analysis. Studies without data on thromboembolic events or definition for a hypercoagulable state by the whole-blood viscoelastic tests were excluded. The quality of the study was assessed according to the study design (e.g. prospective versus retrospective, cohort study versus case-control study), and whether assessors of the thromboembolic events were blinded to the viscoelastic test results. When the reported results were unclear or only available in part, we contacted the corresponding authors of the identified studies to obtain additional data.

Statistical Analysis and Outcomes of Interest

Using a bivariate random-effects model[18], the diagnostic odds ratio (how much greater the odds of developing either arterial or venous thromboembolic events for the people with a positive test result than for the people with a negative test result), sensitivity, specificity, positive and negative likelihood ratios of the eligible studies were pooled. We used the area under the hierarchical summary receiver-operating-characteristic (sROC) curve to assess the overall performance of the viscoelastic tests in predicting objectively proven clinical thromboembolic events (by ultrasound, angiography, CT imaging, or troponin level).

In determining the heterogeneity of the predictive ability of the viscoelastic tests, we used (a) sample size and (b) prevalence of thromboembolism as a covariate in a meta-regression to assess whether these factors were important in affecting the reported results. In addition, a Threshold Analysis by Moses-Shapiro-Littenberg model was used to assess whether the cut-points used to define hypercoagulability were related to the differences in the reported diagnostic odds ratios.

In addition, we conducted a number of subgroup and sensitivity analyses to explore possible reasons for heterogeneity. These included (a) restricting our analysis to only higher quality prospective studies in which assessors of the thromboembolic events were blinded to the test results, (b) restricting our analyses to specific patient populations, (c) comparing the predictive performance of the two viscoelastic tests (TEG® vs ROTEM®), and (d) assessing whether the viscoelastic tests were better in predicting arterial or venous thromboembolic events. Finally, we

used a modified funnel plot technique, recommended by Deeks et al., to assess publication bias[19].

All analyses were performed by Open Meta-Analyst[20], Meta-disc (version 1.4)[21], and SPSS for Windows (version 24.0, IBM, 2016), and a p value <0.05 was taken as significant. This study's protocol was registered at PROSPERO (number CRD42017057968;

https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017057968).

Results

Search results

Of the 4743 studies identified in the databases, 38 studies from 14 countries, including 8748 patients in a variety of clinical settings, met the inclusion criteria and were subject to meta-analysis (**Figure 1**)[22-59]. A list of the studies excluded and the reasons for their exclusion are summarized in **Appendix III**.

Of the 38 studies included in the final analysis, 25 were prospective studies and most were cohort studies in which the viscoelastic test was performed before the thromboembolic events (n=32, 84%). As for the case-control studies, the viscoelastic test was performed subsequent to an interval after cessation of systemic anticoagulation. Blinding of the assessment of the thromboembolic events to the viscoelastic results was used in five studies (13%) including a total of 1599 patients. Twenty-seven studies used the thromboelastography (TEG®) and eleven studies used the rotational thromboelastometry (ROTEM®) to predict thromboembolic events. The majority of the studies (n=33, 87%) used the maximum clot strength

(maximum amplitude on the TEG® or maximum clot firmness on the ROTEM®), either alone or as part of an index, to define a hypercoagulable state. The characteristics of the included studies, including the diagnostic criteria used to define a hypercoagulable state, the prevalence of thromboembolic events and type of patients assessed, are described in detail in **Table 1**.

Ability of viscoelastic tests to predict thromboembolic events

The overall ability of a hypercoagulable state, identified by a viscoelastic test, to predict thromboembolic events was moderate (the area under the sROC curve was 0.71, 95% confidence interval [CI]: 0.65-0.76) (**Figure 2**). The pooled sensitivity, specificity, and diagnostic odds ratio of whole-blood viscoelastic tests to predict thromboembolic events were 55% (95%CI: 42-67), 78% (95%CI: 69-85), and 3.7 (95%CI: 2.6-5.3), respectively (**Figure 3**). The negative and positive likelihood ratios of the viscoelastic tests to predict thromboembolic events in each study and the overall pooled likelihood ratios are summarized in **Appendix IV**.

