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Review Article

Brain Thromboplastin, Biomarkers, and Coagulograms in Traumatic Brain Injury: Translating Pathophysiology Into Point-of-Care Practice

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Abstract

Traumatic brain injury (TBI) is a leading cause of global morbidity and mortality, often complicated by coagulopathy. This narrative review explores how hemostatic disruption drives hemorrhagic progression or thromboembolic events, making early intervention crucial. A central mechanism is the release of tissue factor (TF), brain thromboplastin, from damaged neural tissue, which activates the extrinsic coagulation pathway to create a dynamic state of hypercoagulability, hypocoagulability, and fibrinolysis. These disturbances are further amplified by endothelial injury and brain-derived microparticles. While standard coagulograms and conventional biomarkers provide useful baselines, they lack TBI specificity and fail to capture evolving clot dynamics. Emerging biomarkers such as glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1 offer targeted early risk assessment, while viscoelastic testing provides real-time, functional evaluation of clot formation and lysis. Integrating these novel biomarkers with viscoelastic methods may help guide precise, goal-directed transfusion strategies. Future research must prioritize validating biomarker-driven algorithms, testing-guided therapies, and the targeted modulation of the TF pathway to optimize patient care.

Keywords: Brain thromboplastin, Tissue factor, Biomarkers, Coagulopathy, Traumatic brain injury, Viscoelastic testing

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Introduction

Traumatic brain injury (TBI) represents a critical global public health crisis, affecting an estimated 69 million individuals annually with an overall incidence of over 800 cases per 100 000 population.[1] As a leading cause of trauma-related death and long-term disability worldwide, TBI accounts for nearly 1.5 million deaths each year[2] and carries a profound economic burden costing the global economy roughly $400 billion annually[3] in direct medical care and lost productivity. Beyond the immediate primary insult, secondary injury is heavily driven by systemic and intracranial factors, among which coagulopathy plays a central role. Approximately one-third of patients with moderate-to-severe TBI develop coagulation disturbances, which directly exacerbate hemorrhagic progression, increase transfusion requirements, and worsen neurological outcomes.[4-13]

TBI-associated coagulopathy is distinct from systemic trauma-induced coagulopathy.[5] A key mechanism is the release of brain thromboplastin, or tissue factor, from damaged

parenchyma, astrocytes, and vascular structures. This triggers the extrinsic coagulation cascade, leading to thrombin generation and consumptive coagulopathy. Brain-derived microparticles and endothelial dysfunction further sustain coagulation activation and fibrinolysis, producing a spectrum of disturbances ranging from hypercoagulability[14] to hypocoagulability.[5]

Laboratory evaluation is essential for early recognition and management. The standard coagulogram (prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time [aPTT], and platelet count) remains widely used but is often insensitive to the rapid, dynamic changes seen in TBI. Viscoelastic tests[5-6] (TEG, Haemonetics Corporation, US; ROTEM, TEM Innovations GmbH, Germany; and ClotPro, Haemonetics Corporation, US) and platelet function assays provide real-time, functional insights into clot formation and breakdown. Additionally, biomarkers such as fibrinogen, D-dimer, glial fibrillary acidic protein (GFAP), and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) are increasingly recognized for diagnostic and prognostic value.[5-10, 15-20]

This review synthesizes current knowledge on brain thromboplastin mechanisms, hemostatic and brain injury biomarkers,[5] and coagulogram interpretation, aiming to support effective point-of-care management in anesthetic and critical care practice.

Pathophysiological Basis

Brain Thromboplastin and Tissue Factor Release

The release of brain thromboplastin, also known as tissue factor (TF), is a hallmark event in TBI. Under physiological conditions, TF is localized to perivascular cells, astrocytes, and the vascular endothelium, remaining largely sequestered from circulating blood. Following a traumatic insult, disruption of the blood-brain barrier and direct parenchymal injury expose TF-rich structures to the systemic circulation.[10, 14]

This exposure activates the extrinsic coagulation pathway. TF binds with factor VII/VIIa to convert factor X to Xa, generating thrombin. This thrombin burst forms fibrin clots and activates platelets. It also amplifies coagulation via feedback on factors V, VIII, and XI.[5] However, excessive TF release in the cranial compartment causes uncontrolled thrombin production. This rapidly depletes clotting factors, creating a paradoxical state of consumption coagulopathy. Ultimately, this explains why TBI patients face dual risks: expanding intracranial hemorrhages and systemic thrombotic complications.[5, 7, 21]

