Use Of Thromboelastography in the Evaluation And Management of Patients With Traumatic Brain Injury: A Systematic Review

Supplemental Digital Content

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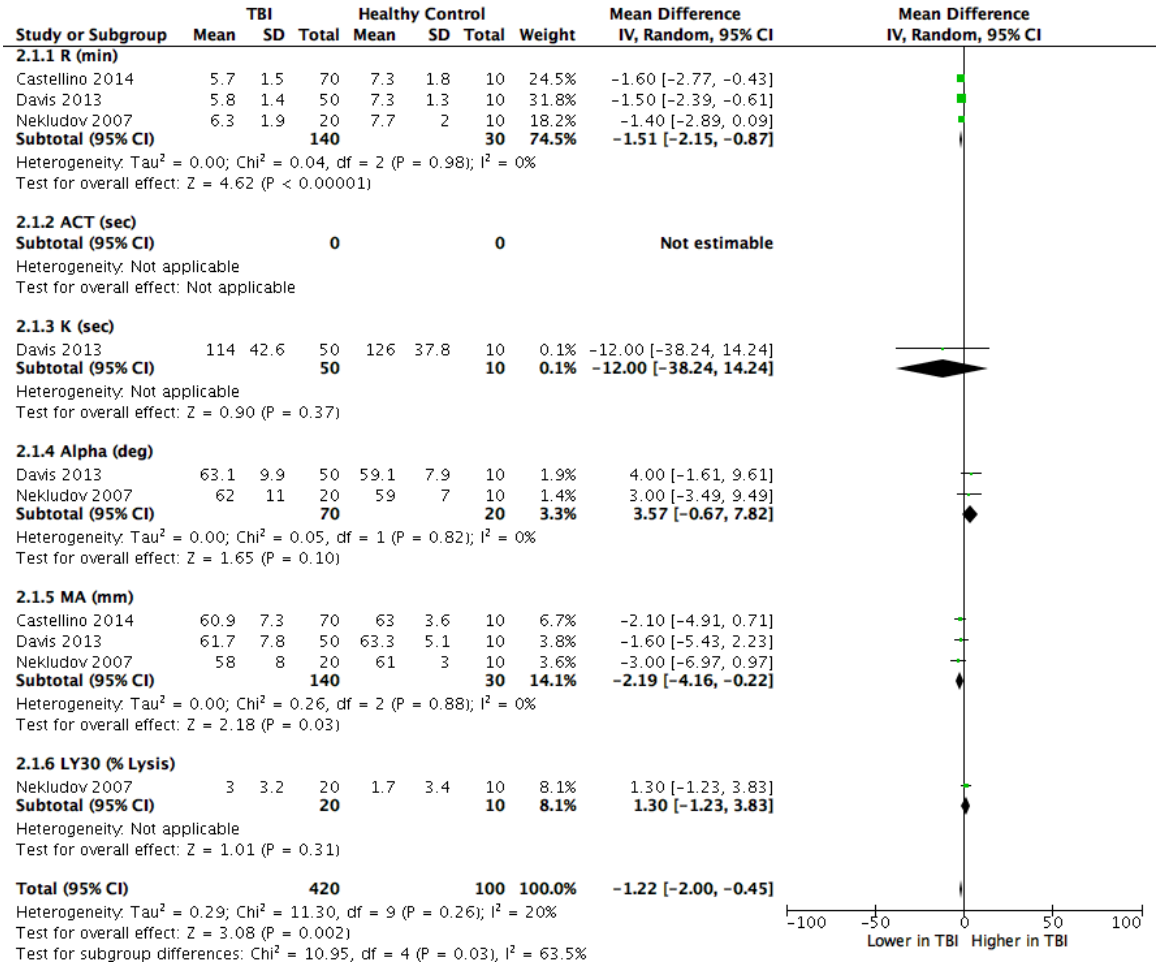
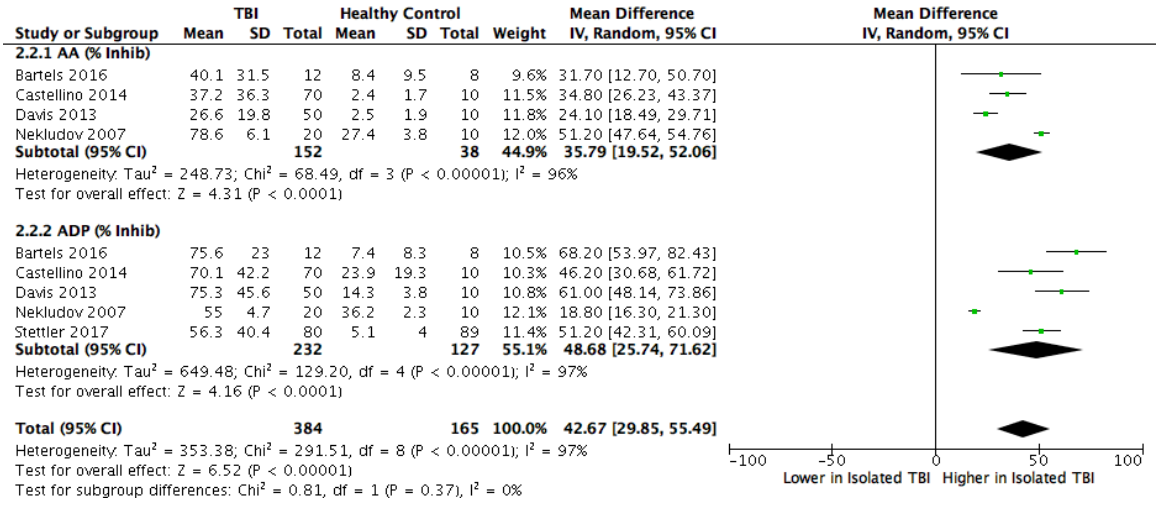
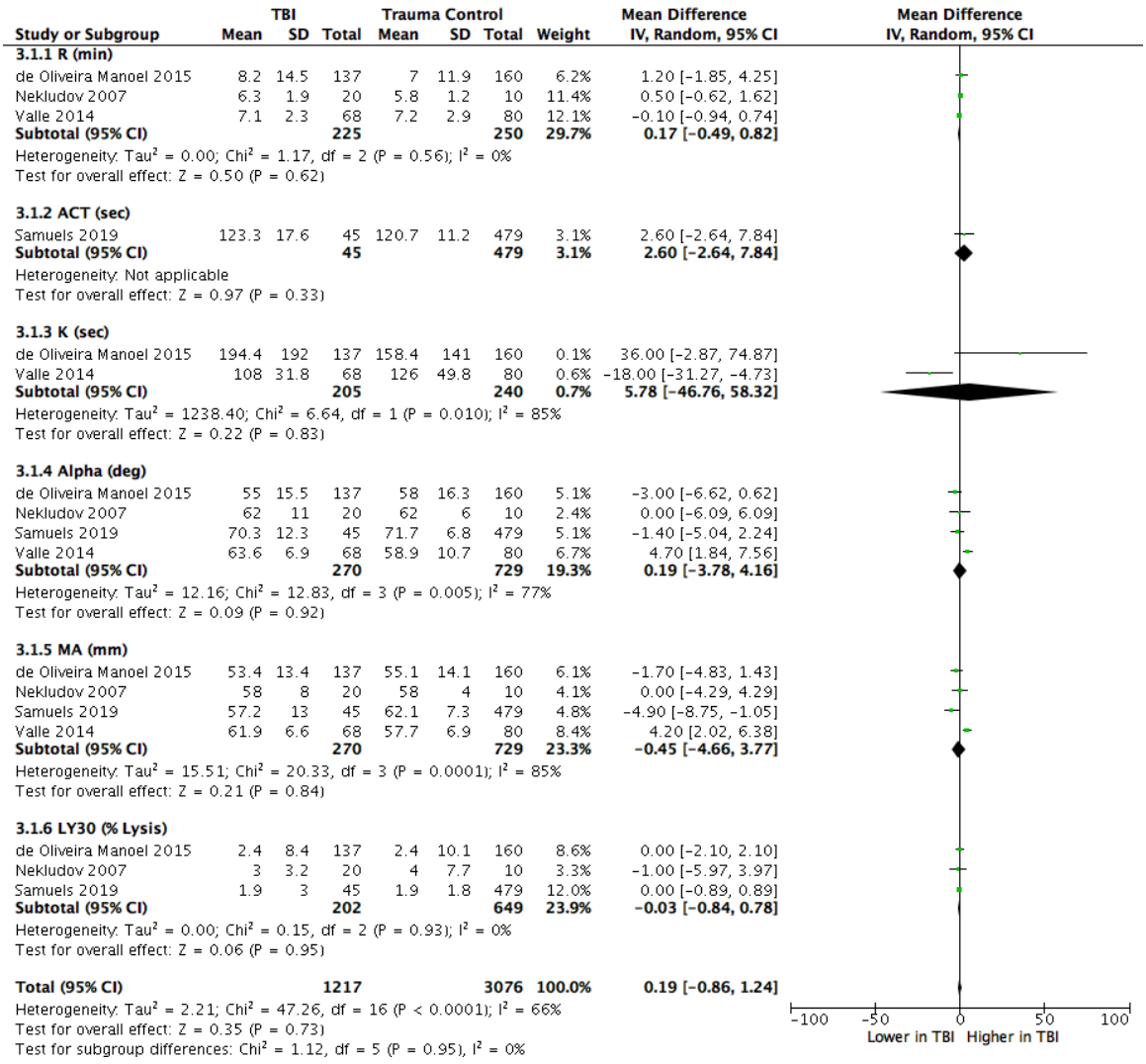
Supplemental Methods

