

# Substitution of ROTEM FIBTEM A5 for A10 in Trauma: An Observational Study Building a Case for More Rapid Analysis of Coagulopathy

Alexander Blayney (✉ [alexblayney@hotmail.co.uk](mailto:alexblayney@hotmail.co.uk))

Gold Coast Health <https://orcid.org/0000-0003-1969-1027>

James P. A. McCullough

Gold Coast University Hospital

Elizabeth Wake

Trauma Service, Gold Coast University Hospital

Kerin Walters

Intensive Care Unit, Gold Coast University Hospital

Don Campbell

Trauma Service, Gold Coast University Hospital

Debbie Ho

Intensive Care Unit, Gold Coast University Hospital

Erick Chan

Intensive Care Unit, Gold Coast University Hospital

Aashish Chalasani

Intensive Care Unit, Gold Coast University Hospital

James Winearls

Intensive Care Unit, Gold Coast University Hospital; Intensive Care Unit, St Andrews War Memorial Hospital; University of Queensland; Monash University

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## Original research

**Keywords:** ROTEM, rotational thromboelastometry, fibrinogen, trauma, haemorrhage, coagulopathy, resuscitation

**Posted Date:** October 28th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-97393/v1>

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# Abstract

## Background

Rotational thromboelastometry (ROTEM®) allows guided blood product resuscitation to correct trauma induced coagulopathy in bleeding trauma patients. FIBTEM amplitude at 10 minutes (A10) has been widely used to identify hypofibrinogenaemia; locally a threshold of < 11 mm has guided fibrinogen replacement. Amplitude at 5 minutes (A5) carries an inherent time advantage. The primary aim was to explore the relationship between FIBTEM A5 and A10 in a large cohort of trauma patients and subgroups. Secondary aim was to investigate the use of A5 as a surrogate for A10 within a fibrinogen-replacement algorithm.

## Methods

Retrospective observational cohort study of 1539 consecutive trauma patients at a Level 1 trauma centre in Australia who received ROTEM on arrival to hospital. Consistency of agreement between FIBTEM A5 and A10 was assessed by the intra-class correlation coefficient (ICC) and Bland-Altman plot. Sub-group analysis was performed for number of packed red blood cell transfusions and by International Trauma Severity Score (ISS). A new fibrinogen replacement threshold was developed for A5 using the A5 – A10 bias and clinically compared to the existing A10 threshold.

## Results

FIBTEM A5 displayed excellent consistency of agreement with A10. ICC = 0.972 (95% confidence interval [CI] 0.969 – 0.974) in the whole cohort. This was maintained within the sub-group analyses. Bias of A5 to A10 was -1.49 (95% CI 1.43 -1.56) mm. 19.34% patients met the original local threshold of A10 < 11 mm; 19.28% patients met the new, bias-adjusted threshold of A5 < 10 mm.

## Conclusions

We demonstrate that ROTEM FIBTEM A5 reliably predicts A10 within the trauma setting. Importantly, this strength of agreement is demonstrated within major haemorrhage patients and those with major trauma. This further validates use of the A5 result over A10 for more rapid interpretation of results in time-critical resuscitation of trauma patients. Early analysis suggests that a modification of -1 to the A10 threshold might be appropriate for use with the A5 value in trauma patients. Further work is required to analyse this prospectively.

## Background

Trauma is a major cause of mortality globally and estimated to cause 4.5 million deaths annually (1). 25–50% of trauma deaths are due to exsanguination (2, 3), and swift control of haemorrhage with replacement of blood products underpins the resuscitation of trauma patients. An alternative to standard, fixed-ratio major haemorrhage protocols involves targeted resuscitation guided by point-of-care

viscoelastic haemostatic assays (VHAs) such as ROTEM (ROTEM®, Werfen, Barcelona, Spain) which identify deficient and dysfunctional coagulative components. This allows patient-specific administration of blood products to correct coagulopathy (4). Observational data (5) and a single centre randomised control trial have suggested VHA might increase survival versus fixed-ratio blood product resuscitation (6); reproducibility is currently being assessed in a multicentre randomised control trial (7).