Difference between predicting venous and arterial thromboembolic events

Nineteen and five studies assessed the viscoelastic test's ability to predict *solely* deep vein thrombosis (DVT) / pulmonary embolism (PE) and arterial thromboembolic events, respectively. Viscoelastic tests appeared to have a better ability in predicting arterial thromboembolic events (sROC 0.74, 95%CI: 0.61-0.87; pooled diagnostic odds ratio 6.6, 95%CI: 2.6-17.2; sensitivity 66%, 95%CI: 57-75; specificity 71%, 95%CI: 67-75) than DVT or PE (sROC 0.69, 95%CI: 0.60-0.78; pooled diagnostic odds ratio 3.3, 95%CI: 2.0-5.6; sensitivity 32%, 95%CI: 28-36; specificity 76%, 95%CI: 74-77). Viscoelastic tests also appeared to have a modest

ability to predict portal vein thrombosis in patients with cirrhosis (n=4; sROC 0.75, 95%CI: 0.61-0.88; pooled diagnostic odds ratio 4.4, 95%CI: 1.7-11.1; sensitivity 21%, 95%CI: 14-31; specificity 78%, 95%CI: 72-83).

Effects of sample size and prevalence of thromboembolic events on performance of the viscoelastic tests

The sample size (n=16 to 2067) and prevalence (2.2% to 45% for prospective cohort studies) of the included studies varied substantially (Table 1), but there was no significant association between either the sample size (slope of the regression line =0, 95%CI: -0.001 to 0.001; *P*=0.427) or prevalence of the thromboembolic events (slope of the regression line =0.008, 95%CI: -0.018 to 0.034; *P*=0.536) and the predictive ability of the viscoelastic tests (**Appendices V** and **VI**, respectively).

Sensitivity analyses, Threshold Analysis and publication bias

Overall, lower quality studies tended to yield more favourable results than higher quality studies (prospective: n=25; sROC 0.70, 95%CI: 0.63-0.77 *vs* retrospective: n=13; sROC 0.73, 95%CI: 0.64-0.82 and cohort studies: n=32; sROC 0.70, 95%CI: 0.64-0.75 *vs* case-control study: n=6; sROC 0.83, 95%CI: 0.61-0.99). After restricting the analysis only to the highest quality studies (that were both prospective and blinded; n=5 with 1599 patients), the pooled diagnostic odds ratio (3.4, 95%CI: 1.5-7.8), sensitivity (48%, 95%CI: 23-74), and specificity (79%, 95%CI: 44-95) remained similar to the main results.

Compared to TEG®, ROTEM® had a better ability to predict thromboembolic events (sROC and pooled diagnostic odds ratio 0.69 and 3.3 *vs* 0.78 and 6.3, respectively; difference in areas under the sROC 0.092, *P*<0.001).

The thresholds used to define hypercoagulability were not significantly associated with the reported diagnostic odds ratios of the viscoelastic tests (P=0.874), and the predictive performance of the tests did not vary substantially between different patient populations (cancer patients: sROC 0.77, trauma patients: sROC 0.66, perioperative patients: sROC 0.69, critically ill patients: sROC 0.77). Finally, publication bias was also not observed (**Figure 4**).

Discussion

This meta-analysis showed that whole-blood viscoelastic tests had a moderate ability to discriminate between patients who developed thromboembolism and those who did not in a variety of patient populations. These results are clinically relevant and require further discussion.