Brain-Derived Microparticles

In addition to direct TF exposure, TBI induces the release of brain-derived microparticles (BDMPs),[5] which are small membrane vesicles shed from injured neurons, glial cells, and endothelial cells. BDMPs express phosphatidylserine and TF on their surfaces, providing catalytic sites for assembly of coagulation enzyme complexes. Their procoagulant activity significantly amplifies thrombin generation, serving as a mobile extension of the extrinsic pathway.[4]

The interaction of BDMPs with circulating platelets further accelerates clot formation by enhancing platelet aggregation and degranulation. BDMPs also contribute to endothelial dysfunction by promoting inflammation, increasing vascular permeability, and impairing natural anticoagulant pathways such as thrombomodulin and protein C activation. This creates a feed-forward loop of coagulation activation and vascular injury, intensifying hemostatic imbalance in TBI.[8]

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Balance of Bleeding and Thrombosis in Traumatic Brain Injury

TBI-associated coagulopathy exists on a dynamic spectrum ranging from hypercoagulability to hypocoagulability. In the early phase (typically within minutes to 24 hours postinjury),[5] massive release of TF and BDMPs produces a hypercoagulable state characterized by accelerated thrombin generation and microvascular thrombosis. This may compromise cerebral perfusion and exacerbate secondary ischemic injury.[5, 8]

Conversely, sustained activation of coagulation leads to consumption of clotting factors and platelets, as well as hyperfibrinolysis mediated by tPA released from injured endothelial cells. This hypocoagulable phenotype, which typically emerges between 6 and 24 hours postinjury and can persist for up to 72 hours, manifests as hematoma expansion, progression of contusions, and systemic bleeding risk.[5, 7, 9]

Importantly, TBI-associated coagulopathy does not occur in isolation. In patients with polytrauma, systemic trauma-induced coagulopathy (TIC) overlaps with brain-specific mechanisms. Hypoperfusion, shock, hemodilution, and inflammation can further aggravate coagulation disturbances and alter these phase transitions. The interplay between local (brain thromboplastin-driven) and systemic (trauma-induced) pathways creates a complex, fluctuating balance that challenges clinical assessment and management.[7, 8]

Biomarkers in Traumatic Brain Injury Coagulopathy

Biomarker identification in TBI provides insight into neural injury, hemostatic dysfunction, and prognosis. Biomarkers fall into classical laboratory markers, brain injury-related indicators, and emerging molecular signals (Table 1). Integrating them into clinical practice may help translate pathophysiology into bedside decision-making.[5, 6, 22]

Classical Laboratory Biomarkers

Traditional tests offer indirect measures of coagulation, including 1) fibrinogen: low levels indicate consumptive coagulopathy and correlate with hematoma expansion, higher transfusion needs, and worse outcomes;[6] 2) D-dimer: elevated values reflect fibrin degradation and hyperfibrinolysis, suggesting intracranial bleeding, though nonspecific;[3] and 3) thrombin-antithrombin complex and prothrombin fragment 1+2: indicate thrombin generation and early hypercoagulability but remain mainly research tools. Overall, classical biomarkers have limited specificity and delayed turnaround.[22]

Brain Injury-Related Biomarkers

Several neural-derived proteins are released into the bloodstream following TBI and may serve as complementary tools for assessing both injury severity and coagulopathy, including 1) GFAP: derived from astrocytes, GFAP is highly specific for brain injury. Elevated GFAP has been linked to the severity of injury and correlates with coagulopathy severity in some studies;[9, 23] 2) UCH-L1: a neuronal protein marker that rises rapidly after TBI. Elevated UCH-L1 levels have been associated with worse neurological outcomes and may reflect concurrent hemostatic derangements;[23] and 3) S100B and neuron-specific enolase (NSE): both markers indicate neuronal and glial injury, though their specificity is lower. Elevated levels may predict hemorrhagic progression and systemic complications.[24] These biomarkers are increasingly incorporated into multimodal diagnostic strategies, particularly for early prognostication and risk stratification.[6, 25, 26]