ROTEM FIBTEM assays assess the function of fibrinogen in clotting blood (8). Low clot amplitude is indicative of hypofibrinogenaemia (9), and predictive of the need for massive transfusion (10). In guided resuscitation algorithms this usually triggers fibrinogen replacement using fresh frozen plasma, cryoprecipitate or fibrinogen concentrate. The European Task Force for Advanced Bleeding Care in Trauma advocated for the use of VHAs but did not recommend specific cutoff values to use; “more research is required... physicians should use their own judgement when developing local policies” (11).

Trauma services, including our own, have developed guidelines for fibrinogen replacement using FIBTEM amplitude at 10 minutes (A10) with a threshold for fibrinogen replacement of < 11 mm. Over time local practice moved to using A5 (amplitude at 5 minutes) as a surrogate for A10 values to guide resuscitation more rapidly (Appendix 1: current ROTEM-guided transfusion algorithm). This was performed without changing the threshold value of < 11 mm.

The literature demonstrates that FIBTEM A5 may be better at predicting laboratory-based hypofibrinogenaemia than maximum clot formation (the maximum amplitude reached during a ROTEM assay) in large trials (9, 12). A5 thresholds of 9.5 mm and 10 mm respectively were shown to predict laboratory-based hypofibrinogenaemia with sensitivities (specificities) of 78% (70%) and 70% (76%). However, these studies did not present predictions of hypofibrinogenaemia based on A10 for comparison. The relationship between the two early FIBTEM variables has been inadequately studied. FIBTEM A5 and A10 have been shown to be highly correlated in multiple surgical settings (13–15) and EXTEM A5 and A10 to correlate strongly in the setting of trauma (16). Yet data on the reliability, direction and magnitude of agreement between FIBTEM A5 and A10 are lacking. Clinically this relationship is important to understand for the development of more accurate guided resuscitation algorithms. Given that the clot has had five more minutes to strengthen between the FIBTEM A5 and A10 result, we hypothesised that A5 results reliably predict A10 values that are greater in magnitude. Thus A5 could be used to safely expedite the detection of and response to hypofibrinogenaemia.

## Objectives

The primary objective was to explore the relationship between ROTEM FIBTEM A5 and A10 in a large cohort of trauma patients and in subsets of patients with massive haemorrhage and/or major trauma, as these are the patients for whom the benefits of more rapid ROTEM results might be most apparent. The secondary objectives were to assess the clinical relevance of the difference between A5 and A10 results when applied to our current local fibrinogen-replacement algorithm threshold of < 11 mm, and to compare

these against a modified threshold for A5 developed by using the quantified relationship between FIBTEM A5 and A10 to modify the existing threshold.

## Methods

### Design and Setting

This retrospective observational study is reported according to the STROBE Statement for observational studies (17). The study setting was a 750-bed tertiary health service with a Level 1 Trauma Centre located in Southeast Queensland, Australia. The institution receives over 1500 trauma activations every year with an average of 300 being classed as major trauma (Injury Severity Score (ISS)  $\geq 12$ )(18).

### Participants

Participants included patients of all ages that met the trauma call criteria (briefly: injury to more than one body region or injury involving chest or abdomen, and/or significant mechanism of injury; full criteria in Appendix 2) and received a ROTEM on presentation to the emergency department between April 2014 and December 2016. Patients who did not receive a ROTEM on presentation were excluded.

### Procedure

Each ROTEM sample was collected as part of routine admission blood tests into a 3.5 ml citrated Vacuette tube (Greiner Bio-One, Kremsmünster, Austria) and transported by hand from the Emergency Department to the Intensive Care Unit for analysis. A ROTEM Delta system was used to analyse samples. This is a semi-manual system that requires blood samples to be pipetted in multiple steps by trained operators. The system uses pin and cup technology with different reagent systems in each of the four channels (8). In this study the FIBTEM assay was used (extrinsically activated with tissue factor, the platelet inhibitor cytochalasin D and 300  $\mu$ l of blood). ROTEM measurements were run for a minimum of ten minutes plus clotting time. This meant the minimum results were A5 and A10.