First, evidence suggests that whole-blood viscoelastic tests have the potential to inform the clinicians about the mechanisms of bleeding over and above the information provided by standard coagulation blood tests[14,60]. Because a viscoelastic test assesses the clotting process of whole blood, including platelets, it has a potential to reflect bleeding or thrombotic tendency that is not measurable by activated partial thromboplastin time or prothrombin time, as both tests only use platelet-poor plasma[60]. Our results suggested that a viscoelastic hypercoagulable state is associated with an increased risk of thromboembolism, a 3.7-fold higher odd, compared to those without a hypercoagulable state. And as this was a diagnostic odds ratio, it would not be affected by the prevalence of the thromboembolism[61]. Indeed, our meta-regression did not show any association between the prevalence of thromboembolic events and reported diagnostic odds ratios of the included

studies. sROC is also known to be robust to study heterogeneity[62], and together with the consistency in the results of our multiple sensitivity analyses, the findings of this study are likely to be generalizable to a variety of patient cohorts with different prevalence of thromboembolism.

The relatively high specificity (78%) of a viscoelastic hypercoagulable state would suggest that such result has a low false positive rate in identifying patients who would develop thromboembolism. Withholding anticoagulant prophylaxis for patients with a hypercoagulable viscoelastic test result would thus be not advisable, especially if the patients are also judged to be at high risk of developing thromboembolism, based on either clinical ground (e.g. atrial fibrillation, immobilization, and recent surgery) or thrombotic risk scores[17].

Second, the relatively low sensitivity (55%) of a viscoelastic hypercoagulable result suggested that not all patients who developed thromboembolic events could be identified by this test. As such, a non-hypercoagulable viscoelastic test result does not imply that a patient would not develop subsequent arterial or venous thromboembolism. Any decision to initiate (or withhold) anticoagulant prophylaxis must circumspect the benefits of reducing thromboembolic events and its harms on increased risk of bleeding, using other clinical and laboratory information. There are, at least, a few possible reasons why viscoelastic tests will have a low sensitivity in predicting thromboembolic events. Whole-blood viscoelastic tests use thrombin related activators to activate the clotting process and are not sensitive to measure platelet activity in some diseases or drug effects (e.g. ADP receptor or cyclooxygenase inhibition)[60]. In addition, as an in-vitro blood test, it does not reflect

all pathogenic mechanisms of thromboembolism, including stasis in blood flow, vessel injury, and endothelial activation (e.g. thrombotic microangiopathy)[63]. In addition, the techniques and activators used to perform the viscoelastic test may also be important. Our results suggest that ROTEM® – often a laboratory-based test – appeared to outperform the point-of-care TEG®, in predicting thromboembolism.

Finally, we would like to acknowledge the limitations of this meta-analysis. Although we had included a large number of studies involving a variety of patient populations, the total number of patients analysed was still limited, and hence, the overall pooled results were imprecise. The included studies also used different follow-up durations after the test to detect thromboembolic events, which could introduce heterogeneity because hypercoagulability due to most non-genetic causes may change, in one way or another, with time (e.g. infection). We also noted that none of the included studies assessed the whole-blood viscoelastic tests in conjunction with other prothrombotic biomarkers to predict thromboembolic events[12,13]. Whether viscoelastic tests can supplement other coagulation biomarkers in predicting thromboembolism remains uncertain, but this merits further investigation.

In summary, maximum clot strength on a viscoelastic tracing, either alone or in combination with other parameters, has a modest ability to identify individuals who are hypercoagulable and at increased risk of subsequent either arterial or venous thromboembolic events in a variety of patient populations regardless of the underlying prevalence of thromboembolism. A non-hypercoagulable viscoelastic test result does not, however, imply that a patient will not develop subsequent

thromboembolism. With this caveat in mind, viscoelastic tests can be considered as a useful adjunct to clinical judgement to stratify a patient's risk of developing thromboembolism, in addition to its more established role of guiding blood product transfusion in critical bleeding[14,60].

Conflict of Interest

None.

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Figure legends

Figure 1. Flow chart showing the inclusion and exclusion of studies for the meta-analysis.

Figure 2. Area under the summary receiver-operating-characteristic (sROC) curve of 38 studies summarizing the ability of a hypercoagulable state to predict clinical thromboembolic events was 0.71 (95%CI: 0.65-0.76) using a bivariate random-effects model. Size of the marker is directly proportional to the size of the study in the sROC graph.

