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# Detection of Acute Traumatic Coagulopathy by Viscoelastic Haemostatic Assays Compared to Standard Laboratory Tests: A Systematic Review

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**Keywords**

Viscoelastic assay · Thromboelastography · Acute traumatic coagulopathy · Wounds and injuries · Blood component transfusion

**Abstract**

***Introduction:*** The aim of this systematic review was to investigate whether viscoelastic haemostatic assays (VHAs) offer comparative diagnostic ability of acute traumatic coagulopathy (ATC) compared to the standard laboratory coagulation tests (SLCT). ATC is a complication of major trauma characterized by dysfunctional blood clotting, leading to an increased bleeding risk. Additionally, we aimed to analyse the association of VHA with blood product use and health outcomes. ***Methods:*** The search protocol was pre-published and completed on December 2, 2020, assessing manuscripts from 2000 until the present. We searched MEDLINE, Embase, Cochrane Central, BIOSIS, Emcare, CINAHL, and additional online resources and referenced lists. Included were manuscripts that quantitatively reported the detection of ATC using VHAs and SLCTs. A meta-analysis was undertaken including observational studies that reported on patients with injuries to all body regions and results analysed using a random-effects model and reported using pooled odds ratio with 95% confidence intervals (CI). ***Results:*** There were 14 observational studies and one randomized control trial involving 2,715 participants that satisfied inclusion criteria. We observed significant heterogeneity in the definitions of ATC, study design, setting, and patient population. Among observational studies that reported on patients with injuries to all body regions, VHAs were associated with higher odds of diagnosing ATC compared to SLCT (pooled OR 2.4; 95% CI: 1.4–4.1). There was inadequate evidence to suggest VHAs were associated with reduced blood product usage or lower mortality. ***Conclusion:*** VHAs detected more patients with ATC compared to SLCTs. However, the clinical significance and applicability of this finding remains unknown as translation to management was not adequately reported.



## Introduction

Trauma is a leading cause of death for young adults worldwide. Despite ongoing medical and public health improvements, the incidence of trauma is increasing in Victoria, Australia and with it, death due to trauma [1]. Approximately 40% of trauma of deaths results from haemorrhage, disproportionately affecting patients within the first 24 h after injury [2]. The management of haemorrhagic shock requires clinically driven trauma protocols and algorithms to address the hypovolaemic status and haemostatic dysfunction. Such damage control resuscitation (DCR) strategies have been developed to help guide clinicians with empirical treatments targeting the conditions that exacerbate haemorrhage [3]. These include a number of surgical, non-invasive and medical interventions.

In the setting of critical bleeding, acute traumatic coagulopathy (ATC) is a common complication after injury

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that leads to significant challenges in management and poor patient outcomes [4]. ATC causes a dysfunction in blood clotting leading to an increased bleeding risk. It occurs early and independently after injury, driven by hypoperfusion and is present in approximately a quarter of trauma patients [5, 6]. It is frequently present in the patients with higher injury severity scores and increasing degrees of hemorrhagic shock. The detection of ATC is difficult due to the acute, dynamic, and complex mechanisms behind it. Accurate diagnosis is important as inappropriate transfusion of blood products has been associated with harm [7]. Furthermore, timely diagnosis is essential to prevent worsening of coagulopathy and clinical deterioration to the point of irreversible physiological derangements.

Traditionally, standard laboratory coagulation tests (SLCT) are used for the detection of ATC, but are slow and only provide a limited snapshot of the clotting time when the sample was taken. Clinical laboratories perform SLCTs in approximately 15–30 min, with additional time to reporting results taking up to an hour from sampling [8]. Point of care devices for the measurement of traditional times to blood clotting have been reported as unreliable in the diagnosis of ATC [9]. By comparison, point of care Viscoelastic Haemostatic Assays (VHAs) have offered the potential for a quicker diagnosis of ATC and ongoing monitoring of transfusion requirements based on coagulation abnormalities [10]. This is a functional, dynamic, and repeatable set of parameters designed to assess clot formation, timing, strength, and dissolution. The two most commonly used VHA devices are Thromboelastography (TEG) (Haemonetics®, Boston, USA) and Rotational Thromboelastometry (ROTEM) (Tem Innovations GmbH, Munich, Germany). The Automated Thromboelastometry (TEM-A) (Framar Biomedica, Rome, Italy) is not currently used.

The use of VHA has been associated with mortality benefit in other areas of medical and surgical care [11, 12]. However, the current published literature has been unable to demonstrate a clear and definitive benefit established for acute trauma resuscitation due to the lack of available and comparable studies [13, 14]. The aim of this systematic review was to determine whether the use of VHA during trauma resuscitation detects a different population of patients with ATC compared to SLCTs. The association of any such difference with patient outcomes was explored as secondary outcome measures.

## Methods

*Information Sources and Search Technique*

A systematic search of databases was conducted on the December 2, 2020 to identify relevant manuscripts. This included MEDLINE, Cochrane Central, Embase, Emcare, BIOSIS, and CINAHL. As a result of ATC first appearing in literature in 2003 and the relatively novel nature of viscoelastic technology being used in trauma, we decided to restrict our search to studies published from 2000 onwards in all databases and secondary searching. Only human trials and full-text available manuscripts were included in the final review.

In addition to the databases listed above, additional searching of bibliographies of included texts, grey literature, websites, and registries including; clinical trials.gov, WHO trials registry, LILACs, Hemonetics, and the transfusion library was conducted. The study protocol was prospectively registered on Prospero [15].

