Traumatic brain injury: Advances in coagulopathy (Review)

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Received May 26, 2024; Accepted August 5, 2024

DOI: 10.3892/br.2024.1844

Abstract. Trauma is a prevalent cause of coagulopathy, with traumatic brain injury (TBI) accompanied by coagulation disorders particularly linked to adverse outcomes. TBI is distinguished by minimal bleeding volume and unique injury sites, which precipitate complex coagulation disturbances. Historically, research into trauma-induced coagulopathy has primarily concentrated on the molecular biology and pathophysiology of endogenous anticoagulation and inflammation. Nonetheless, recognizing that cells are the fundamental units of structure and function in all living organisms, the present review aimed to distill our understanding of coagulopathy post-TBI by elucidating the intricate cellular mechanisms involving endothelial cells, neutrophils and platelets. Additionally, this study evaluates the strengths and weaknesses of various diagnostic tools and discusses the characteristics of pharmacological treatments and potential therapies for patients with TBI and coagulation disorders. The aim of this review is to amalgamate recent updates in mechanistic research and innovative diagnostic and therapeutic methodologies, thereby fostering the progression of precision medicine within this specialized domain.

Contents

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Key words: traumatic brain injury, coagulopathy, platelet dysfunction, endotheliopathy, neutrophil extracellular traps

1. Introduction

Traumatic brain injury (TBI) encompasses a series of complex pathological processes wherein brain tissue structure and function are compromised due to mechanical force applied to the head, stemming from various causes. Of considerable interest is the potential link between genetic modifications and an augmented susceptibility to TBI. Specifically, the polymorphisms within the apolipoprotein E promoter region, the TAU gene (1) and the brain-derived neurotrophic factor gene have been implicated in elevating the risk of concussion and contributing to adverse outcomes subsequent to a TBI episode. Additionally, alterations in the dopamine receptor D_2 gene may potentiate brain injury risk by impacting cognitive functions and behavioral traits in affected individuals. Nevertheless, the precise contribution of NEFH gene mutations to the pathology of concussion remains an area requiring further elucidation through research (2).

The incidence and mortality rates of TBI are notably higher in low- and middle-income countries compared with high-income countries (3), affecting an estimated 10 million individuals worldwide annually (4). Falls are the predominant cause of TBI, especially among individuals >50 years old (5). This demographic often presents with comorbidities and may be using anticoagulant medications prior to injury, factors that amplify the complexity and mortality risk associated with coagulation abnormalities post-TBI (6). Coagulopathy in patients with TBI typically manifests as abnormalities in conventional coagulation assays. However, the prevalence of early coagulopathy varies widely due to inconsistent definitions and differences in the severity of the injury (7).

Most patients with severe TBI demonstrate abnormal coagulation test results shortly after injury, whereas this is less common in those with mild injuries (8). The severity of TBI is generally assessed utilizing the Glasgow Coma Scale, categorizing injuries as mild (14-15 points), moderate (9-13 points) and severe (3-8 points) (9). The mortality rate for severe TBI cases is approximately one-third, and ~60% of survivors suffer from enduring physical, mental and social deficits (10). Patients with TBI accompanied by coagulopathy are often closely associated with poor prognosis (11), thus advancing research and treatment for coagulopathy following TBI is of paramount importance.

In the human body, cells are the fundamental units of structure, function and biological processes. The present review updated and simplified the series of coagulopathy-related events occurring after TBI by summarizing the

mechanistic changes and roles of three types of cells [endothelial cells (ECs), neutrophils and platelets] in the coagulation process post-TBI. Additionally, by consolidating the pharmacological treatments and potential therapeutic applications for patients with TBI with coagulation dysfunction, the present study aimed for this review to provide more insights into precision medicine by summarizing updated mechanistic studies and innovative diagnostic and therapeutic techniques. To facilitate a better understanding of the content for the readers, definitions for the specialized terminology mentioned in this article have been provided (Table I).