Figure 3. Forest plot showing the pooled diagnostic odds ratio (3.7, 95%CI 2.6-5.3) of a hypercoagulable state to predict clinical thromboembolic events.

Figure 4. The funnel plot, with the regression line in dash line (P=0.984), shows no obvious publication bias. ESS, effective sample size. ESS= (4xn1xn2)/(n1+n2) where n1 = number of patients with thromboembolism and n2= number of patients without thromboembolism in the study. Pooled diagnostic odds ratio from 38 studies was 3.7 (=0.57 in $\log_{10}$ scale on the X-axis) and is defined by the vertical continuous line.

Appendices Index

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Table 1. Characteristics of the studies included in the meta-analysis (N=38)[22-59].

Author, year, sample size, country of origin [reference]	Type of patients	Whole-blood viscoelastic parameter(s) used to define hypercoagulability	Prospective or retrospective, and cohort or case-control study	Blinding of outcomes	Prevalence (and nature) of clinical thromboembolic events
Zheng, 2014, n=378, China[22]	Hospitalized patients >65 years old	MA on TEG >69mm	Retrospective, cohort	No	20.6% (myocardial infarction, ischemic stroke, DVT, and PE)
Gary, 2016, n=1818, USA[23]	Patients with severe extremity trauma	MA on TEG >72mm	Retrospective, cohort	No	3.3% (DVT or PE)
Pommerening, 2015, n=795, USA[24]	Adult trauma patients	MA or angle on TEG > upper limit of normal	Prospective, cohort	Yes	6.4% (myocardial infarction, ischemic stroke, DVT, and PE)
Parameswaran, 2016, n=101, India[25]	Patient with hip / knee fracture or arthritis for arthroplasty	MA on TEG >69mm	Prospective, cohort	No	6.9% (DVT)
Gurbel, 2009, n=84, USA[26]	Patients requiring non-emergent percutaneous coronary interventions	MA on TEG >71mm	Prospective, cohort	No	26.2% (recurrent coronary ischemic events)
Schreiber, 2005, n=64, USA[27]	Adult trauma patients	R-time <3.7 minutes on TEG	Prospective, cohort	No	6.3% (DVT or PE)
Gurbel, 2005, n=191, USA[28]	Patients requiring non-emergent percutaneous coronary interventions	MA on TEG >72mm	Prospective, cohort	No	19.9% (recurrent coronary ischemic events)
Rafiq, 2012, n=194, Denmark[29]	Patients undergoing coronary artery bypass grafting	MA on TEG >69mm	Prospective, cohort	Yes	10.3% (myocardial infarction, ischemic stroke)
Tartamella,	Critically ill adult patients	Thrombodynamic ratio	Prospective, cohort	Yes	10.5% (DVT or PE)

2016, n=57, Italy[30]		(MA x α-angle/R-time) >10.6 on TEG			
Allen, 2015, n=74, USA[31]	Adult trauma patients	Either R-time >9 minutes, α-angle >58^0, or MA >64mm on TEG	Prospective, cohort	No	17.6% (DVT or PE)
Zacho, 2013, n=124, Denmark[32]	Patients undergoing coronary artery bypass grafting	MA on TEG >69mm	Prospective, cohort	No	20.2% (major adverse cardiovascular and cerebral events including myocardial infarction and ischemic stroke)
Hvitfeldt Poulsen, 2006, n=98, Denmark[33]	Patients referred to thrombophilia investigation after an episode of thromboembolism and healthy controls	MaxVel values on ROTEM outside 2 standard deviations from the reference intervals	Retrospective, case-control	No	13.3% (based on the case to control ratio, arterial or venous thrombosis)
Ho, 2015, n=126, Australia[34]	Critically ill adult patients	MA and α-angle on TEG >72mm and 74^0, respectively	Prospective, cohort	No	7.9% (DVT or PE)
Toukh, 2014, n=40, Canada[35]	Patients with prostatic cancer and controls	Three or more of the followings, R-time, K-time, α-angle, MA or coagulation index on TEG, were outside average +/- one standard deviation of the controls	Prospective, cohort	No	25% (among those with prostatic cancer, 20% if controls were included, DVT, PE or myocardial infarction)
Cotton, 2012, n=2067, USA[36]	Adult trauma patients	MA on TEG >72mm	Retrospective, cohort	No	2.6% (PE)
Wen, 1997, n=76,	Oncology patients requiring Port-A-Cath	R-time, α-angle and MA on TEG <6	Prospective, cohort	No	14.5% (thrombosis of the Pot-A-Cath requiring