*Eligibility Criteria and Study Selection*

We aimed to include randomized control trials (RCTs) as well as observational studies. The patient population was adult major trauma patients, as defined by individual manuscripts, excluding children and animal studies. Amongst these manuscripts, those that reported on both VHAs and SLCTs during the trauma resuscitation were selected. Our outcome measures were the proportion of patients with ATC detected on either VHA and SLCT and whether the difference in detection was associated with variation in blood product use in the first 24 h of admission.

*Data Abstraction and Analysis*

Two reviewers (EF and BM) independently screened the results from the search and collected data according to set of predetermined parameters as per guidance from the study team. The data extracted from each article included author, year, country, sample size, age range, mechanism of injury, injury severity score, VHA model, VHA timing, SLCT tests, and the ATC definition as per the VHAs and SLCTs used. Our primary outcome was reported as the number of patients identified as coagulopathic with VHA and SLCT and the number of those identified as not coagulopathic with VHA and SLCT. Other outcomes were documented as per the authors' reported results in the manuscript.

Two authors (EF and BM) independently assessed the risk of bias from the included studies as per the Newcastle-Ottawa II Scale [16]. Each manuscript was rated to establish the risk of bias from the selection processes, measurement acquisition, result reporting procedures, and loss to follow-up.

Among the included studies that reported on all major trauma patients, we performed a meta-analysis to assess the differential diagnosis of ATC between VHA and SLCTs. Manuscripts that reported on selected subgroups of injured patients, e.g., traumatic brain injury, were excluded from the meta-analysis. Data were analysed using STATA v 15.1 (College Station, TX, USA). A random-effects model was used to account for the assumption that the study effect estimates would show more variance than when drawn from a single population. To accommodate this assumption and minimize the imprecision of the effect estimations, the pooled odds ratios were analysed using the DerSimonian-Laird methods and reported with 95% confidence intervals. Statistical heterogeneity was assessed using the $\chi^2$ test.

## Results

The search yielded 2,579 studies after removal of duplicates, of which 47 articles fulfilled criteria for inclusion. The results of the search and respective levels of screening are outlined in the PRISMA flowchart in Figure 1 [17].