2. Cellular mechanisms of coagulopathy following TBI

The mechanisms underpinning coagulopathy subsequent to TBI are multifaceted, encompassing a broad spectrum of cellular alterations. These primarily include alterations in ECs, neutrophils and platelets (Fig. 1).

Endothelium and blood-brain barrier (BBB). The endothelium and BBB are pivotal in maintaining hemostatic balance. Under normal conditions, the ECs function as a barrier to prevent the release of procoagulant factors, such as cerebral microvesicles, into the circulation (12,13). However, these cells can sustain rapid damage during the acute phase of trauma, thereby intensifying coagulation disorders (14,15). Research from 2003 demonstrated that systemic coagulopathy can manifest within minutes following TBI (16), characterized by activation of protein C and enhanced fibrinolysis (17). Ordinarily, tissue-type plasminogen activator (tPA) struggles to access fibrin structures shielded by platelet aggregates, thus impeding the efficiency of subsequent enzymatic reactions essential for clot resolution (18). Moreover, the mechanical forces imparted on the brain during TBI mechanically disrupt the BBB in a pattern akin to a Gaussian distribution (19), precipitating secondary ischemic and inflammatory injuries. These injuries enhance the permeability of adjacent BBB segments, exacerbating the condition. Brain-derived microvesicles (BDMVs) enriched with tissue factor (TF) and phosphatidylserine (PS) are implicated in the exacerbation of brain injury, the initiation of early coagulation abnormalities and the promotion of hyperfibrinolysis (12). The elevated presence of TF and PS (12) in brain tissue not only facilitates the expansion of brain injury (20,21) but also instigates platelet dysfunction and depletion, as well as disseminated intravascular coagulation (DIC) (22,23). Lactoferrin, through its interaction with these microvesicles, has shown promise in mitigating coagulation disturbances and enhancing prognosis in a mouse model of TBI (24). Nonetheless, the specific mechanisms through which lactoferrin exerts its effects and the precise operational definitions of these cellular microvesicles continues to be elusive.

Neutrophils. Upon bodily injury, neutrophils are among the first cells to respond (25). Neutrophil extracellular traps (NETs), which are web-like structures released by activated neutrophils under specific conditions into the extracellular space, play a crucial role in entrapping and neutralizing microorganisms. The formation of NETs is a form of the programmed cell death process (26). Allen *et al* (27) have revealed that in the context of acute TBI, neutrophils are capable of penetrating cerebral vascular ECs and initiating the release of extracellular traps. This process triggers the release of procoagulant factors, including brain-derived microparticles and damage-associated molecular patterns (DAMPs) (27). The delayed apoptosis of neutrophils leads to an exacerbation of NETs formation and coagulation dysfunction during the acute phase of TBI (28). Platelet-neutrophil aggregation interactions play a pivotal role in traumatic coagulopathy. In patients with TBI who exhibit coagulation abnormalities, activated platelets enhance the formation of NETs generation through the secretion of high mobility group box 1 protein (HMGB1) (29,30). NETs exacerbate the disruption of the EC barrier by promoting phosphatidylserine exposure and TF expression on ECs (28,31,32). Moreover, NETs induce a procoagulant phenotype in ECs through the action of interleukin-1α and cathepsin G (33), which contributes to neurological impairment (34,35). Furthermore, inflammation plays a critical role in underlying secondary injury following TBI (36), with NETs significantly mediating the interaction between inflammation and coagulation (37). Given the comprehensive implications of these processes, NETs may offer a novel therapeutic targets for coagulopathy associated with TBI.