### Data Collection

A Trauma Registry was maintained contemporaneously comprising demographic and clinical data including injury mechanism, injury severity score and mortality. This was supplemented by data from the electronic patient records including ROTEM results, baseline laboratory tests and blood product administration in the first 24 hours.

### Outcomes

The primary outcome was consistency of agreement between pairs of FIBTEM A5 and A10 results in the whole cohort and by subgroup analyses of patients with massive transfusion ( $\geq 10$  units packed red cells in 24 hours) and major trauma (ISS  $\geq 12$ ). Secondary outcomes included the measured bias (mean difference) between A5 and A10 pairs, and assessment of the clinical relevance of this difference by counting numbers of patients meeting fibrinogen-replacement threshold within our algorithm using the

original A10 < 11 mm; current A5 < 11 mm; and a calculated new threshold for A5 (generated by applying the bias to the < 11 mm threshold).

## **Statistical Methods**

Data were analysed using STATA (StataCorp, 2017, Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and Microsoft Excel (Microsoft 2019, Version 1912 (Build 12325.20288)). ROTEM data were first screened and biologically implausible results and patients with missing data were excluded from the analysis. Descriptive data analysis was performed using counts and percentages for categorical data. Continuous data were described using median and interquartile range.

For the primary outcome whole cohort FIBTEM A5 and A10 values were assessed for consistency of agreement using the intra-class correlation coefficient (ICC) based on a two-way mixed-effects model where the A5 and A10 tests were treated as fixed effects and the blood samples as random effects. Agreement was also assessed using a Bland-Altman plot which plots the mean of the two scores to the difference between scores and can identify systematic bias and heterogenous variation.

Subgroup analyses were performed. In the first, participants were grouped by number of red cell transfusions in the first 24 hours (nil; one to three units; four to nine units; ten or more units). Ten or more units was selected as the last group as this traditionally represents massive transfusion. In a second analysis participants were grouped by Injury Severity Score (ISS; zero to seven, eight to eleven, twelve or more). The latter group represented major trauma (18).

For the secondary outcomes numbers of patients reaching ROTEM-guided threshold for fibrinogen replacement according to local fibrinogen replacement algorithm (FIBTEM amplitude < 11 mm) were counted using the A5 and A10 results to assess clinical relevance of any difference between A5 and A10 results.

Based on the bias (mean difference) between the A5 and A10 results the threshold for fibrinogen replacement was modified for A5 values and the number of patients reaching this new threshold was counted. Numbers of patients who actually received fibrinogen were counted in each case for comparison.

## **Ethics**

Ethics approval was obtained from the Gold Coast Hospital and Health Service Human Research Ethics Committee (HREC number blinded for peer review) Waived consent was granted as Sect. 2.3 of the National Statement on Ethical Conduct in Human Research.

## **Results**

## **Participants**

Over the three-year period between 20/1/14 to 30/12/16, 4495 patients met the trauma call criteria and 1539 patients had ROTEM FIBTEM performed. One patient's data was removed due to implausible ROTEM results and 13 patients did not have an A10 value recorded. This left 1525 patients for the primary analysis (Fig. 1).

Of the 1525 patients used for primary analysis, 1124 (73.70%) were male. All continuous variables displayed non-normal distributions. Median age was 37 years (interquartile range [IQR] 25–54). Blunt trauma comprised the main mechanism of injury, present in 1391 (91.21%) cases. 474 patients (31.08%) were classified as major trauma ( $ISS \geq 12$ ) and 123 (8.07%) received packed red cell transfusions in the first 24 hours from arrival. Further descriptive statistics can be found in Table 1.

In the whole cohort, median (IQR) FIBTEM A5 values were 13 (10–16) mm and A10 values 14 (11–18) mm; laboratory-measured Clauss fibrinogen was 2.9 (2.5–3.4) g/l. ROTEM values for the subgroups are displayed in Table 2.