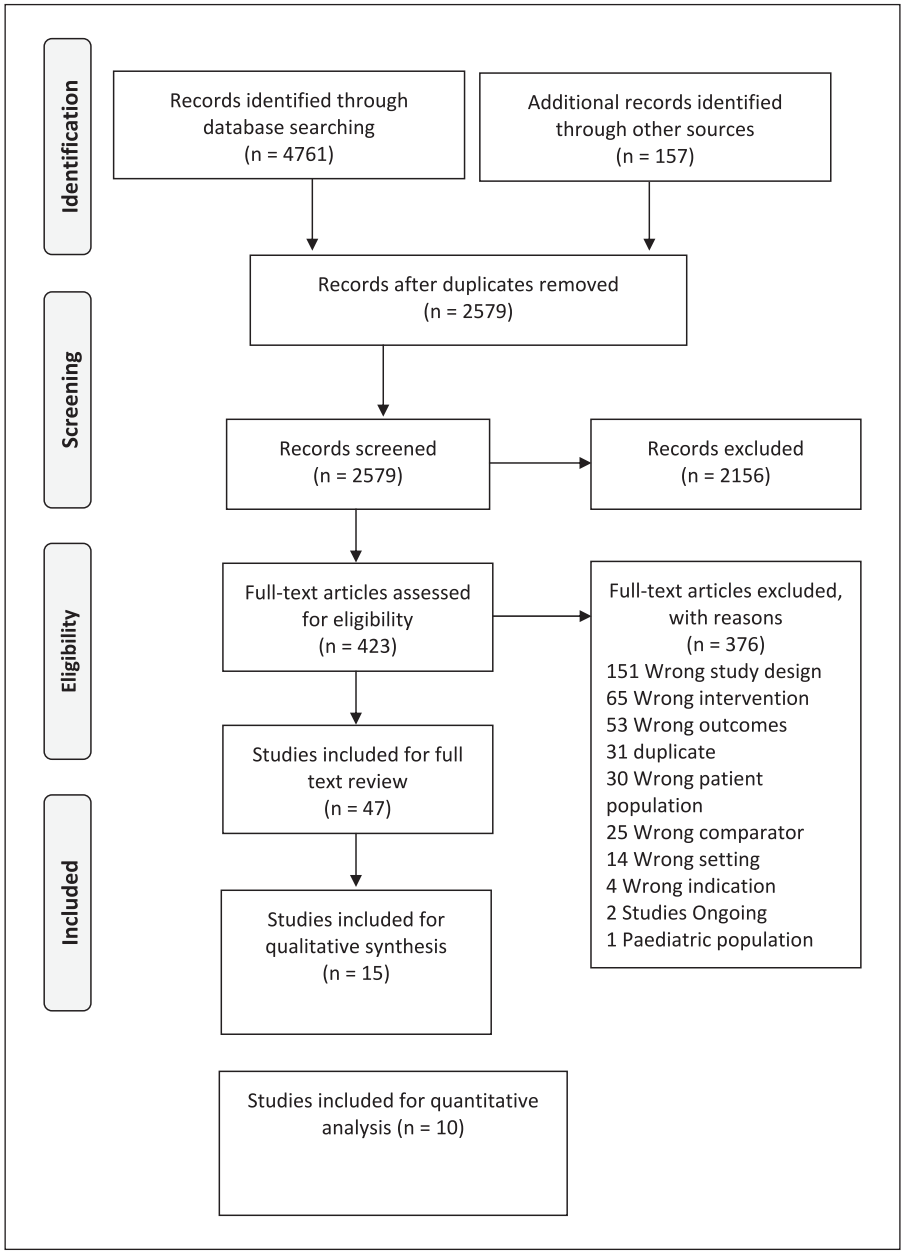


**Fig. 1.** Selection of studies, PRISMA flow diagram.

Of those 47 articles, there were only 15, comprising of 2,715 patients, which had published data that could be used to quantitatively assess our primary outcome [18–32]. There was one RCT identified and remaining manuscripts were either retrospective or prospective observational studies of moderate methodological quality. Descriptions of the 15 included study characteristics are presented in Table 1. Therefore, the remaining 32 manuscripts were excluded from this analysis as they did not numerically report on the detection rates of ATC between VHA and SLCT [33–64]. The characteristics of these studies are outlined in Table 2.

Five of the studies used VHA-guided resuscitation, incorporating the results into their treatment algorithms. Baksaas-Aasen et al. [32] compared TEG-, ROTEM-, and SLCT-guided resuscitation protocols in the RCT for implementing treatment algorithms for the correction of trauma induced coagulopathy (iTACTIC). Gratz et al. and Bouzat et al. [27, 31] used ROTEM-guided resuscitation with SLCTs performed in conjunction for clinical assessment. Zwinkels et al. [18] applied two different protocols separately to compare ROTEM-guided treatment with SLCT-guided treatment. Tauber et al. [20] used either SLCTs, ROTEM or both to guide clinical practice. Amongst the other studies, treatment was guided by SLCTs and traditional resuscitation protocols, with the VHA results obtained only for research purposes and not provided to the treating doctors [19, 21, 23, 25, 26, 29, 30].

**Table 1.** Description of included studies for systematic review

| Article | Study design | *N* | Population | VHA model | SLCT test |
|---|---|---|---|---|---|
| Baksaas-Aasen et al. 2020 UK [32] | Randomized Control Trial | 396 | Age: 18+ years<br>ISS: 26 (17–36)<br>Blunt/Penetrating (%): 67/33% | ROTEM + TEG (model not specified) | INR, fibrinogen, platelets |
| Bouzat et al. 2019 Germany, France [31] | Multi-centre Retrospective Cohort | 149 | Age: 18+years<br>ISS: 28 (20–42)<br>Blunt/penetrating (%): 62/38% | ROTEM Delta + ROTEM Sigma | INR and/or fibrinogen |
| Cohen et al. 2019 Afghanistan [30] | Prospective Cohort study | 40 | Age: 16+ years<br>ISS: 22 (14–27)<br>Combat | ROTEM (model not specified) | INR |
| Doran et al. 2010 UK [29] | Prospective cohort study | 31 | Age: 18+ years<br>Combat | ROTEM (model not specified) | PT, aPTT |
| Gozal et al. 2017 USA [28] | Retrospective cohort | 190 | Age: 18+ years<br>TBI only<br>Anticoagulant use 9% | TEG (model not specified) | Not specified |
| Gratz et al. 2019 [27] | Multi-centre Prospective Cohort | 32 | Age: 18+ years<br>ISS: 43 (26–50)<br>TBI only | ROTEM Sigma | INR, aPTT, fibrinogen |
| Jeger et al. 2009 Switzerland [26] | Prospective Cohort study | 20 | Age: 16+ years<br>ISS: 29 (16–65)<br>Blunt/penetrating (%): 100/0% | TEG 5000 | INR, TT, aPTT, platelet count |
| Plotkin et al. 2008 USA [24] | Retrospective Cohort | 44 | Age: unspecified<br>ISS: 21 +/– 9.4<br>Blunt/penetrating (%): 0/100%<br>Combat | TEG 5000 | aPTT, PT, INR |
| Schochl et al. 2011 Austria [23] | Retrospective cohort | 88 | Age: 15+ years<br>ISS: 20 (16–26.25)<br>TBI only | ROTEM (model not specified) | PT, aPTT, fibrinogen, platelet count |
| Subramanian et al. 2014 India [22] | Retrospective cohort | 150 | Age: 16+ years<br>ISS: 28.4 +/– 11.3 | TEM-A | PT and aPTT and/or INR |
| Sumislawski et al. 2019 USA [21] | Prospective cohort | 839 | Age: 18+ years<br>ISS: 10 (2–26)<br>Blunt/penetrating (%): 51/49% | TEG 5000 | INR, aPTT |
| Tauber et al. 2011 Austria [20] | Prospective cohort | 334 | Age: 18+ years<br>ISS: 34 (24–45)<br>Blunt/penetrating (%): 100/0%<br>Polytrauma patients | ROTEM (model not specified) | INR, aPTT, fibrinogen, plaelet count |
| Tonglet et al. 2018 Belgium [19] | Prospective cohort | 50 | Age: 14+ years<br>ISS: 13 (9–20) | ROTEM (model not specified) | INR, fibrinogen |
| TurMartinez et al. 2018 Spain [25] | Retrospective cohort | 230 | Age: 15+ years<br>ISS: 10 (1–54)<br>Blunt/penetrating (%): 96/4%<br>Polytrauma patients<br>Anticoagulant use 15% | TEG (model not specified) | INR, aPTT, PT |