Platelets. Low platelet counts and/or functional platelet defects in platelets markedly enhance the risk of bleeding; a platelet count below $175x10^9$/l is associated with an elevated risk of progressive intracranial hemorrhage progression, and counts below $100x10^9$/l are strongly associated with increased mortality (38,39). This clinical presentation contrasts with traumatic coagulopathy (TIC), which is distinct from DIC, the latter typically characterized by thrombocytopenia (40). Firstly, in patients with TBI a reduced level of platelet reactivity is positively associated with improved prognoses (41,42). During TBI, the depletion of von Willebrand factor hampers platelet aggregation *in vitro* (43). This impairment is exacerbated by diminished platelet responsiveness to agonists such as adenosine diphosphate (ADP) and/or arachidonic acid (AA), leading to a specific defect in aggregation defects due to inhibition of ADP and AA receptors a phenomenon closely linked to TBI severity (22,44). These defects occur independently of hemorrhagic shock or the absolute platelet count (22,45). Additionally, elevated circulating levels of catecholamine platelet agonists, such as epinephrine and norepinephrine, are associated with compromised platelet aggregation function in patients with TBI (46).

This observation elucidates why even patients with mild injuries may exhibit suppressed platelet function *in vitro* (47). Variations in platelet activity may relate to systemic ischemia-reperfusion and oxidative stress (48), with declining platelet counts closely associated with injury severity and increased mortality risk (42,49). Overactive platelets may lead to secondary thrombocytopenia, heightening the risk of bleeding (22). Patients with TBI often exhibit moderately low platelet counts, with frequent activation of these cells, which generate microvesicles and display procoagulant activity (50,51). Secondly, platelet adhesion dysfunction is recognized as a pivotal factor in trauma response. Studies have revealed that in the aftermath of severe trauma, a notable reduction in in platelet adhesion to collagen is observed (52,53), along with diminished expression of specific receptors on platelets (54,55). These alterations may

Table I. Definitions of specialized terminology.

Specialized terminology	Explanation
Gaussian distribution pattern	A pattern of injury where the brain tissue at the center of the trauma experiences the highest and most severe damage, with the severity of the injury diminishing radially outward.
Brain-derived cell microvesicles	Small vesicles secreted by brain tissue cells and vascular endothelial cells containing biomolecules such as proteins, DNA and RNA from their cell of origin.
Lactoferrin	A member of the transferrin family with antioxidant and anti-inflammatory properties.
Neutrophil extracellular traps	Web-like structures released extracellularly by activated neutrophils containing components such as DNA and histones that have the ability to trap and kill pathogens among other functions.
Damage-associated molecular patterns	Endogenous molecules released by host cells upon injury which include high mobility group box 1, DNA and RNA, triggering immune and inflammatory responses.
Platelet-derived extracellular vesicles	Vesicles released by platelets through budding or exocytosis, participating in processes such as inflammation and immunomodulation. Platelet-derived exosomes represent a specific subset of these extracellular vesicles.
Multimodality monitoring	A comprehensive monitoring method that combines multiple monitoring technologies and parameters to assess the functional status of the brain. This approach aims to provide an integrated view of cerebral pathophysiology in real-time.