		minutes, $>60^0$ and $<70mm$, respectively			re-implantation)
Taiwan[37]	implantation				
Welsh, 2014, n=81, USA[38]	Patients on cardiopulmonary bypass with bleeding requiring hematology consultation	R-time on TEG <5 minutes	Retrospective, cohort	No	8.6% (DVT or PE)
Krzanicki, 2013, n=117, UK[39]	Patients undergoing liver transplantation	G index (5000xMA/(100-MA) on TEG >7100	Retrospective, cohort	No	5.1% (hepatic artery thrombosis)
McCrath, 2005, n=240, USA[40]	Patients undergoing a wide variety of surgical procedures	MA on TEG >68mm	Prospective, cohort	Yes	39.6% (DVT, PE, ischemic stroke or myocardial infarction)
Abrahams, 2002, n=46, USA[41]	Patients undergoing neurosurgical procedures	Thrombotic index (= -0.1227 x R-time + 0.0092 x K-time + 0.1655 x MA – 0.0241 x α-angle – 0.5022) on TEG >/=3.57	Prospective, cohort	No	2.2% (DVT)
Cerutti, 2004, n=10, Italy[42]	Patients undergoing donor liver hepatectomy	Coagulation index (= -0.3258 x R-time – 0.1886 x K-time + 0.1224 x MA + 0.0759 x α-angle – 7.7922) on the TEG >3	Retrospective, cohort	No	10% (DVT)
O'Donnell, 2004, n=87, UK[43]	Patients with a personal or family history of thrombotic event	MA on TEG >62.5mm	Prospective, cohort	No	29.9% (DVT, PE or ischemic stroke)
Kashuk, 2009, n=152, USA[44]	Critically ill surgical patients	G index (5000xMA/(100-MA) on TEG >12.4 dynes/cm^2	Retrospective, cohort	No	10.5% (DVT, PE, mesenteric arterial and venous thrombosis)
Kapoor, 2009,	Patients with extrahepatic	Thrombotic index (= -	Retrospective,	No	61.2% (based on the

n=49, India[45]	portal vein thrombosis (cases) and non-cirrhotic portal fibrosis (controls)	0.1227 x R-time + 0.0092 x K-time + 0.1655 x MA – 0.0241 x α-angle – 0.5022) on TEG >2.5	case-control		case to control ratio, portal venous thrombosis)
Koopman, 2009, n=38, Netherlands[46]	Patients with cerebral venous thrombosis (cases) and without thrombosis (controls)	One or more of the followings, R-time, K-time, α-angle, or MA, were outside the reference range towards a hypercoagulable state	Prospective, cohort ("cases" & "controls")	No	34.2% (based on but the case to control ratio, cerebral venous thrombosis)
Traverso, 1993, n=100, Spain[47]	Patients undergoing elective abdominal surgery > 1hr	MA on TEG > normal	Prospective, cohort	No	45% (DVT, PE)
Dumitrescu, 2015, n=16, Sweden[48]	Patients undergoing major liver surgery	MCF on at least 1 of 3 ROTEM tests (INTEM/EXTEM/FIBTEM) > reference value	Prospective, cohort	No	12.5% (PE)
Hincker, 2014, n=313, USA[49]	Patients undergoing major non-cardiac surgery	MCF on at least 1 of 3 ROTEM tests (INTEM/EXTEM/FIBTEM) > reference value	Prospective, cohort	Yes	3.2% (DVT, PE, arterial thrombosis and vascular catheter thrombosis)
Kolbenschlag, 2014, n=181, Germany[50]	Patients undergoing reconstructive microsurgery	MCF on INTEM or EXTEM ROTEM >72mm or on FIBTEM >25mm	Retrospective, cohort	No	15.5% (thromboembolic flap loss)
Spiezia, 2008, n=70, Italy[51]	Patients with acute DVT (cases) and healthy age-matched controls	MCF on ROTEM >72mm	Prospective, cohort ("cases" & "controls")	No	42.9% (based on the case to control ratio, DVT)
Davies, 2015, n=139, UK[52]	Patients with lung cancer (cases) and age-matched	Either with a shortened CFT (INTEM>100s or	Prospective, cohort	No	14.9% (among the lung cancer patients, 4.3%