**Table 1** (continued)

| Article | Study design | *N* | Population | VHA model | SLCT test |
|---|---|---|---|---|---|
| Zwinkels et al. 2020 Netherlands [18] | Retrospective cohort | 122 | Age: 18+ years<br>ISS: 34 (27–48)<br>Blunt/penetrating (%): 55/45%<br>Polytrauma + Massive transfusion patients | ROTEM Delta | INR |

VHA, viscoelastic haemostatic assays; SLCT, Standard Laboratory Coagulation Tests; ISS, injury severity score – reported as either median (Interquartile range) or mean +/− standard deviation; TBI, traumatic brain injury, TEG, thromboelastography; ROTEM, rotational thromboelastometry; TEM-A, automated thromboelastometry; aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio.

The remainder did not report whether the VHA results were available to the treating team or not [22, 24, 28].

To undertake a meta-analysis of observational data exploring the differential diagnosis of ATC, we excluded the manuscripts by Gozal, et al., Gratz, et al., and Schochl et al. [23, 27, 28] as the populations had been restricted to traumatic brain injury (TBI) patients only. Additionally, we excluded the manuscript by Plotkin, et al. [24] as the population only included patients suffering from penetrating injuries [24]. Finally, the RCT by Baksaas-Aasen et al. [32] was excluded from a meta-analysis combining observational studies.

The risk of bias assessment for the observational articles included in the meta-analysis is presented in Table 3 [16]. As per the Newcastle-Ottawa II Scale, the manuscripts were rated as good, fair or unclear, with seven manuscripts rated good [19–22, 25, 26, 31], and three as fair quality [18, 29, 30].

The results of the meta-analysis are shown in Figure 2. There was significant statistical heterogeneity detected among manuscripts ($p < 0.001$), which was adjusted for using random-effects model. The pooled odds ratio for ATC favoured VHA, where viscoelastic testing was associated with higher odds of diagnosing ATC (pooled OR 2.4; 95% CI: 1.4–4.1).

There were four studies included in our analysis that reported a significant benefit in using VHAs to detect the presence of coagulopathy, demonstrating either significant association with the corresponding SLCT parameters or a comparable negative predictive value (NPV) [19, 20, 23, 26]. Sumislawski et al. [21] reported no significant diagnostic benefit and supported the combined use of VHAs and SLCTs, as the SLCTs were able to identify acutely coagulopathic patients with the highest mortality. Subramanian et al. reported that the diagnostic accuracy of ROTEM increased from 46.6% to 66% when using a set of values predetermined by prior research of the specified population, instead of using the manufacturers ranges [22]. The manufacturers' ranges for ROTEM and TEG are presented in Table 4.

Additionally, another six articles reported on the relationship with blood product consumption. Cohen et al. reported the use of ROTEM increased the identification of patients requiring a massive transfusion by 22%, and had a higher sensitivity than using an INR >1.2 [30]. Tonglet et al. [19] determined a normal ROTEM was able to rule out patients at risk of needing >5 units RBC and >3 units plasma in 24 h as well as 30-days mortality with a NPV of 100% and 95.2%, respectively [19]. Plotkin et al. [24] found that the TEG parameters were more accurately able to indicate blood product requirements than SLCTs and the combined use of TEG, platelet count and haematocrit could guide transfusion. Tauber et al. [20] demonstrated that ROTEM MCF was significantly associated with reduced risk for RBC transfusion. Zwinkels et al. [18] compared VHA-guided resuscitation with SLCT-guided resuscitation and discovered that whilst fibrinogen, platelets, and calcium were given more frequently, the rate of plasma transfusions decreased with VHA-guided care. The iTACTIC trial found that patients in the VHA group were more likely to receive a study intervention of blood or blood product than their SLCT group counterparts (VHA 67% vs. SLCT 36%) [32]. It was also reported that the VHA group received those study interventions on average 21 min earlier than the SLCT group. The VHA group received more fibrinogen supplementation. However, at 24 h there was no significant difference in the rate of massive transfusion with an odds ratio of 1.15 and 95% confidence interval of 0.76–1.73. Except in a subgroup analysis of TBI patients, there was an improvement in 28-day mortality in VHA patients [32].

There were 3 studies using ROTEM that reported on early mortality risk or 30-days survival [19, 20, 23]. However, in a comparison of VHA and SLCT-guided resuscitation, Zwinkels et al. [18] demonstrated no significant benefit on 30-days mortality, and ICU or hospital length