Table 1  
Descriptive statistics of cohort

	N or Median	% or IQR
<b>Total</b>	<b>1525</b>	<b>100</b>
Age	37	25–54
Male	1124	73.70%
Female	401	26.30%
ISS	5	1–14
ISS $\geq$ 12	474	31.08%
Died < 24 hr	12	0.79%
<b>Mechanism</b>		
Blunt	1391	91.21%
Penetrating	119	7.80%
Burns	12	0.79%
Immersion	3	0.20%
PRBC transfusion in 24 hr	123	8.07%
Massive transfusion ( $\geq$ 10 units PRC)	14	0.92%
<b>Initial Blood Results</b>		
INR	1.0	1.0–1.1
INR > 1.3	47	3.08%
pH	7.36	7.32–7.39
pH < 7.30	197	12.9%
Base excess (mmol/l)	0.0	-1.8–1.4
Base excess < -2.0 mmol/l	262	17.2%
Lactate (mmol/l)	1.7	1.2–2.6
Lactate > 2.5 mmol/l	307	20.1%
<b>Legend:</b> Values given as a count with percentage of total or as median (interquartile range). IQR (interquartile range), ISS (injury severity score), PRC (packed red cell), INR (international normalised ratio)		

Table 2  
ROTEM and laboratory fibrinogen values

	n	A5 median (IQR) mm	A10 median (IQR) mm	Clauss Fibrinogen median (IQR) g/l
Whole cohort	1525	13 (10–16)	14 (11–18)	2.9 (2.5–3.4)
No PRC	1402	13 (10–16)	14 (12–18)	3.0 (2.6–3.5)
1–3 PRC	65	14 (10–19)	14 (11–21)	2.8 (2.3–3.3)
4–9 PRC	44	10 (6.8–13)	10.5 (7.8–13.3)	2.0 (1.5–2.6)
≥ 10 PRC	14	8.5 (5.3–12)	9.5 (6.3–14)	2.5 (1.2–2.9)
ISS 0–8	846	13 (10–16)	14 (11–18)	2.9 (2.5–3.5)
ISS 9–11	206	13 (10–16)	14 (11–17)	3.0 (2.5–3.4)
ISS ≥ 12	473	13 (10–16)	14 (11–18)	2.9 (2.3–3.4)

**Legend:** ROTEM FIBTEM and laboratory-measured Clauss Fibrinogen for the whole cohort and for sub-groups. Sub-groups by packed red cell transfusion quantity in the first 24 hours and by ISS. A5 (amplitude at 5 minutes), IQR (interquartile range), A10 (amplitude at 10 minutes), PRC (packed red cell units transfused in 24 hr), ISS (injury severity score)

## Primary Outcomes

In the whole cohort A5 and A10 values had an ICC of 0.972 (95% CI 0.969–0.975). ICC values above 0.90 are considered to represent an excellent level of agreement (19).

ICCs reflecting excellent agreement levels were also observed in all sub-groups when broken down by numbers of PRC transfused in 24 hours or ISS (Table 3). Within the massive transfusion group (n = 15) the A5-A10 ICC was 0.987 (0.962–0.996). In patients with major trauma (n = 473) the A5 A10 ICC was 0.972 (0.966–0.976).

Table 3  
Intraclass correlation values

	95% Confidence Intervals			
	n	ICC	Lower CI	Upper CI
Whole cohort	1525	0.972	0.969	0.975
No transfusion	1402	0.970	0.966	0.973
1–3 PRCs	64	0.984	0.974	0.990
4–9 PRCs	44	0.992	0.985	0.995
≥ 10 PRCs	15	0.988	0.963	0.996
ISS 0–9	846	0.973	0.969	0.976
ISS 9–11	206	0.969	0.959	0.976
ISS ≥ 12	473	0.972	0.966	0.976

**Legend:** Intraclass correlation values and confidence intervals for A5 A10 comparison in sub-groups split by quantity of packed red cell transfusions in the first 24 hours and by Injury Severity Score. ICC (intraclass correlation), CI (95% confidence interval), PRC (packed red cells), ISS (Injury Severity Score)

Bland-Altman plots were also constructed to indicate agreement and plots for the whole cohort and the subgroups of massive haemorrhage and major trauma (Fig. 2)

## Secondary Outcomes

From the whole cohort Bland-Altman plot the calculated bias (mean difference) between A10 and A5 values was observed to be 1.49 mm (95% CI 1.43–1.56 mm) indicating the average A10 value was 1.49 mm greater than its counterpart A5 value.