		EXTEM >148s) or an increase in MCF on ROTEM >72mm			when healthy individuals were included) (DVT or PE)
Van Haren, 2014, n=52, USA[53]	Patients with thoraco-abdominal malignancies requiring surgery	One or more of the followings, clotting time, CFT, or MCF on ROTEM were suggestive of hypercoagulable	Prospective, cohort	No	5.8% (DVT or PE)
Koçak, 2016, n=39, Turkey[54]	Patients with perinatal arterial ischemic stroke (cases) and healthy controls	One or more of the followings, clotting time, CFT, or MCF on ROTEM were suggestive of hypercoagulable	Retrospective, case-control	No	51.3% (based on the case to control ratio, ischemic stroke)
Rossetto, 2013, n=98, Italy[55]	Patients with non-neoplastic portal vein thrombosis (cases) and healthy volunteers or cirrhotic patients (controls)	One or more of the followings, clotting time, CFT, MCF or the angle on ROTEM were abnormal and suggestive of hypercoagulable	Retrospective, case-control	No	50% (based on the case to control ratio, portal vein thrombosis)
Taura, 2014, n=109, Spain[56]	Patients with obesity undergoing laparoscopic bariatric surgery	G index >/= 11 dynes/cm^2	Prospective, cohort	No	0.9% (DVT or PE)
Liu, 2016, n=376, China[57]	Patients with gynecological oncology condition	Coagulation index (-0.6516 x R-time – 0.3772 x K-time + 0.1224 x MA + 0.0759 x α-angle – 7.7922) >/=2.55	Retrospective, cohort	No	10.4% (DVT or PE)
Thorson,	Patients undergoing	At least 1 of the 9	Prospective, cohort	No	6.9% (DVT or PE)

2014, n=72, USA[58]	exploratory laparotomies for intra-abdominal malignancies	ROTEM parameters evaluated (CT, CFT, MCF in EXTEM or INTEM, MCF in FIBTEM) towards a hypercoagulable state according the reference range			
Zanetto, 2017, n=76, Italy[59]	Patients with cirrhosis, with and without hepatocellular carcinoma	At least 1 hypercoagulable parameter (CT, CFT or MCF) on 1 or more of the 3 ROTEM tests (EXTEM/INTEM/FIBTEM)	Prospective, cohort study	No	18.4% (portal vein thrombosis)

CFT = clot formation time (to 20mm above baseline on ROTEM®); CT = clotting time; DVT = deep vein thrombosis; K- time = clot formation time to 20mm above baseline on TEG®; PE = pulmonary embolism; MA = maximum amplitude on the TEG®; MCF = maximum clot firmness on ROTEM®; R-Time = reaction time; ROTEM® = rotational thromboelastometry; TEG® = thromboelastography.