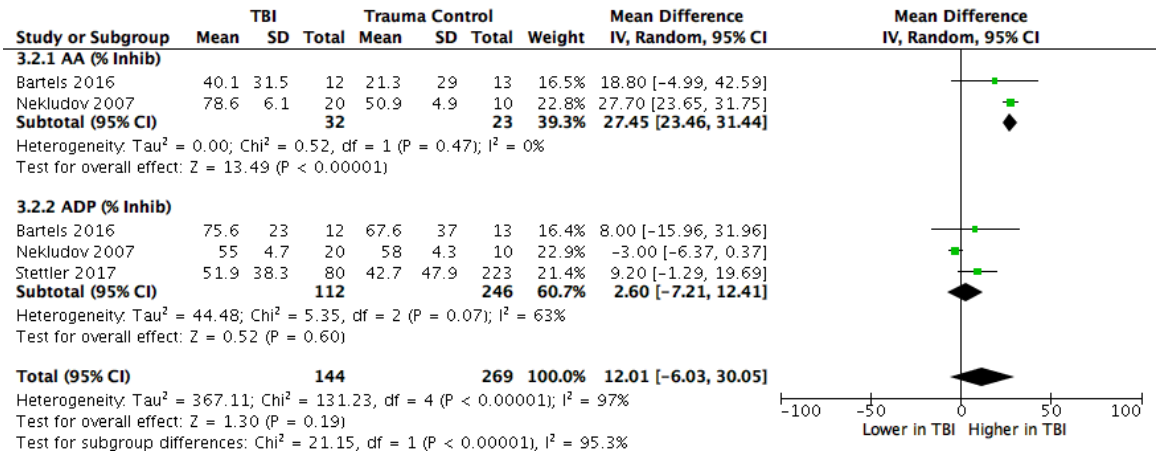
Results from studies considered for quantitative analysis were abstracted by two authors (J.W.C. and J.D.D.). Review Manager (RevMan, Cochrane Collaboration, version 5.4.1) was used for meta-analysis calculations. A random-effects methodology was used to assess mean differences in TEG and TEG-PM values between study groups and to evaluate the prognostic role of TEG and TEG-PM given inter-study heterogeneity. Mantel-Haenszel fixed-effects meta-analysis was used to evaluate 28-day mortality in TBI patients managed with VHA-guided resuscitation in two randomized control trials. Publication bias was assessed with funnel plot analysis. For studies reporting median and interquartile range, mean difference was calculated using the methodology endorsed by the Cochrane Collaboration (Wan X, Wang W, Liu J, et al.: Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med. Res. Methodol.* 2014; 14:135). Summary mean difference figures were created with the forestplot package in R 4.0.3 (The R Foundation for Statistical Computing, http://www.R-project.org). Quality of the evidence was assessed using the GRADE methodology (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 [developed by Evidence Prime, Inc.]. Available from gradepro.org).