**Table 2.** Description of included studies for full-text review but excluded from analysis

| Article | Study Design | *N* | Population | VHA model | SLCT test |
|---|---|---|---|---|---|
| Albert et al. 2019 India [33] | Prospective cohort | 58 | Age: 18+<br>Isolated severe TBI, GCS <8 | TEM-A | PT, aPTT, INR |
| Baksass-Aasen et al. 2019 UK [34] | Multi-centre prospective cohort | 2,287 | Age: 18+<br>ISS: 13 (5–25)<br>Blunt/Penetrating (%): 85/15% | ROTEM Delta, TEG 5000 | INR, aPTT, fibrinogen, platelets |
| Coleman et al. 2018 USA [35] | Prospective cohort | 343 | Age: 18+<br>NISS:18 (6–34)<br>Blunt/Penetrating (%): 52/48% | TEG 5000 | INR, aPTT, fibrinogen, platelets |
| Cotton et al. 2011 USA [36] | Prospective cohort study | 272 | Age: 18+<br>ISS: 14 (8–25)<br>Blunt/Penetrating (%): 72/28% | TEG 5000 | PT, aPTT, INR, platelet |
| Davenport et al. 2011 UK [37] | Prospective cohort study | 300 | Age: 15+<br>ISS: 12 (4–25)<br>Blunt/Penetrating (%): 79/21% | ROTEM (model not specified) | PT, platelets, fibrinogen |
| David et al. 2016 France [38] | Retrospective cohort study | 358 | Age: 18+<br>ISS: 26 (17–34)<br>Blunt/Penetrating (%): 94/6% | ROTEM (model not specified) | INR, aPTT, fibrinogen, platelets |
| Gonzalez et al. 2016 USA [39] | RCT | 111 | Age: 18+<br>ISS: 47.5 (22–59)<br>Blunt/Penetrating (%): 68/32% | TEG (model not specified) | INR, aPTT, fibrinogen, platelets |
| Guth et al. 2019 France [40] | Retrospective cohort + prospective cohort comparison | 372 | Age: 18+<br>ISS: 28 (18–38)<br>Blunt/Penetrating (%): 93/7% | ROTEM Delta | PT, aPTT, fibrinogen |
| Holocomb et al. 2012 USA [41] | Retrospective cohort study | 1,974 | Age: 18+<br>ISS: median 17 | TEG 5000 | PT, aPTT, INR |
| Hota et al. 2019 USA [42] | Retrospective cohort | 118 | Age: 18+<br>ISS: mean 16<br>Anticoagulated + TBI patients | TEG (model not specified) | Not specified |
| Jeger et al. 2012 Switzerland [43] | Prospective cohort study | 76 | Age: 16+<br>ISS: mean 18<br>Blunt/Penetrating (%): 83/17% | TEG 5000 | aPTT, INR, TT |
| Johansson et al. 2009 Denmark [45] | Retrospective cohort study | 832 | Age: 15+<br>MT patients | TEG (model not specified) | Platelets, aPTT, INR |
| Johansson et al. 2013 Denmark [44] | Prospective cohort study | 182 | Age: 18+<br>ISS: 17 (9–26)<br>Blunt/Penetrating (%): 92/8% | TEG 5000 | INR, aPTT, platelets, fibrinogen |
| Kashuk et al. 2009 USA [46] | Retrospective cohort | 44 | Age: 18+<br>ISS: 29 (23–35)<br>Blunt/Penetrating (%): 80/20% | TEG 5000 | INR, fibrinogen, platelet |
| Kashuk et al. 2012USA [47] | Prospective cohort study | 68 | Age: 18+<br>Blunt/Penetrating (%): 68/32%<br>MT patients | TEG 5000 | INR, aPTT |
| Kobayashi et al. 2018 USA [48] | Prospective cohort study | 182 | Age: 18+<br>ISS: 9 (4–13)<br>Anticoagulated trauma patients | TEG (model not specified) | aPTT, INR |
| Lammers et al. 2020 USA [49] | Retrospective cohort study | 3,320 | Age: 18+<br>ISS: median 18.8<br>Blunt/Penetrating (%): 84/16%<br>Combat patients<br>Male: 98% | ROTEM (model not specified) | INR |
| Leemann et al. 2010 [50] | Retrospective cohort study | 53 | Age: 18+<br>ISS: 31.1 +/– 1.7<br>Blunt/Penetrating (%): 100/0% | ROTEM (model not specified) | INR, aPTT, platelets |

**Table 2** (continued)

| Article | Study Design | *N* | Population | VHA model | SLCT test |
|---|---|---|---|---|---|
| Mohamed et al. 2017 USA [51] | Retrospective cohort study | 134 | Age: 18+<br>ISS: mean 29<br>Blunt/Penetrating (%): 63/37%<br>MT patients | TEG 5000 | Not specified |
| Nystrup et al. 2011 Denmark [52] | Retrospective cohort | 89 | Age: 18+<br>ISS: 21 (19–23)<br>Blunt/Penetrating (%): 85/15% | TEG (model not specified) | aPTT, INR, platelets |
| Peng et al. 2019 Canada [53] | Prospective | 45 | Age: 18+ | TEG 5000, ROTEM Delta | INR, PT, aPTT, fibrinogen, platelets |
| Pezold et al. 2012 USA [54] | Retrospective cohort study | 80 | Age: 15+<br>ISS: 29 +/– 1<br>Blunt/Penetrating (%):38/62% | TEG 5000 | INR, aPTT |
| Prat et al. 2017 Afghanistan [55] | Retrospective Cohort | 219 | Age: 18+<br>ISS: 21 (14–29)<br>Blunt/Penetrating (%): 16/84%<br>Combat patients | ROTEM Delta | INR, platelets |
| Rugeri et al. 2007 France [56] | Prospective cohort | 88 | Age: 18+<br>ISS: 22 (12–34) | ROTEM (model not specified) | INR, PT, aPTT, fibrinogen, platelets |
| Schochl et al. 2010 Austria [57] | Retrospective cohort | 131 | Age: 18+<br>ISS: 38 +/– 15<br>MT patients | ROTEM (model not specified) | Fibrinogen, aPTT, PT |
| Smith et al. 2020 USA [58] | Retrospective cohort | 301 | Age: 18+<br>ISS: >15<br>Blunt/Penetrating (%): 89/11% | ROTEM (model not specified) | INR |
| Stettler et al. 2018 USA [59] | Prospective cohort | 222 | Age: 18+<br>NISS: 46.5 (38–57) | ROTEM, TEG (model not specified) | INR, aPTT |
| Tapia et al. 2013 USA [60] | Retrospective cohort | 289 | Age: 18+<br>ISS: 23+/– 14<br>Blunt/Penetrating (%): 34/66%<br>MT patients | TEG (model not specified) | Not specified |
| Unruh et al. 2019 USA [61] | Retrospective cohort | 67 | Age: 18+<br>ISS: 26.7 +/– 14.7<br>Blunt/Penetrating (%): 76/24%<br>MT patients | TEG 5000 | PT, INR, fibrinogen |
| Van Wessem et al. 2017 Netherlands [62] | Prospective cohort | 135 | Age: 18+<br>ISS: 29 (22–38)<br>Blunt/Penetrating (%): 96/4%<br>ICU polytrauma patients | TEG (model not specified) | aPTT, PT, platelets |
| Walters et al. 2018 Australia [63] | Retrospective cohort | 326 | Age: 18+<br>ISS: median 22<br>ICU trauma patients | ROTEM (model not specified) | Not specified |
| Yin et al. 2014 China [64] | Retrospective cohort | 60 | Age: 18+<br>ISS: 15.2 +/– 6.9<br>Blunt/Penetrating (%): 83/17%<br>Abdominal trauma | TEG 5000 | INR, aPTT |