295 (19.34%) patients met the original local ROTEM threshold (A10 < 11 mm) for fibrinogen replacement. 424 (27.80%) patients met the current ROTEM threshold (A5 < 11 mm) for fibrinogen replacement (see Appendix 1). A minority of patients in both groups actually received fibrinogen replacement (indicating that they had met the second clinical criterion of active bleeding): 45 (2.95% of total) and 51 (3.34% of total) patients respectively.

The calculated new trial threshold for A5 (after subtracting the bias from the original A10 threshold of < 11 mm) was A5 < 10 mm (rounded to the nearest integer due to the precision of the ROTEM machine readouts). Using this new threshold 294 (19.28%) patients would have met the ROTEM criterion for fibrinogen replacement. Numbers of patients meeting these criteria are displayed in Table 4.

Table 4  
Patients meeting different fibrinogen replacement criteria for FIBTEM A5 and A10

	Current Threshold	Original Threshold	New Threshold
	A5 < 11 mm	A10 < 11 mm	A5 < 10 mm
Met ROTEM threshold	424 (27.80%)	295 (19.34%)	294 (19.28%)
Fibrinogen replaced	51 (3.34%)	45 (2.95%)	47 (3.08%)
Fibrinogen not replaced	373 (24.46%)	250 (16.39%)	247 (16.20%)
<b>Legend:</b> Summary of numbers of patients from the whole cohort who would have met different ROTEM FIBTEM fibrinogen replacement thresholds and which of those patients actually received fibrinogen replacement. Current local guidelines recommend fibrinogen replacement when A5 < 11 mm AND there is a clinical assessment of significant bleeding.			

## Discussion

The study has demonstrated an excellent consistency of agreement of ROTEM FIBTEM A5 and A10, with an ICC (95% CI) of 0.972 (0.969–0.975) across a large cohort of trauma patients. This level of consistency of agreement was maintained within all subgroups analysed and importantly in the groups of major trauma (ISS  $\geq$  12) and massive transfusion ( $\geq$  10 units PRCs in 24 hr). These sub-groups who are critically unwell are most likely to derive a treatment benefit from quicker identification and treatment of hypofibrinogenaemia during resuscitation and in which demonstrating reliability of FIBTEM A5 as a surrogate for A10 is most useful. Based on ROTEM results, locally published data demonstrate that teams can expect to deliver fibrinogen concentrate to such patients within 30 minutes or cryoprecipitate within 60 minutes (20, 21). Early ROTEM values (by virtue of being point-of-care) have shorter turnaround times than urgent laboratory coagulation studies; FIBTEM A5 has been measured to have a turnaround time of 12 minutes versus 37 minutes for Clauss fibrinogen (15). The authors of this study are not aware of a study directly measuring turnaround time of A5 versus A10 results, but theoretically a five-minute difference would be expected. In severely bleeding patients, this potentially allows for identification and correction of coagulopathy earlier. It should be noted that multiple assays are often performed over the course of a resuscitation and this time benefit could be present at each stage. This study further supports the use of FIBTEM A5 over A10 as a rapid decision-making tool for targeted resuscitation of coagulopathy in trauma.

To the authors' knowledge the consistency of agreement and magnitude of differences between FIBTEM A5 and A10 has not been reported previously in the field of trauma. Strong correlations (albeit inappropriate Pearson or Spearman correlation (22)) have been demonstrated in elective surgery (cardiac and non-cardiac) studies (13–15). Similarly, strong correlations have been observed in trauma between other related ROTEM values: FIBTEM A5 and MCF; A10 and MCF (23) and EXTEM A5 and A10 and MCF (16). The intra-class correlation was used in this study (versus Pearson correlation) as it validly provides

a more robust measure of consistency of agreement for the comparison of two diagnostic tests measuring the same clinical concept (24, 25).