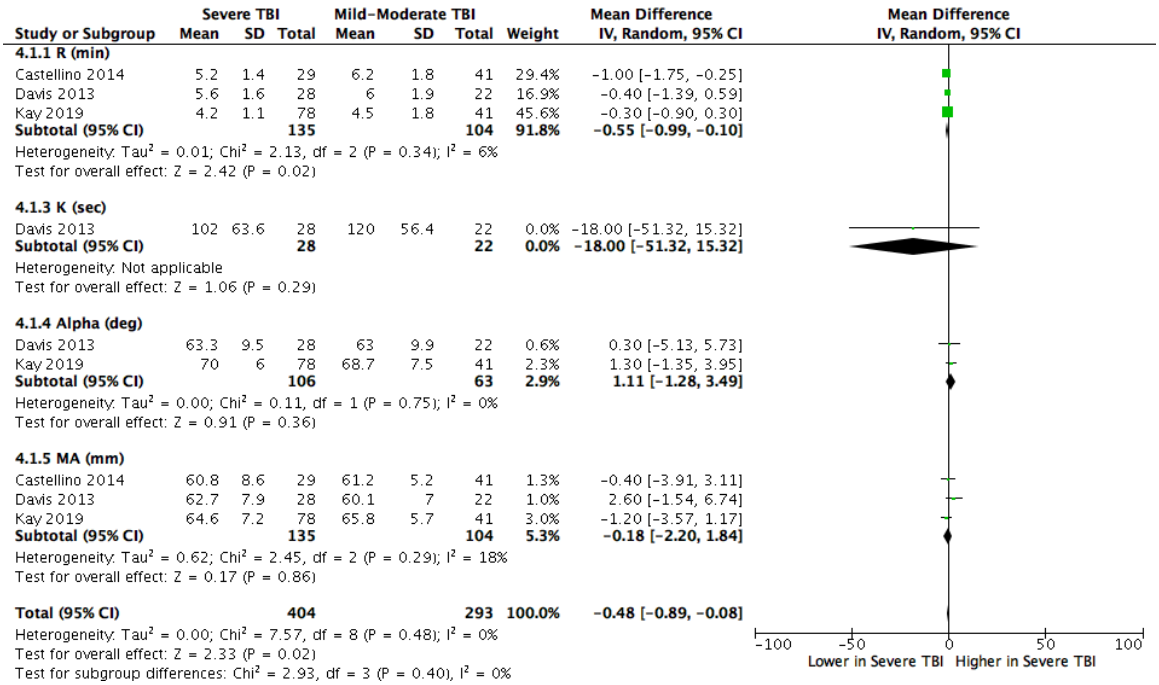


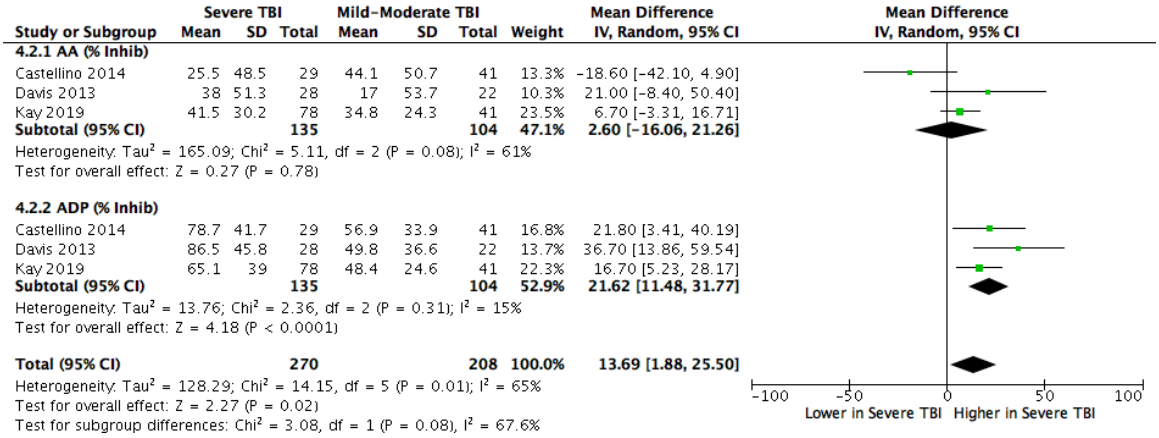
Supplemental Figure 1. TEG and TEG-PM values in TBI patients vs Healthy Controls