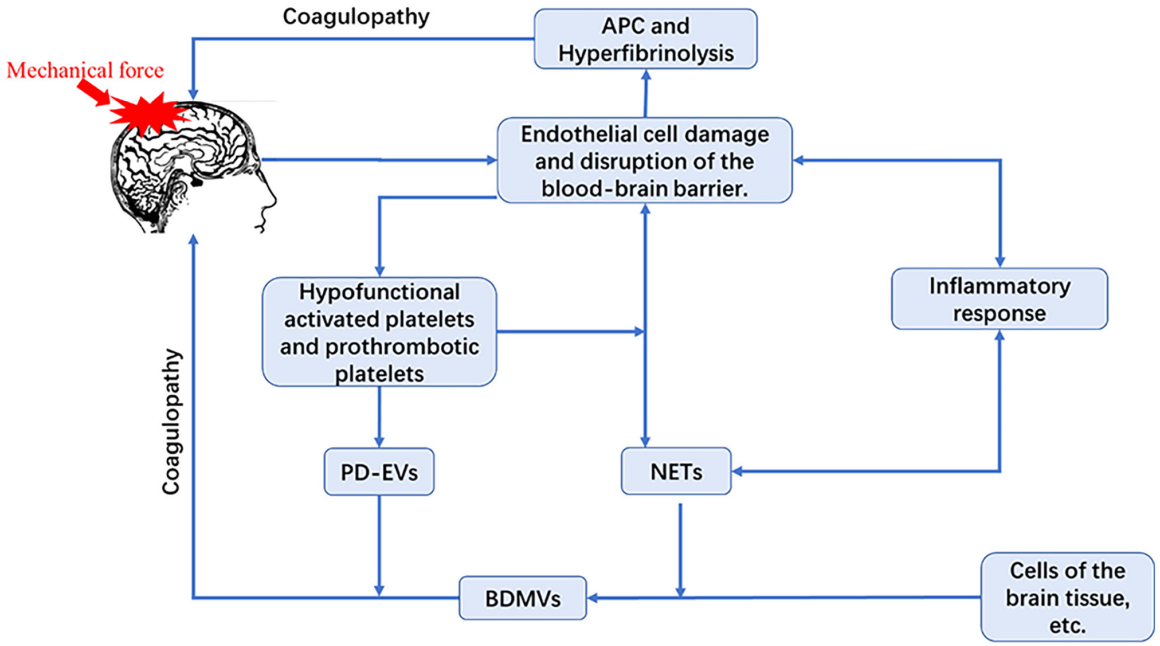

Figure 1. Schematic illustration of cellular mechanisms following TBI. At the time of brain injury, direct forces and subsequent inflammatory responses cause progressive damage to the endothelium and the blood-brain barrier, extending outward peripherally. Simultaneously, there is a massive accumulation of TF and thrombin, the latter of which participates in the activation of protein C, alongside tPA-mediated hyperfibrinolysis. BDMVs increase under the influence of NETs produced by neutrophils, binding to TF and PS in the circulation; however, lactoferrin can phagocytose and degrade BDMVs. Brain injury promotes platelet activation, which although can enhance NET production, leading to a vicious cycle between NETs and inflammatory responses, further exacerbating tissue damage. However, due to hyporeactivity to various platelet agonists in circulation, it results in impaired platelet aggregation. Moreover, shedding of the GPVI receptor (an important receptor on the surface of platelets that participates in collagen binding) leads to adhesion defects in activated platelets. 'Swollen morphology' prothrombotic platelets and PMVs generated by activated platelets also contribute to the occurrence of coagulopathy. TBI, traumatic brain injury; TF, tissue factor; tPA, tissue-type plasminogen activator; BDMV, brain-derived microvesicles; NETs, neutrophil extracellular traps; PS, phosphatidylserine; PMVs, platelet microvesicles; GPVI, platelet glycoprotein VI.

stem from fibrin-induced shedding of glycoprotein VI (GPVI) receptor (an important receptor on the surface of platelets that participates in collagen binding) (56) and interference with its signaling pathway (57).

Research conducted by Montague *et al* (58) has illustrated that inhibiting GPVI shedding by obstructing the fibrin-GPVI interaction offers a potential therapeutic avenue. Furthermore, GPVI shedding is predominantly facilitated by

the metalloprotease ADAM10 (59). In the context of trauma, platelets exhibit a distinctive 'procoagulant' phenotype, characterized by an unusual 'swollen morphology'. This phenotype involves the translocation of PS from the inner to the outer leaflet of the cell membrane, thereby exposing PS on the platelet surface and creating a high-affinity substrate interface for thrombin generation (60). The prevalence of this morphological alteration correlates with injury severity, and these procoagulant platelets demonstrate compromised functionality in primary hemostasis (61). This indicates not only a diminished capacity for platelet aggregation in severe cases but also elevated markers of thrombin generation (62).

Collagen and thrombin, frequently found at sites of endothelial damage, conjointly stimulate the central mechanism for the development of procoagulant platelets *in vitro*, amplifying thrombin production (63). This process is accompanied by significant release of extracellular vesicles (EVs) (64). Certain studies have reported increased levels of platelet-derived EVs in plasma following major trauma, suggesting that purified platelet-derived EVs could potentially ameliorate thrombotic events post-trauma (65-68). Consequently, targeting the emergence of procoagulant platelets presents a promising therapeutic strategy for TIC.