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Hemostatic Molecular Biomarkers

Novel biomarkers more directly linked to coagulation activation in TBI are under investigation, including 1) TF activity: plasma assays of TF activity correlate with disease severity and risk of disseminated intravascular coagulation; 2) BDMPs: as discussed earlier, BDMP levels rise significantly after TBI and strongly correlate with procoagulant activity. Measurement of BDMP concentration or surface TF activity may become a practical research tool for predicting hemostatic imbalance;[4, 6] and 3) endothelial injury markers (eg, soluble thrombomodulin, syndecan-1): these reflect endotheliopathy, which plays a role in both TBI-associated coagulopathy and systemic trauma-induced coagulopathy.[5]

Prognostic and Monitoring Roles

The combined use of biomarkers may help predict hematoma expansion (eg, low fibrinogen, elevated D-dimer, high GFAP/UCH-L1);[6, 7, 23] identify patients at risk of poor outcome by integrating neural injury markers with coagulation profiles; and guide therapy and monitoring, particularly in settings where advanced viscoelastic testing is unavailable.

However, challenges remain in translating biomarkers into clinical practice. Assay availability, standardization, cost, and turnaround time limit routine use. Future directions involve developing rapid point-of-care assays and combining biomarker panels with coagulogram and imaging data to provide real-time risk assessment.[6, 16]

Table 1. Classical Laboratory Biomarkers vs Brain-Injury-Related Biomarkers[6, 7, 9, 26-30]

Category	Classical Laboratory Biomarkers	Brain-Injury-Related Biomarkers
Primary use	General health and metabolic screening	Brain injury detection and prognosis
Common examples	CBC, Electrolytes, BUN/Creatinine, LFTs, CRP, ESR, Coagulation	S100B, NSE, GFAP, UCH-L1, Tau, MBP
Target tissues/systems	Blood, liver, kidneys, immune and coagulation systems	Neurons, astrocytes, axons, and glia
Mechanism of release	Systemic illness, inflammation, or organ dysfunction	Cellular injury (neurons, astrocytes, and axons)
Time to elevation after injury	Hours to days	Minutes to hours
Specificity to brain injury	Low (altered in many conditions)	High (most are CNS-specific)
Clinical settings used	Routine medical/surgical care	Trauma, stroke, cardiac arrest, and concussion
Interpretation challenges	Confounded by infection, dehydration, or medications	Confounded by extracranial injury (eg, bone fractures affect S100B)
Typical uses in neuro context	Rule out metabolic causes for altered consciousness	Diagnose TBI severity and predict outcomes
Linked to brain monitoring	Glucose and sodium (affect edema and seizures)	GFAP/UCH-L1 (FDA-cleared for mild TBI); S100B (screening)
Use in prognostication	CRP, lactate (nonspecific)	Tau, NSE, GFAP (predict neuro outcomes)

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; CNS, central nervous system; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDA, Food and Drug Administration; GFAP, glial fibrillary acidic protein; LFTs, liver function tests; MBP, myelin basic protein; NSE, neuron specific enolase; S100B, protein S100 beta; Tau, tau protein; TBI, traumatic brain injury; UCH-L1, ubiquitin C-terminal hydrolase-L1.

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Coagulograms in Traumatic Brain Injury

Laboratory and point-of-care coagulation testing play a central role in the assessment of TBI-associated coagulopathy. While the conventional coagulogram remains the cornerstone of initial evaluation, its limitations have prompted the incorporation of functional assays such as viscoelastic testing and platelet function testing (Tables 2 and 3). Together, these modalities offer a more complete picture of the dynamic hemostatic alterations seen in TBI.[6, 8]

Routine Coagulogram

The routine coagulogram includes 1) PT/INR: reflects the extrinsic and common pathways. Prolongation in TBI suggests factor consumption from TF release but is insensitive to early abnormalities;[5] 2) aPTT: assesses intrinsic and common pathways. Prolongation occurs in consumptive states but is less common than PT/INR changes in isolated TBI;[3] 3) platelet count: thrombocytopenia is uncommon in isolated TBI; however, platelet dysfunction may occur despite normal counts, limiting usefulness;[7] and 4) fibrinogen: declines with worsening coagulopathy and correlates with hematoma expansion; low levels guide replacement therapy.[5, 7]

Standard coagulogram tests are slow, static, and lack functional assessment, underscoring the need for complementary tools.[5, 6, 7, 12]

Viscoelastic Testing

Viscoelastic assays such as thromboelastography (TEG), rotational thromboelastometry (ROTEM), and the newer ClotPro provide dynamic, whole-blood evaluation of coagulation.