VHA, viscoelastic haemostatic assays; SLCT, standard laboratory coagulation tests; ISS, injury severity score – reported as either median (Interquartile range) or mean +/– standard deviation; NISS, new injury severity score; TBI, traumatic brain injury; TEG, thromboelastography; ROTEM, rotational thromboelastometry; TEM-A, automated thromboelastometry; aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; ICU, intensive care unit.

**Table 3.** Risk of bias assessment – Newcastle-Ottawa quality assessment for cohort studies

| Study | Selection | | | | Comparability | | Outcome | | | Rating | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | representativeness of the exposed cohort | selection of non-exposed cohort | ascertainment of exposure | outcome not present at the start | study controls for age and sex | study controls for at least 3 other variables | assessment of outcome | adequate follow-up | loss to follow-up | overall quality score | rating |
| Bouzat et al. 2019 [31] | * | * | * | * | – | – | * | * | * | 7/9 | Good |
| Cohen et al. 2019 [30] | – | * | * | – | * | * | * | * | – | 6/9 | Fair |
| Doran et al. 2010 [29] | – | * | * | – | * | * | * | * | – | 6/9 | Fair |
| Jeger et al. 2009 [26] | * | * | * | * | * | * | * | * | * | 9/9 | Good |
| Subramanian et al. 2014 [22] | * | * | * | * | * | * | * | * | * | 9/9 | Good |
| Sumislawski et al. 2019 [21] | * | * | * | * | * | * | * | * | – | 8/9 | Good |
| Tabuer et al. 2011 [20] | * | * | * | * | * | * | * | * | * | 9/9 | Good |
| Tonglet et al. 2018 [19] | * | * | * | – | * | * | * | * | * | 8/9 | Good |
| TurMartinez et al. 2018 [25] | * | * | * | – | * | * | * | * | * | 8/9 | Good |
| Zwinkels et al. 2020 [18] | * | * | * | – | – | – | * | * | * | 6/9 | Fair |

Refer to http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, for explanation of the Newcastle-Ottawa Quality Assessment Scale for cohort studies. The stars (*) represent higher degrees of quality in the respective areas of assessment for each article.

of stay with VHA. The iTACTIC randomized control trial (RCT) found no significant difference between VHA and SLCT groups in the rate of multiple organ failure, number of ventilator-free or ICU-free days, hospital length of stay, quality of life scores, and cause of death profiles [32]. Additionally, they reported that at 24 h, 28 days, and 90 days, there remained no significant differences in the mortality rate.

## Discussion

This systematic review demonstrated that the use of VHAs was associated with a higher proportion of patients being diagnosed with ATC when compared to SLCTs. Whilst there was some indication that VHAs may lead to a reduction in blood and blood product use, benefits on patient outcomes were not conclusive and could not be demonstrated from the only RCT on the topic. The clinical significance of early detection of abnormalities on viscoelastic measures of blood clotting is therefore questioned.

The variability of VHA tools including ROTEM Sigma, ROTEM Delta, TEG 5000 versus TEG 6 s and TEM-A added to the heterogeneity of the observations. Additionally, blood was obtained at different times after injury for analysis and this was not always reported on in the included articles. Some authors repeated the assay at either the clinician's discretion or at regular intervals, where others simply obtained the initial result for diagnostic purposes. There was also a variation in whether the VHA results were available to the treating clinicians, research team only or used as the primary method for guiding resuscitation efforts. Those studies that implemented VHA-guided protocols registered an adherence rate of 65–92%, potentially reducing the number of eligible patients from which to draw significant conclusions [18, 27].