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┌─────────────────────────────────────┐
│ MEDLINE, EMBASE and Cochrane Trial  │
│    Registry databases between       │
│      1966 and October 2017          │
│           (N=4743)                  │
└─────────────────────────────────────┘
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                  │
┌─────────────────────────────────────┐
│  Studies with results in the abstract│
│ suitable for further evaluation (N=68)│
└─────────────────────────────────────┘
                  │
                  │                    ┌──────────────────┐
                  │                    │ Studies excluded │
                  ├────────────────────│   because of     │
                  │                    │ insufficient data│
                  │                    │   (n=28) or      │
                  │                    │ duplicated study │
                  │                    │     (n=2)        │
                  │                    │  (Appendix 1)    │
                  │                    └──────────────────┘
┌─────────────────────────────────────┐
│     Studies with usable data for    │
│         the meta-analysis           │
│  (N=38, total number of patients    │
│        included = 8748)             │
│       1.    Studies using           │
│          thromboelastography        │
│            (TEG®, n=27)             │
│    1.   Studies using rotational    │
│          thromboelastometry         │
│            (ROTEM®, n=11)           │
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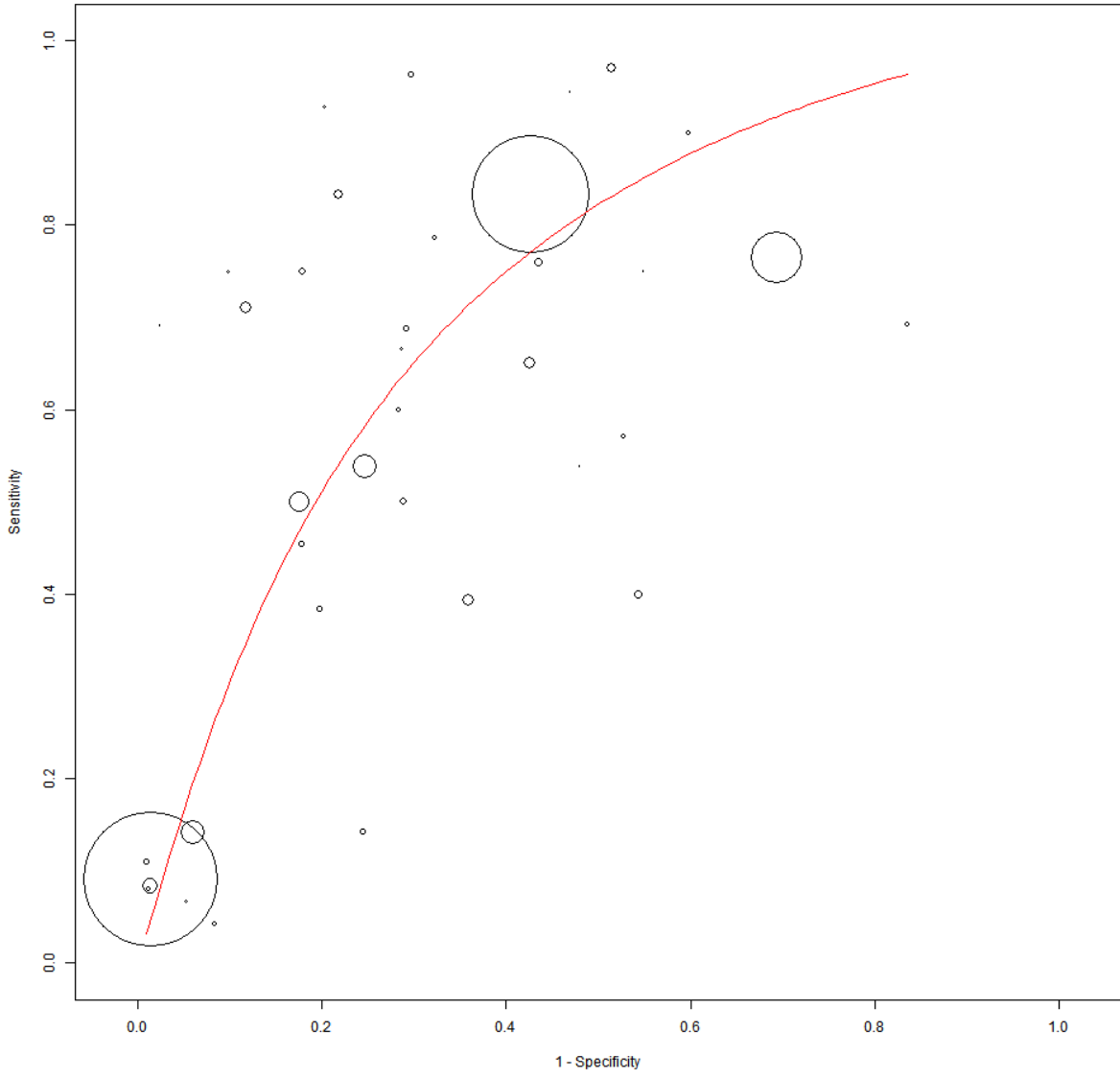
Studies	Estimate (95% C.I.)	(TP * TN)/(FP * FN)
Traverso1993 1993	5.397 (2.288, 12.735)	1209/224
Toukh2014 2014	19.194 (1.022, 360.512)	136/0
Wen1997 1997	0.478 (0.025, 9.256)	0/55
Dumitrescu2015 2015	2.500 (0.124, 50.444)	10/4