Key parameters include 1) R-time/clotting time (CT): clot initiation, prolonged in factor deficiency or anticoagulation;[10] 2) maximum amplitude/maximum clot firmness (MA/MCF): clot strength, reduced in platelet dysfunction or low fibrinogen;[27] and 3) lysis at 30 minutes/clot lysis index (LY30/CLI): fibrinolysis; hyperfibrinolysis is common in severe TBI.

Advantages include 1) rapid bedside results; 2) detection of functional deficits missed by standard tests, including platelet dysfunction and fibrinolysis; and 3) prediction of hemorrhagic progression, transfusion needs, and mortality from abnormal profiles.[11]

Limitations are device variability, limited availability, and need for expert interpretation.

Viscoelastic testing increasingly guides targeted transfusion therapy in TBI.[6]

Platelet Function Testing

Platelet dysfunction is a key but often overlooked feature of TBI-associated coagulopathy. Even with normal counts, impaired aggregation increases bleeding risk.[5, 6]

Point-of-care assays include 1) Multiplate: measures aggregation to adenosine diphosphate, arachidonic acid, or thrombin activated peptide-6;[31] 2) VerifyNow: assesses aspirin or P2Y12 inhibitor effects, useful when preinjury antiplatelet use is suspected; and 3) TEG Platelet Mapping: quantifies platelet contribution to clot strength.[6]

Clinically, these assays detect subclinical dysfunction in isolated TBI, guides platelet transfusion or antiplatelet reversal, and helps identify patients at risk of hemorrhage expansion despite normal labs.

Challenges include cost, limited access, and uncertain treatment thresholds.[8, 32]

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Table 2. Feature Comparisons of Routine Coagulograms, Viscoelastic Testing and Platelet Function Tests[5, 6, 10, 13, 14, 29, 31-33]

Feature	Routine Coagulogram (PT, INR, aPTT, Platelet Count and Fibrinogen)	Viscoelastic Testing (TEG, ROTEM, Quantra and ClotPro)	Platelet Function Testing (PFA-100, Multiplate, VerifyNow, and LTA)
Primary goal	Assess coagulation pathways (extrinsic and intrinsic) and clotting factors	Evaluate whole-blood clot formation, stability, and fibrinolysis	Assess platelet activation, aggregation, and function
Sample type	Citrated plasma	Whole blood	Whole blood (typically), sometimes platelet-rich plasma
Turnaround time	30-60 min	5-10 min for initial results; 30-60 min full curve	10-15 min depending on device
Platelet evaluation	Only platelet count (not function)	Partially (strength of clot influenced by platelet contribution)	Yes (direct assessment)
Fibrinogen evaluation	Yes (Clauss method)	Yes (eg, FIBTEM in ROTEM)	No
Hyperfibrinolysis detection	No	Yes (LY30/ML; strong capability)	No
Heparin effect detection	aPTT prolongation; insensitive at low levels	Yes (heparinase channels)	Limited
Clinical use	Preoperative screening, liver disease, DIC, and anticoagulant monitoring	Trauma, obstetric hemorrhage, cardiac surgery, liver transplant, and perioperative bleeding	Monitoring antiplatelet therapy (aspirin and clopidogrel) and inherited platelet disorders
Point-of-care use	Rare	Yes (widely used)	Yes (in many systems)
Strengths	Widely available, inexpensive, and standardized	Dynamic real-time assessment; guides targeted transfusion	Highly specific for platelet defects and antiplatelet drugs
Limitations	Slow, poor correlation with actual bleeding, and does not assess clot strength	Requires training, cost, and affected by hematocrit	Does not assess coagulation cascade or fibrinogen
Best for	Baseline coagulation status	Managing acute bleeding and transfusion strategies	Assessing platelet dysfunction and drug responsiveness

Abbreviations: aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; FIBTEM, fibrin-based thromboelastometry; INR, international normalized ratio; LTA, light transmission aggregometry; LY30, lysis at 30 minutes; ML, maximum lysis; PT, prothrombin time.