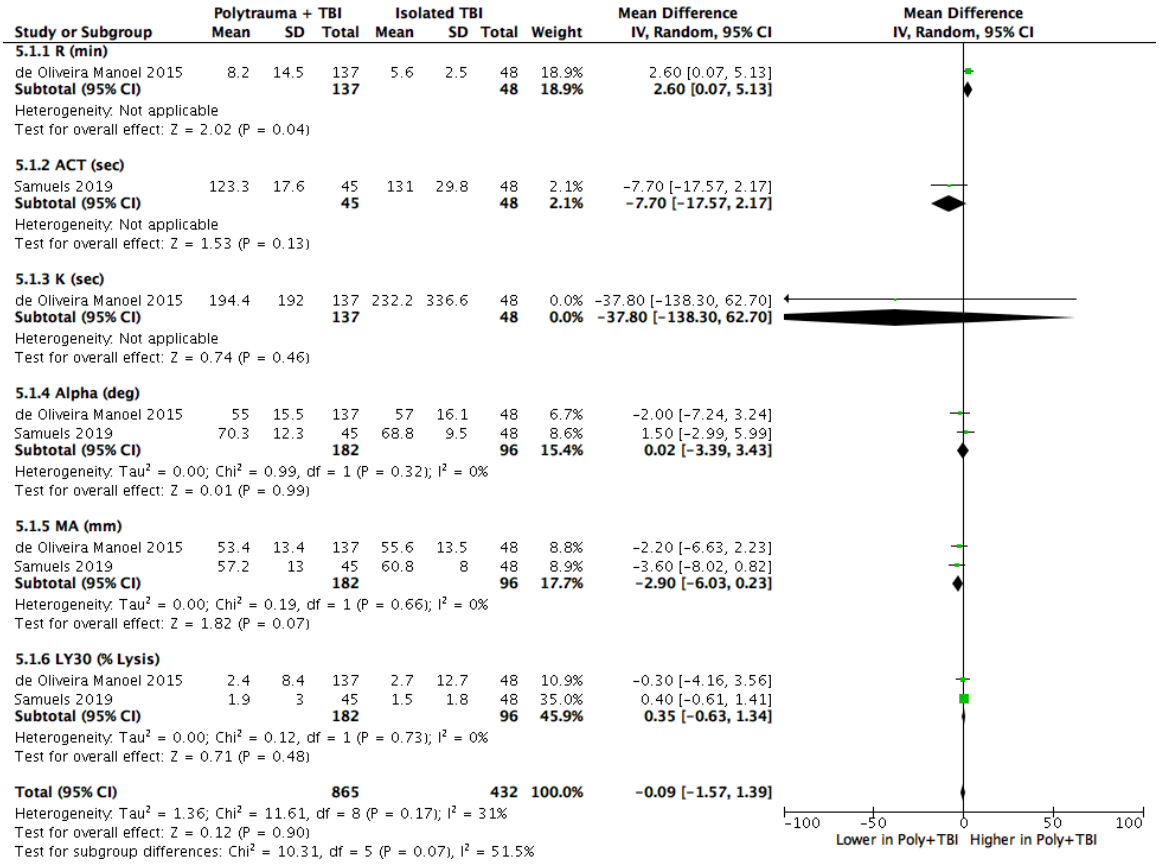


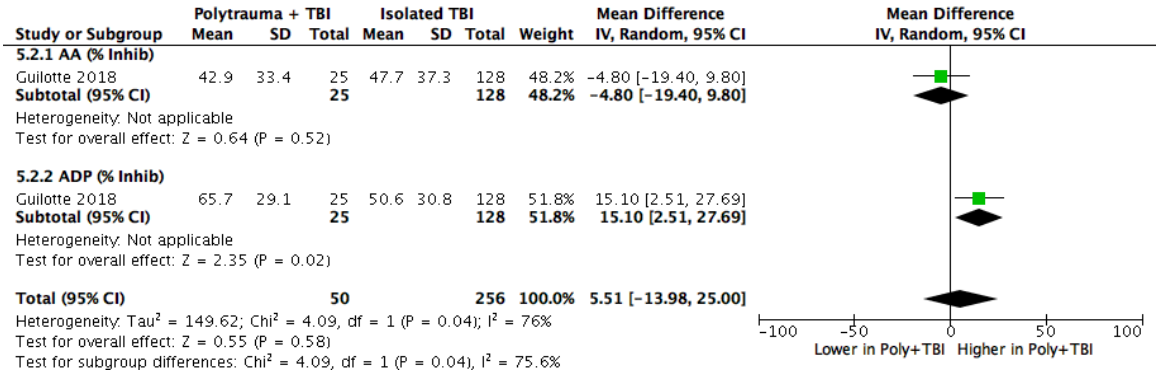
Supplemental Figure 2. TEG and TEG-PM values in TBI patients vs Trauma Controls