Hincker2014 2014	4.717 (1.319, 16.873)	1250/265
Welsh2014 2014	1.197 (0.250, 5.723)	140/117
Krzanicki2013 2013	2.469 (0.473, 12.883)	237/96
McCrath2005 2005	6.575 (1.365, 31.673)	1144/174
Cerutti2004 2004	2.455 (0.079, 76.132)	4/0
Abrahams2002 2002	27.667 (0.975, 784.770)	41/0
Kolbenschlag2014 2014	1.153 (0.504, 2.637)	1078/935
O'Donnell2004 2004	2.552 (0.928, 7.016)	490/192
Spiezia2008 2008	7.105 (0.329, 153.666)	80/0
Kashuk2009 2009	31.128 (1.831, 529.253)	1056/0
Kapoor2009 2009	1.286 (0.108, 15.237)	36/28
Ho2015 2015	0.561 (0.150, 2.093)	212/378
Cotton2012 2012	6.439 (3.700, 11.205)	45552/7074
HvitfeldtPoulsen2006 2006	64.059 (3.667, 1118.958)	780/0
Koopman2009 2009	1.264 (0.330, 4.843)	91/72
Davies2015 2015	17.931 (2.015, 159.598)	520/29
Allen2015 2015	0.441 (0.113, 1.717)	90/204
Tartamella2016 2016	51.381 (2.676, 986.654)	246/0
VanHaren2014 2014	5.000 (0.419, 59.657)	70/14
Kocak2016 2016	87.000 (4.528, 1671.628)	266/0
Rossetto2013 2013	12.236 (0.658, 227.605)	245/0
Rafiq2012 2012	2.510 (0.954, 6.599)	1300/518
Gurbel12005 2005	18.409 (7.818, 43.346)	3645/198
Zheng2014 2014	2.572 (1.160, 5.701)	3102/1206
Schreiber2005 2005	6.041 (0.311, 117.311)	96/0
Gurberl22009 2009	3.864 (1.335, 11.179)	510/132
Parameswaran2016 2016	0.514 (0.059, 4.500)	71/138
Gary2016 2016	6.704 (3.378, 13.307)	50350/7510
Pommerening2015 2015	1.436 (0.738, 2.794)	8892/6192
Taura2014 2014	13.769 (0.540, 350.832)	89/0
Zacho2013 2013	4.124 (1.517, 11.212)	1064/258
Liu2016 2016	3.570 (1.815, 7.023)	5334/1494
Thorson2014 2014	3.789 (0.586, 24.499)	144/38
Zanetto2017 2017	7.700 (1.931, 30.705)	462/60
Overall (I^2=57.71 % , P< 0.001)	3.699 (2.608, 5.247)	130042/27605

0.02 0.05 0.12 0.25 0.49 1.24 2.47 3.7 12.36 24.71 49.42 123.55 247.11 494.21 1235.53

Diagnostic Odds Ratio (log scale)

P value for the regression line = 0.984