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Table 3. Pathophysiological Basis of Coagulogram[5-7, 14]

Parameter	Physiological Role	Clinical Significance in TBI
PT/INR	Reflects extrinsic and common pathways (factors I, II, V, VII, X)	Prolongation indicates consumption coagulopathy or liver dysfunction; INR > 1.2 is linked to hematoma expansion and poor outcomes
aPTT	Reflects intrinsic and common pathways (factors VIII, IX, XI, XII)	Prolonged aPTT suggests factor depletion or DIC, associated with severe injury and increased mortality
Platelet count	Critical for primary hemostasis	Thrombocytopenia (< 100 × 10^9/L) increases risk of rebleeding and surgical complications
Fibrinogen level	Essential for fibrin clot formation	Low fibrinogen (< 150 mg/dL) reflects hyperfibrinolysis and predicts worsening intracranial hemorrhage
D-dimer	Marker of fibrin degradation	Elevated levels indicate hyperfibrinolysis and ongoing clot breakdown, often associated with TBI severity
Thrombin time(optional)	Assesses conversion of fibrinogen to fibrin	Prolonged in dysfibrinogenemia or heparin exposure

Abbreviations: aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; INR, international normalized ratio; PT, prothrombin time; TBI, traumatic brain injury.

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Translating Evidence Into Point-of-Care Practice

Understanding TBI-associated coagulopathy and coagulogram tools can improve bedside management. Anesthetists, intensivists, and trauma teams must make rapid hemostatic decisions, making structured algorithms, fast diagnostics, and targeted therapy essential.

Point-of-care coagulation testing offers several advantages, including 1) rapid results: viscoelastic and platelet function tests provide actionable data within 10-20 minutes, faster than central laboratory tests;[6, 33] 2) integration: portable viscoelastic testing devices and handheld platelet analyzers can be used directly in trauma bays and operating rooms to guide early interventions;[6] and 3) prehospital potential: emerging studies show usefulness in major trauma, though routine prehospital application in TBI is still limited.[8]

Targeted Hemostatic Therapy

Point-of-care testing supports a shift from empirical transfusion to goal-directed therapy, including 1) fibrinogen replacement: triggered by low fibrin-based thromboelastometry (FIBTEM)/TEG MA or fibrinogen levels, using cryoprecipitate or fibrinogen concentrate;[6] 2) platelet transfusion: guided by platelet function assays or reduced MA/MCF, especially in patients on antiplatelet drugs;[31] 3) antifibrinolytics (tranexamic acid [TXA]): used early when hyperfibrinolysis (eg, shortened clot lysis times) is detected,[5] CRASH-3 suggests benefit within 3 hours, though debate continues;[7] and 4) prothrombin complex concentrate (PCC)/recombinant factor VIIa: reserved for refractory coagulopathy or anticoagulant reversal, with attention to thrombotic risk.[5]

Goal-directed therapy minimizes unnecessary transfusions while correcting key coagulation defects.[34]

Integrating Biomarkers With Coagulograms

Emerging strategies suggest that combining biomarker panels with point-of-care coagulogram data such as GFAP/UCH-L1 and viscoelastic testing, may predict hemorrhagic expansion more accurately than either test alone,[28] and BDMPs and endothelial injury markers could refine prognostication and risk stratification for thrombotic complications. In the future, biomarker-driven algorithms may help identify subgroups of TBI patients who benefit most from aggressive hemostatic intervention.[28]

Multidisciplinary Approach to Bedside Algorithms

Effective implementation requires coordination between anesthetists, neurosurgeons, trauma surgeons, hematologists, and intensive care unit teams. The suggested algorithm includes 1) initial evaluation: routine coagulogram (PT, aPTT, fibrinogen, and platelet count);[5] 2) parallel point-of-care testing: viscoelastic testing and/or platelet function assays within 10-15 minutes;[5] 3) integration with clinical/radiologic findings: consider clotting time evidence of hematoma expansion; 4) targeted therapy: based on deficiencies (eg, fibrinogen concentrate, TXA, and platelets); and 5) monitoring and repeat testing: reassess every 2-4 hours or after interventions. This structured, iterative process ensures that therapy is both dynamic and patient-specific.[12, 28, 33]

Barriers and Implementation Challenges

Resource limitations: viscoelastic testing and platelet assays are costly and not universally available.[6] Training requirements: the interpretation of viscoelastic assays requires specialized knowledge. Standardization issues: the lack of universal thresholds across devices hampers widespread adoption. Evidence gaps: although growing, high-level evidence supporting outcome improvement with point-of-care guided therapy in isolated TBI remains limited.