Adding to the heterogeneity of VHA measurement tools and timing, there was variability in the definition of ATC by the VHAs and SLCTs. Many studies used a number of arbitrary thresholds to determine the diagnosis of ATC. These introduce significant clinical heterogeneity to this review (online suppl. Material; for all online suppl. material, see www.karger.com/doi/10.1159/000526217). The VHA ranges used were either provided by the manufacturers, a result of author experience, or predetermined for the specific patient population. Subramanian et al. [22] found an improved diagnostic accuracy using values created against a gold-standard SLCT in their laboratory rather than the ROTEM manufacturer reference set. This may impact the comparison of studies between specific trauma populations if the reference ranges also vary in cut-offs and efficacy.

**Table 4.** VHA manufacturer reference ranges [65, 66]

| ROTEM | | | | | | |
|---|---|---|---|---|---|---|
| parameter | CT (s) | CFT (s) | alpha angle, ° | A10, mm | MCF, mm | LI30, *n* (%) |
| EXTEM | 38–79 | 34–159 | 63–83 | 43–65 | 50–72 | 94–100 |
| INTEM | 100–240 | 30–110 | 70–83 | 44–66 | 50–71 | 94–100 |
| HEPTEM | 100–240 | 30–110 | 70–83 | 44–66 | 50–71 | 94–100 |
| | Comparison with INTEM. A better clot formation in HEPTEM as compared with INTEM indicates the presence of heparin or heparin-like anticoagulants in the sample | | | | | |
| APTEM | 38–79 | 34–159 | 63–83 | 43–65 | 50–72 | n/a |
| | Comparison with EXTEM. A better clot formation in APTEM as compared with EXTEM is a sign of hyperfibrinolysis | | | | | |
| FIBTEM | n/a | n/a | 30–70 | 7–23 | 9–25 | n/a |
| TEG | | | | | | |
| parameter | R value, min | K time, min | alpha angle, ° | A10, mm | MA, mm | LY30, n (%) |
| CK-TEG | 4.6–9.1 | 0.8–2.1 | 63–78° | n/a | 52–69 | 0–2.6 |

Citrated Kaolin TEG (CK-TEG), EXTEM, INTEM, HEPTEM, APTEM, and FIBTEM refer to the different reagents used to assess various clot dynamics. CT, clotting time; CFT, clot formation time; MCF, maximum clot firmness; A10, clot amplitude at 10 min; LI30 & LY30, clot lysis at 30 min, *R* value, reaction time; K time, kinetics; MA, maximum amplitude.

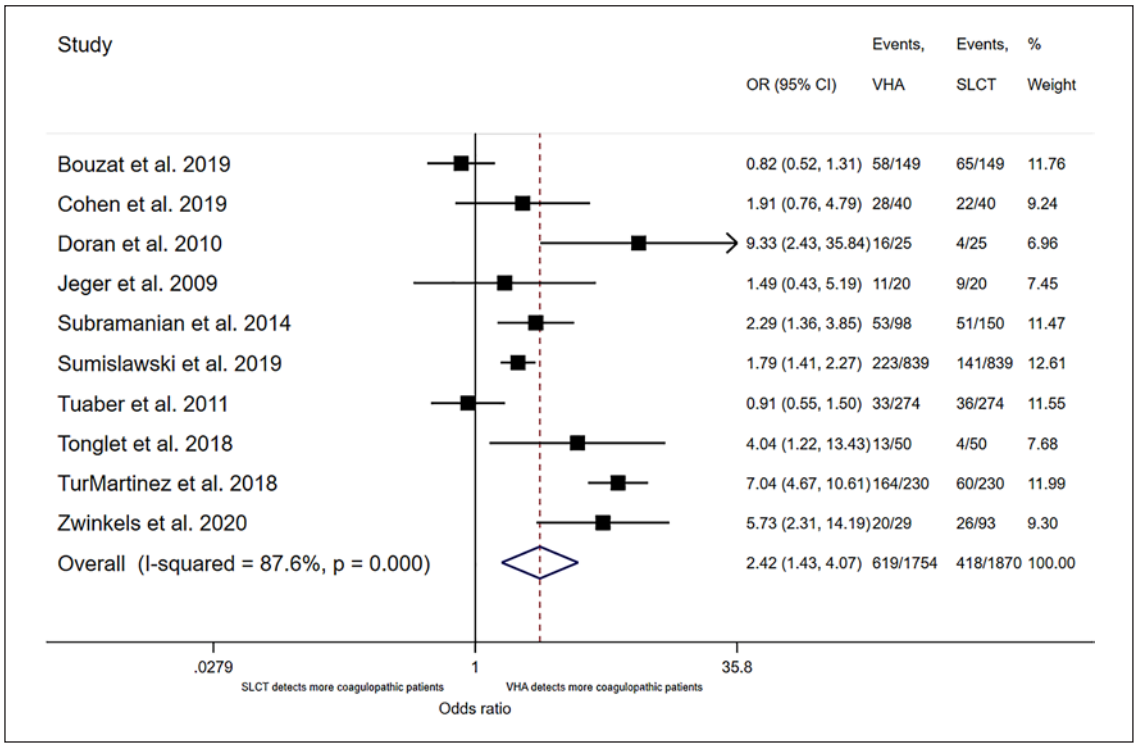


**Fig. 2.** Meta-analysis of studies assessing general trauma patients.

In recent observational studies, an overall reduction in transfusion rates has been demonstrated using VHA-guided treatment [45, 51, 55, 61, 64]. Some evidence comparing various TEG and ROTEM measurements to SLCTs suggests the ability to forecast outcomes and predict transfusion requirements [19, 20, 24, 35–37, 50, 52, 58, 59]. A systematic review published in 2016, identified that the ROTEM measurements for clot amplitude at 5

min (CA5) and maximum clot firmness (MCF) were able to predict transfusion requirements and mortality [65]. These analyses pose an issue in application of such statistical predictions in a clinical setting that is highly variable, dynamic, and fast-paced, often with unstable patients. It is common practice to identify this correlation using VHA results only obtained for research purposes in patients treated according to their SLCT results. In 2013, Johansson et al. discovered that when they compared TEG parameters obtained during TEG-guided resuscitation, it weakened the statistical signal for prediction of mortality and massive transfusion [44].