The findings demonstrate FIBTEM A10 had a bias of 1.49 mm from A5 (A10 result was on average 1.49 mm greater than its corresponding A5 result). This was in line with our hypothesis: a positive difference is to be expected as the blood clot has had five more minutes to strengthen between the A5 and A10 result. This bias was used to modify our existing fibrinogen replacement threshold with cautious success. Our institution's protocol for fibrinogen replacement in trauma haemorrhage has two criteria: 1) clinical suspicion of significant ongoing haemorrhage and 2) ROTEM FIBTEM A5 < 11 mm (Appendix 1). The protocol was initially constructed as A10 < 11 mm as this was felt to better represent hypofibrinogenaemia at the time. Over time this was approximated to A5 < 11 mm to give a time-saving benefit.

Our analyses identified that 27.8% patients (424 of 1525) met the current ROTEM threshold (A5 < 11 mm) for fibrinogen replacement. Use of the original threshold (A10 < 11 mm) would have resulted in 19.3% (295 of 1525) meeting criteria. Use of the A5 value with the original threshold for replacement therefore qualified an additional 129 patients (8.5%): this is a relative increase of 43.7%. Only a small minority of these extra patients (six) received fibrinogen replacement. The most likely reason for this is that for the majority there was no clinical suspicion of bleeding. Nonetheless, use of the current A5-based criterion might predispose to increased replacement of fibrinogen. Unnecessary replacement of fibrinogen with fibrinogen concentrate, cryoprecipitate or fresh frozen plasma is undesirable. There is a relatively unknown degree of risk of iatrogenic harm from the products themselves (26, 27); misinterpretation of a 'step-wise' algorithm could lead to failure to correct other abnormal variables; and all methods of replacement are financially costly (28).

Our modification of the A5 threshold resulted in 19.28% meeting the replacement criterion. This is noted to be almost exactly the same proportion as using the original threshold of A10 < 11 mm. In similar cohorts of trauma patients, Rourke et al (9) and Baksaas Aasen et al (12) found that FIBTEM A5 thresholds of 9.5 mm and 10 mm respectively were optimal for detecting laboratory Clauss hypofibrinogenaemia of < 1.5 g/l and < 2.0 g/l with sensitivities (specificities) of 78% (70%) and 70% (76%). The current study did not include receiver operating curve analysis comparing FIBTEM A5 to Clauss fibrinogen and so we cannot provide direct validity to these thresholds. These studies demonstrate that there is no consensus as to what level of hypofibrinogenaemia should trigger transfusion. However, it is likely that our threshold of FIBTEM A5 < 10 mm corresponds to Clauss hypofibrinogenaemia < 1.5–2.0 g/l. Further work is required to develop a consensus ROTEM FIBTEM threshold for replacement of fibrinogen in the context of trauma(11).

The authors acknowledge several limitations to the current study. Whilst it includes every patient who had a ROTEM on admission, not all trauma patients had a ROTEM. However, the likely bias in the study in this case would be towards including more severe trauma and this is the cohort of most clinical relevance. The particular viscoelastic haemostatic device used was ROTEM Delta. This is a multi-step, partially

manual assay that was performed by clinicians in an emergency trauma setting. Whilst all users had training there are multiple stages where errors could occur. The fully automated ROTEM Sigma assay was not studied. Finally, the analyses of numbers of patients meeting different FIBTEM criteria for fibrinogen replacement were retrospective and theoretical: throughout the study period the clinical criterion used was the 'current' threshold of  $A5 < 11$  mm.

## Conclusions

This study provides further evidence to validate the use of ROTEM FIBTEM A5 in place of A10 in trauma. In a large cohort of trauma patients FIBTEM A5 has excellent agreement with A10 and this is preserved in the subgroups of major trauma and massive transfusion. There is a small difference in magnitude between A5 and A10 results in the same patient and interchangeable use of values is inadvisable as it might identify quite different numbers of patients as deficient in fibrinogen. Our findings back previous work suggesting a FIBTEM A5 threshold of  $< 10$  mm may be appropriate for targeted fibrinogen replacement when used in the context of traumatic haemorrhage. Useful future work might involve receiver operating curve analyses of ROTEM FIBTEM A5 versus A10 in the same cohort of patients and similar work with EXTEM values to guide platelet transfusion.