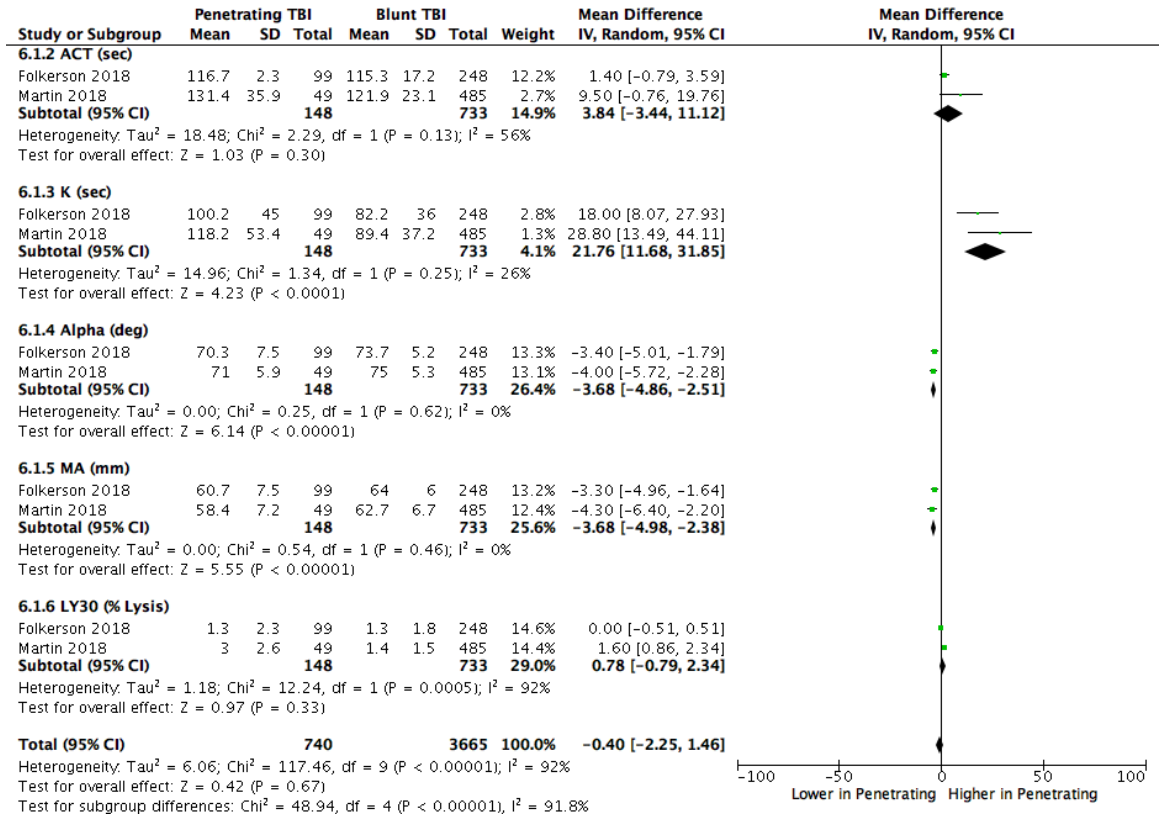


Supplemental Figure 3. TEG and TEG-PM values in Severe TBI vs Mild-Moderate TBI

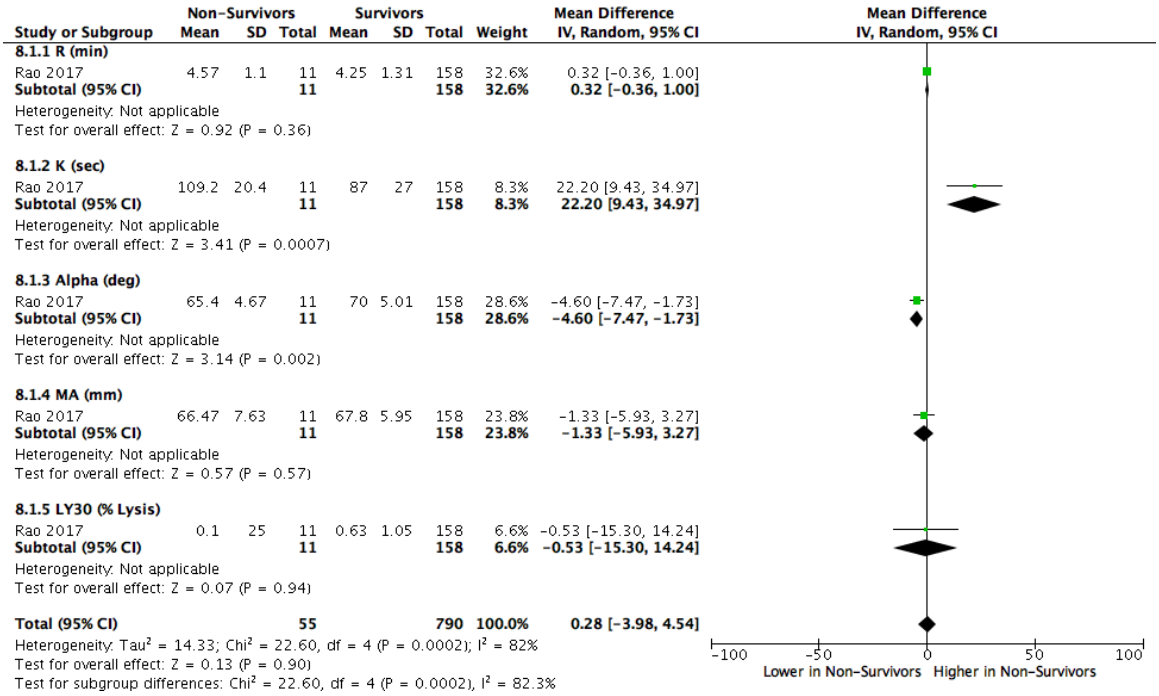


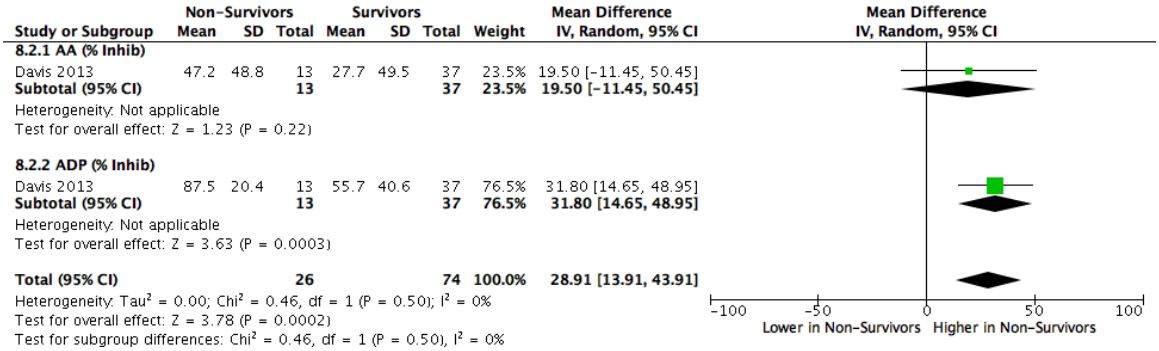


Supplemental Figure 4. TEG and TEG-PM values in Severe TBI vs Mild-Moderate TBI

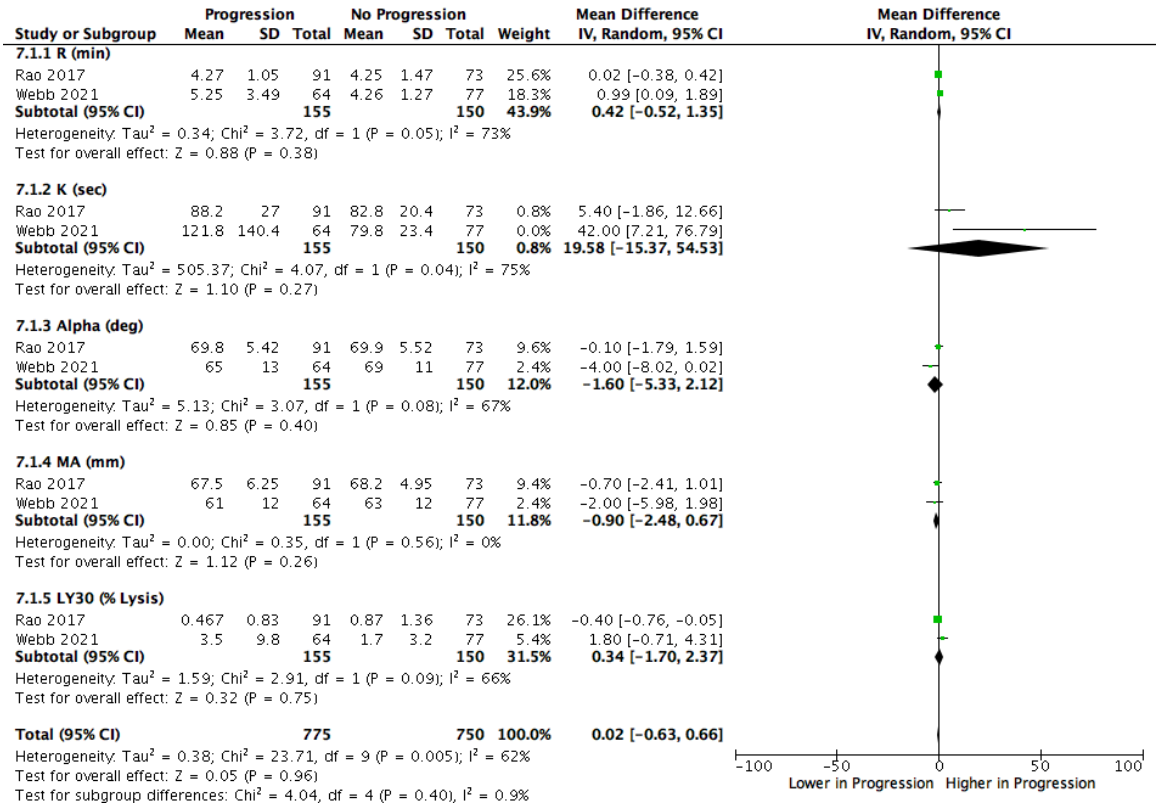


Supplemental Figure 5. TEG values in Penetrating TBI vs Blunt TBI

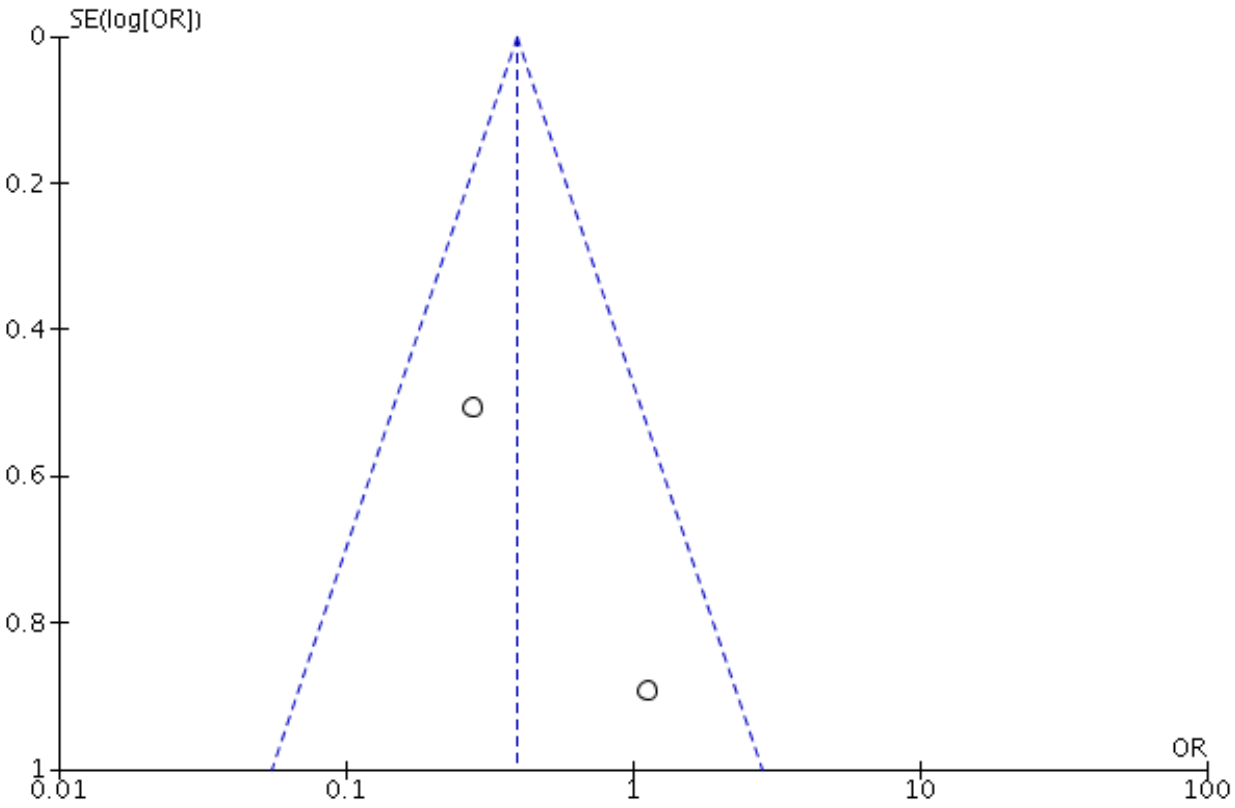




Supplemental Figure 6. TEG and TEG-PM values in TBI Non-Survivors vs Survivors



Supplemental Figure 7. TEG values in TBI patients with Progression vs No Progression



Supplemental Figure 8. Publication bias assessment of manuscripts describing the outcomes of traumatic brain injury patients managed under a viscoelastic hemostatic assay-guided resuscitation protocol compared to conventional coagulation tests.