Whilst the iTACTIC trial saw a 1.8 times increase in the number of interventions given in the VHA group, they were unable to ascertain whether those additional therapies provided were able to effectively correct the coagulopathy and achieve haemostasis [32]. Furthermore, the iTACTIC trial demonstrated increased fibrinogen supplementation in the VHA treated patients. This may be due to the time delay in SLCTs identifying low fibrinogen levels compared to VHAs, resulting in faster and more frequent detection of low fibrinogen and subsequent supplementation. However, it is important to consider that the iTACTIC trial assessed VHA groups using both TEG and ROTEM devices combined, but research shows that the fibrinogen-based clot integrity levels reported are different between the two devices. This indicates that the potential of VHAs overall to guide fibrinogen supplementation therapy without factoring in this difference may lead to inconsistent and/or inaccurate treatment [66].

In regards to mortality, several articles from 2010 to 2020 showed a trend towards increased survival when using VHA-guided treatment [44, 45, 49, 60], but equally as many studies displayed no significant benefit [18, 40, 42, 47, 51, 62]. A previous study by Mohammed et al. reported only a significant decrease in mortality for patients <30 years old and none overall [51]. They also noted that repeating TEGs had no impact on survival. There are two published RCTs on VHA in trauma, one shows rapid-TEG-guided treatment led to an improved 28-day survival and decreased the rate of early haemorrhage [39], whereas the most recent multi-centre RCT concludes no difference in the mortality and massive transfusion outcomes [32]. A recent publication by Lammers et al. [49], showed a 57% reduction in overall mortality after implementing ROTEM in trauma [49]. In this analysis the reported benefit for 24 h, 30-days and overall mortality with VHA use was inconsistent amongst the studies comparing the VHA- and SLCT-guided resuscitation. Therefore, whilst an identifiable trend is evident in the literature, no further conclusions can be made from this study.

This systematic review was limited in only including one RCT, the wide heterogeneity of repeatable VHA techniques, inconsistent data reporting and lack of comparable definitions for ATC and massive transfusion. Unfortunately, the only other RCT on VHA in trauma by Gonzalez et al. [39] did not have data available on the proportion of patients with and without coagulopathy in each of the two groups, and could not be included in the analysis. Furthermore, there were a handful of studies that focused on certain subgroups of trauma, being TBI [23, 27, 28], penetrating injury [24], anticoagulant usage [25, 28], and combat setting [24, 29, 30]. This is not an accurate reflection of the distribution of patients in a large portion of civilian trauma hospitals. Additionally, there is an evident link between TBI and coagulopathy, although it is not clear if this predisposes to ATC or is a separate phenomenon [67, 68]. The iTACTIC trial reported an unexpected finding of mortality improvement in subgroup analysis of TBI patients in the VHA group. This may indicate an area for future improvement in trauma care as TBI has typically been excluded on the basis that it is unlikely to be affected by changes to haemostatic management due to severity and underlying pathology [32].

One of the more practical considerations in comparisons of VHA- and SLCT-guided resuscitations is the cost of implementing new treatment modalities. Whilst none of our included studies directly reported on the cost effectiveness of VHA in their analysis, a 2015 UK study compared the costs of the TEG and ROTEM devices available at the time and concluded that the cost effectiveness of the VHA devices dominated the SLCTs. The estimated cost savings were £688 for ROTEM and £721 for TEG when compared to the SLCTs. It is, however, worth noting that the authors had minimal access to data on the effectiveness of VHA in trauma and so the results were more "indicative of the potential cost-effectiveness" rather than definitive for trauma patients [69].

The retrospective studies were at risk of selection bias in that they did not assess patients with clinical signs of bleeding and may have missed those who were coagulopathic and not bleeding and vice versa. In regard to the multi-centre articles, Sumislawski et al. [21] noted that they did not have identical transfusion protocols between the two centres for accurate collation and comparison of data. Moreover, there was distinct statistical heterogeneity from variation in sample size between included manuscripts. The marked variation in literature, combined with scarcity of studies, leads to poor clinical applicability and decidedness on the ability of VHA to improve outcomes in trauma.

## Conclusion

The current literature on detection of ATC by VHA is predominantly observational and displays variability regarding the utility of VHA. Use of VHAs during trauma resuscitation detected higher rates of ATC, faster time to results, and the potential to anticipate massive transfusions. However, the clinical significance of findings of abnormalities remains unknown. Prospective trials that combine investigations towards ATC with evidence-based therapeutic strategies may further elucidate the benefits of early investigations.

## Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

This is an original project with the initial concept proposed by Biswadev Mitra. Ellen Forster was primarily involved in creating and executing the search strategy, data analysis, and manuscript write-up. Biswadev Mitra and Simon Hendel were involved in the editing, draft review, concept construction, and overall direction of the paper. The work presented here is completely original and does not contain any material previously published elsewhere by another author, except where appropriate references have been made.

## Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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