## Abbreviations

ROTEM – rotational thromboelastometry; A5 – amplitude at five minutes; A10 – amplitude at ten minutes; MCF – maximum clot firmness; TIC – trauma-induced coagulopathy; DCR – damage control resuscitation; ICC – intra-class correlation; ISS – injury severity score; PRC – packed red cells; INR - international normalised ratio; IQ - interquartile

## Declarations

### **Ethics / consent:**

Ethics approval was obtained from the Gold Coast Hospital and Health Service Human Research Ethics Committee on the 26<sup>th</sup> March 2014 (HREC/14/QGC/17). Waived consent was granted as section 2.3 of the National Statement on Ethical Conduct in Human Research.

### **Consent for publication:**

Not applicable.

### **Availability of data and materials:**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing interests:**

The authors declare that they have no competing interests.

### **Funding:**

The authors declare no external funding sources.

### **Authors contributions:**

AB consolidated the databases and wrote the manuscript. JM ran the statistical analyses. KW, EW, DH, EC, AC collected the primary data. DC facilitated the running of the study and data collection. JW led the study. All authors read and reviewed the manuscript prior to submission.

### **Acknowledgements:**

Dr Ian Hughes: Office for Research Governance and Development, Gold Coast Health

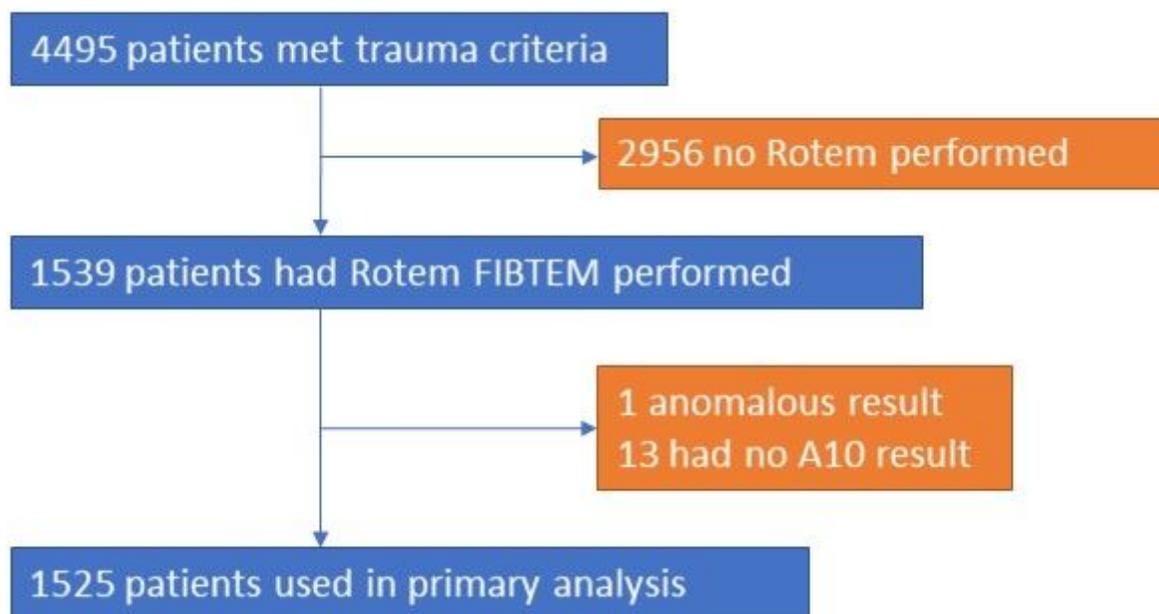
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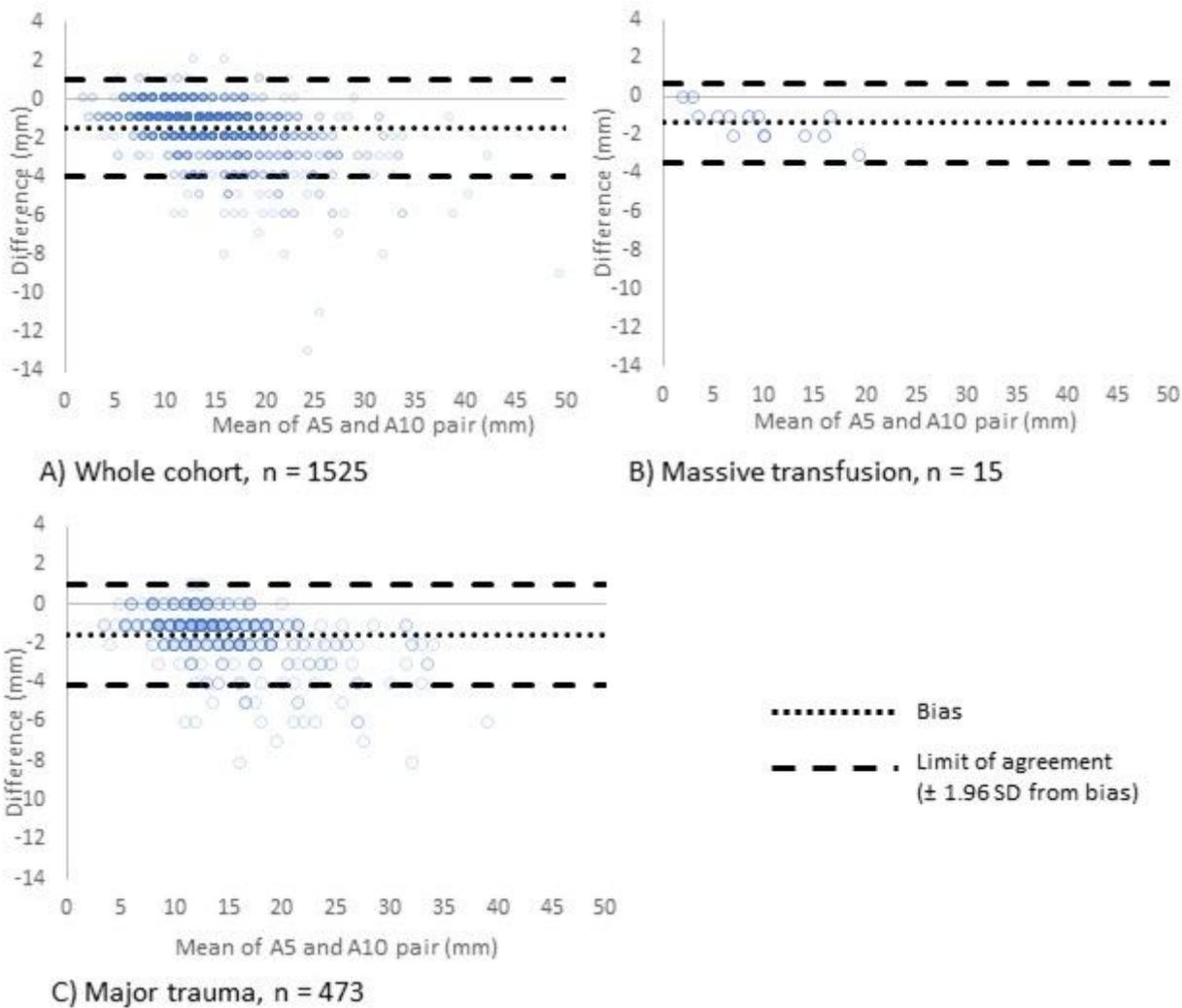
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## Figures



**Figure 1**

Flow chart representing patients included in primary analysis Legend: Fig 1 displays numbers of patients and inclusions / exclusions for the primary analysis.



**Figure 2**

Bland-Altman plots demonstrating level of agreement between FIBTEM A5 and A10 Legend: Bland-Altman density plots demonstrating the distribution of the means of pairs of A5 and A10 against their the difference between their values, for the whole cohort and subgroups of massive transfusion ( $\geq 10$  units of packed red cells transfused in 24 hours) and major trauma (Injury Severity Score  $\geq 12$ ). Bolder colour indicates a greater density of points. SD (standard deviation)

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