Supplemental Table 1: Search Strings

MEDLINE and PubMed Central search string
((head OR crani* OR cerebr* OR brain* OR forebrain* OR hemispher* OR intracran*) AND (injur* OR trauma* OR damag* OR lesion* OR wound* OR destruction* OR oedema* OR edema* OR contusion* OR fracture*) OR craniocerebral trauma [mh]) AND (thromboelasto* OR teg OR thrombelasto* OR plateletmapping)

Embase search string
((head OR crani* OR cerebr* OR brain* OR forebrain* OR hemispher* OR intracran*) AND (injur* OR trauma* OR damag* OR lesion* OR wound* OR destruction* OR oedema* OR edema* OR contusion* OR fracture*) OR 'craniocerebral trauma') AND (thromboelasto* OR teg OR thrombelasto* OR plateletmapping) NOT 'medline'

CENTRAL search string
"brain" in Title Abstract Keyword AND "injur" in Title Abstract Keyword OR "trauma" in Title Abstract Keyword AND "TEG" in Title Abstract Keyword OR "Thromboelastograph" in Title Abstract Keyword - in Cochrane Reviews, Cochrane Protocols, Trials (Word variations have been searched)

Supplemental Table 2. Inclusion and Exclusion Criteria for the Literature Search

Inclusion criteria	Exclusion criteria
Studies of adult humans or human blood samples	Pediatric studies, non-human studies, any studies done in animals
Case series, clinical trials	Reviews, meta-analyses, editorials, responses, comments, congress abstracts
Reports data relevant to traumatic brain injury	No relevant brain injury data
Utilization of standard TEG or TEG-PM (5000 or 6s) in the context of traumatic brain injury assessment, or predicting or improving patient outcomes	No Viscoelastic testing reported
	Use of viscoelastic testing reported but not directly linked to assessment/treatment of traumatic brain injury
	Standard TEG or TEG-PM (5000 or 6s) not reported

The PubMed and EMBASE search results were filtered to exclude any manuscript published prior to 1999 (the year the TEG 5000 analyzer was first introduced), manuscripts in non-human subjects, and any language other than English. A second screen was carried out using the same inclusion and exclusion criteria to review the full text of all non-excluded articles. In addition to the articles identified in the search, additional manuscripts were suggested by the authors which had been published later than the search cut-off date, were not PubMed-indexed, or did not have an abstract so they were missed by the initial search. These were added and screened as per the inclusion/exclusion criteria. PRISMA guidelines for systematic reviews were followed in reporting the results. All manuscripts that met the predefined inclusion/exclusion criteria were included for full text review. Article screening was performed by two individuals independent from but financially supported by Haemonetics. Differences in screening selection were adjudicated by a third individual. All authors were involved in the qualitative and quantitative evaluation of the papers selected for inclusion. TEG, thromboelastography; TEG-PM, thromboelastography with platelet mapping

Supplemental Table 3. United States Food and Drug Administration TEG and TEG-PM Indications for Use

TEG 5000
The TEG® 5000 Thromboelastograph® Hemostasis Analyzer System (Haemonetics Corporation, Boston, MA) is a non-invasive diagnostic instrument designed to monitor and analyze the hematological state of a blood sample in order to assist in the assessment of patient clinical hemostasis conditions. The TEG Hemostasis System is indicated for use with adult patients where an evaluation of their blood hemostatic properties is desired. Hemostasis evaluations are commonly used to assess clinical conditions such as post-operative hemorrhage and/or thrombosis during and following cardiovascular surgery, organ transplantation, trauma, and cardiology procedures.
TEG 6s
The indication for TEG 6s System (Haemonetics Corporation, Boston, MA) use is with adult patients (18 years or older) where an evaluation of their blood hemostasis properties is desired. Hemostasis evaluations with the TEG 6s Citrated: K, KH, RT, FF Assay Cartridge and the TEG PlateletMapping® ADP & AA Cartridge are commonly used to assess clinical conditions in cardiovascular surgery and cardiology procedures to assess hemorrhage or thrombosis conditions before, during and following the procedure. Hemostasis evaluation with the TEG 6s Hemostasis System using the Citrated: K, RT, FF Assay Cartridge is used to assess clinical conditions in a trauma setting to assess hemorrhage or thrombosis conditions.

AA, arachidonic acid; ADP, adenosine diphosphate; FF, functional fibrinogen; RT, R-time; TEG, thromboelastography; TEG-PM, thromboelastography with platelet mapping

Supplemental Table 4. Overview of Studies Included for Quantitative Analysis of TEG Profiles in TBI Patients

Manuscript	Type of patients	Study type	SIGN 50 Assessment*
Bartels 2016 (32)	TBI vs non-TBI trauma (consecutively activated level 1 traumas) vs healthy controls; 12 TBI patients	Prospective observational study	++
Castellino 2014 (33)**	Trauma patients with isolated TBI (Severe vs mild-to-moderate) vs healthy controls; 70 TBI patients	Subset of patients from a prospective observational study	+
Davis 2013 (36)**	TBI patients not treated with anticoagulants or platelet inhibitors; 50 TBI patients	Subset of patients from a prospective observational study	+
de Oliveira Manoel 2014 (37)	Isolated severe TBI vs multisystem trauma with severe TBI vs non-TBI trauma; 48 isolated TBI patients, 137 multisystem trauma with TBI	Post-hoc analysis of a large prospective observational study	+
Folkerson 2018 (38)	Blunt vs penetrating TBI; 347 TBI patients	Retrospective study	+
Guillotte 2018 (39)	TBI; 153 patients	Prospective observational study	+
Kay 2019 (26)	Isolated blunt TBI; 119 patients	Retrospective study	+
Martin 2018 (40)	TBI; 534 patients	Retrospective study	+
Nekludov 2007 (41)	Severe isolated TBI vs general trauma without TBI vs chronic alcohol abuse vs healthy controls; 20 TBI patients	Prospective observational study	+
Samuels 2019 (35)	Isolated TBI vs multisystem trauma with TBI vs non-TBI trauma ; 48 isolated TBI, 45 multisystem trauma with TBI	Retrospective study	+
Stettler 2017 (42)	Trauma activations; 80 TBI patients	Retrospective study	+
Valle 2014 (34)	Polytrauma patients with TBI vs non-TBI trauma; 68 TBI patients	Prospective observational study	+