Future Perspectives

Point-of-care microfluidic platforms are compact devices capable of simultaneously assessing coagulation, platelet function, and fibrinolysis in real time. Artificial intelligence (AI) integration involves algorithms that combine biomarker, coagulogram, and imaging data to generate automated treatment recommendations. Personalized hemostatic medicine involves tailoring interventions to the patient's unique coagulation profile rather than applying uniform transfusion strategies.

Special Considerations

Managing patients requires adjustments based on age, medication use, and injury complexity to minimize complications and optimize outcomes.

Pediatric vs Geriatric Patients

Pediatric patients have a higher metabolic rate, immature organ systems, sensitive cardiovascular response, small airways, and variable drug metabolism require weight-based dosing, careful airway management, and age-appropriate sedation.[29]

Geriatric patients have reduced organ function, polypharmacy, frailty, slower recovery, and higher delirium risk necessitate dose adjustments, multidisciplinary planning, and close monitoring.

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Anticoagulated/Antiplatelet Patients

An increased bleeding risk requires evaluation of the drug type, dose, timing, and coagulation status. Elective procedures may require treatment adjustment, whereas emergencies may necessitate reversal agents.

Close monitoring and multidisciplinary coordination are essential to balance bleeding and thrombotic risks.[35]

Isolated vs Polytrauma-Associated Traumatic Brain Injury

Patients with isolated TBI require a focus on cerebral perfusion, ICP control, euvolemia, and neurological monitoring; surgical intervention as needed.

Patients with TBI and polytrauma require simultaneous management of extracranial injuries, careful resuscitation, multisystem monitoring, and coordinated interdisciplinary care to optimize outcomes.[13]

Future Directions

Advances in TBI-related coagulopathy aim to improve diagnostic accuracy, personalize therapy, and enhance outcomes. Key priorities include standardizing definitions, developing novel biomarkers, integrating multimodal monitoring, conducting high-quality trials, and targeting specific molecular pathways.

Standardizing Definitions

Current definitions of TBI coagulopathy vary widely, limiting study comparability and clinical decision-making. Creating unified criteria will improve patient stratification, prognostication, and guideline development.

Novel Biomarkers

Microparticles and proteomic panels may better reflect endothelial injury and coagulation abnormalities. These biomarkers could allow earlier diagnosis, predict progression, and guide individualized treatment before abnormalities appear on standard tests.

Multimodal Monitoring

Combining imaging with biomarkers and viscoelastic testing offers a fuller picture of injury severity and hemostatic status. This approach may enhance risk assessment, guide therapy, and monitor response in real time.[6]

Randomized Controlled Trials on Viscoelastic Testing-Guided Therapy

Evidence for viscoelastic testing in isolated TBI remains limited. Robust randomized trials are needed to determine whether viscoelastic testing-guided therapy improves mortality, hematoma progression, or functional recovery.[6, 36]

Translational Research: Tissue Factor Pathways

TBI releases brain-derived tissue factor, driving systemic coagulation. Targeted therapies such as TF pathway inhibitors or monoclonal antibodies may mitigate secondary injury and provide more precise hemostatic control.[37]

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Conclusions

TBI-associated coagulopathy, driven by blood-brain barrier disruption and the systemic release of brain thromboplastin, is a critical determinant of clinical outcomes that demands rapid recognition. Because conventional coagulograms miss real-time clot dynamics, integrating viscoelastic testing with novel endothelial and platelet biomarkers is essential for accurately characterizing hemostatic failure. Translating these diagnostic synergies into targeted, goal-directed therapies is vital to prevent hematoma expansion, highlighting the need for future randomized trials to validate point-of-care algorithms and establish individualized, evidence-based transfusion protocols.

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