*SIGN 50 methodology quality rating using the case-control study checklist: **High quality (++):** Majority of criteria met. Little or no risk of bias. Results unlikely to be changed by further research. **Acceptable (+):** Most criteria met. Some flaws in the study with an associated risk of bias. Conclusions may change in the light of further studies. **Low quality (0):** Either most criteria not met or significant flaws relating to key aspects of study design. Conclusions likely to change in the light of further studies.
Numbers in () refer to the reference in the primary manuscript.
**Overlapping study subjects
TBI, traumatic brain injury

Supplemental Table 5. Summary of Relative Admission TEG Profiles in Different Patient Populations

Population	R (min)	ACT (sec)	K (sec)	α (deg)	MA (mm)	LY-30 (% Lysis)	AA (% Inhib)	ADP (% Inhib)
TBI vs Healthy Control	↓	ND	-	-	↓*	-	↑	↑
TBI vs Trauma Control	-	-	-	-	-	-	↑	-
Severe TBI vs Mild-Moderate TBI	↓	ND	-	-	-	ND	-	↑
Polytrauma + TBI vs Isolated TBI†	↑	-	-	-	-	-	-	↑
Penetrating TBI vs Blunt TBI	ND	-	↑	↓	↓	-	ND	ND
TBI Non-Survivors vs TBI Survivors†	-	ND	↑	↓	-	-	-	↑
TPI Progression vs No Progression	-	ND	-	-	-	-	ND	ND

Arrow directionality indicates the abnormality in the first population relative to the second. For example, the R time is shorter in TBI compared to healthy controls. The fill color indicates whether the difference results in a hyper-coagulable state (green) or hypo-coagulable state (red). A dash (-) indicates no measurable difference while ND indicates no data for the parameter in the given population. *Pooled mean difference of questionable clinical significance as the delta is less than 5% of the abnormal threshold for the given parameter. †Results based on one study each for both standard TEG parameters and TEG-PM parameters.

Supplemental Table 6. Overview of Studies Included for Quantitative Analysis of Mortality and Progression in TBI Patients

Manuscript	Type of patients	Study type	SIGN 50 Assessment*
Davis 2013 (36)	TBI patients not treated with anticoagulants or platelet inhibitors; 50 TBI patients	Subset of patients from a prospective observational study	+
Rao 2017 (28)	TBI with intracranial hemorrhage; 169 patients	Prospective observational study	++
Webb 2021 (29)	Severe TBI patients (initial CGS≤8) with an initial CT Head and TEG available; 141 patients	Retrospective study	+

*SIGN 50 methodology quality rating using the case-control study checklist: **High quality (++):** Majority of criteria met. Little or no risk of bias. Results unlikely to be changed by further research. **Acceptable (+):** Most criteria met. Some flaws in the study with an associated risk of bias. Conclusions may change in the light of further studies. **Low quality (0):** Either most criteria not met or significant flaws relating to key aspects of study design. Conclusions likely to change in the light of further studies. Reject.
Numbers in () refer to the reference in the primary manuscript.
CT, computed tomography; GCS, Glasgow Coma Scale; TBI, traumatic brain injury

Supplemental Table 7. Overview of Included Studies Reporting Management of TBI Patients guided by Viscoelastic Hemostatic Assays

Manuscript	Type of patients	Study type	Risk of Bias Assessment*, **
Baksaas-Aasen 2021 (14)	Trauma patients meeting criteria for massive hemorrhage protocol; 74 TBI patients	Pragmatic RCT	+
Gonzalez 2016 (13)	Injured adults meeting criteria for massive transfusion protocol; 21 TBI patients	Pragmatic RCT	-

* SIGN 50 methodology quality rating using the controlled trials checklist: **High quality (++):** Majority of criteria met. Little or no risk of bias. **Acceptable (+):** Most criteria met. Some flaws in the study with an associated risk of bias. **Low quality (-):** Studies which have poor randomization or treatment allocation concealment with a high risk of bias. **Unacceptable (0):** Reject.
**Further Risk of Bias conducted using RoB 2 methodology as detailed in Figure 4 of the manuscript.
Numbers in () refer to the reference in the primary manuscript.
RCT, randomized controlled trial; TBI, traumatic brain injury

Supplemental Table 8. Evidence Profile for the Management of TBI Patients guided by Viscoelastic Hemostatic Assays

Author(s): JWC, LJK
Question: VHA compared to CCT in TBI
Setting: Hospital
Bibliography:

Baksaas-Aasen K, Gall LS, Stensballe J, Juffermans NP, Curry N, Maegele M, Brooks A, Rourke C, Gillespie S, Murphy J, Maroni R, Vulliamy P, Henriksen HH, Pedersen KH, Kolstadbraaten KM, Wirtz MR, Kleinveld DJB, Schäfer N, Chinna S, Davenport RA, Naess PA, Goslings JC, Eaglestone S, Stanworth S, Johansson PI, Gaarder C, Brohi K. Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial. Intensive Care Med. 2021 Jan;47(1):49-59. doi: 10.1007/s00134-020-06266-1. Epub 2020 Oct 13. PMID: 33048195; PMCID: PMC7550843

Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabyan A, Wohlauer MV, Barnett CC, Bensard DD, Biffl WL, Burlew CC, Johnson JL, Pieracci FM, Jurkovich GJ, Banerjee A, Silliman CC, Sauaia A. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy: A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays. Ann Surg. 2016 Jun;263(6):1051-9. doi: 10.1097/SLA.0000000000001608. PMID: 26720428; PMCID: PMC5432433.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VHA	CCT	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomized trials	serious [a]	serious [b]	serious [c]	serious [d]	none	21/48 (43.8%)	30/46 (65.2%)	**OR 0.39** (0.17 to 0.91)	**230 fewer per 1,000** (from 410 fewer to 22 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Downgraded for risk of bias in several domains.
b. I^2 46% indicating moderate heterogeneity.
c. Subgroup analysis in both studies.
d. Does not meet optimal information size (OIS), estimated to be 97 per group.