3. Treatment of coagulation disorders following TBI

The early rectification of coagulopathy in patients with TBI is critically associated with survival rate (69). The predominant strategy for addressing TBI-induced coagulopathy entails the blood components, with a growing emphasis on the administration of clotting factors and related substances. Moreover, hemostatic agents are an essential element of the therapeutic arsenal employed in these cases, as their indispensable role in the management of coagulopathy post-TBI.

Pharmacological interventions. Tranexamic acid (TXA), a synthetic derivative of lysine, has proven effective in reducing active hemorrhage (70) and mortality (71) in trauma patients when administered within 3 h of injury, as demonstrated by the CRASH-2 trial (clinical randomization of an antifibrinolytic in significant hemorrhage) (71,72). Building on this, the CRASH-3 trial revealed that early administration of TXA within the same timeframe significantly reduces mortality risk in patients with mild-to-moderate TBI (67,73), thus endorsing its immediate use in such scenarios, whereas its efficacy diminishes in patients with severe TBI cases. Considering TXA's ability to enhance platelet function (74), coupled with its cost-effectiveness and proven efficacy in trauma management, it continues to be a dependable therapeutic option for patients with TBI.

Furthermore, desmopressin, as tested in a rat model of hemorrhagic shock, has been observed to elevate von Willebrand factor and factor VIII levels, as well as augment platelet aggregation (75). Given its short-acting nature and relative safety, desmopressin presents as a suitable alternative (76). Additional pharmacological agents such as progesterone, vitamin K2, Butylphthalide and recombinant interleukin-1 receptor antagonist (77) have demonstrated potential in the treatment of TBI. Conversely, administration of high-dose corticosteroids for 48 h to patients with moderate to severe brain injury has been associated with an increased mortality rate at two weeks (78). Amantadine may accelerate the rate of functional improvement in delirium-rating scale scores (79,80); however, due to its heterogeneity when used in patients with TBI (80), the benefits for this patient population requires further robust investigation. Although theoretically cytidine diphosphocholine (CDP-choline) might have positive effects on cell membrane integrity and cellular edema, studies indicate that its impact on cognitive function improvement in brain-injured patients appears to be negligible (81,82). Hemostatic agents can reduce bleeding in trauma patients, but excessive dosing or prolonged use may lead to acquired thrombosis (83). Therefore, when planning treatment, it is important to assess the risk and extent of thrombosis.

Transfusion of blood components following TBI. Post-TBI, blood component transfusions typically refer to the administration of platelets, red blood cells or plasma based on the individual needs of the patient. In scenarios of ongoing hemorrhage, platelet transfusions have not been proven effective in restoring aggregation function (84) nor have they demonstrated improvements in patient outcomes (85). Notably, the administration of refrigerated platelets has shown to confer superior hemostatic benefits compared with those stored at room temperature (86), a protocol now implemented in numerous trauma centers throughout the United States.

Furthermore, transfusions of packed red blood cells (pRBCs) have been recognized to enhance cerebral oxygenation; recent investigations into the combined administration of pRBCs with plasma in patients with TBI with coagulopathy have associated this practice with an escalation in adverse reactions and deteriorated prognoses (87). It is particularly noteworthy that establishing higher transfusion thresholds at 10 g/dl has been correlated with an upsurge in bleeding complications as opposed to a lower threshold of 7 g/dl (88), indicating that transfusion decisions should extend beyond mere adherence to rigid hemoglobin level. Consequently, a restrictive strategy for pRBC transfusion is advocated, except in instances where patients exhibit intolerance to anemia (89). The determination of the optimal timing and volume of transfusions remains a pivotal focus of ongoing research.

Hemostatic factors and associated substances. In recent years, advancements in the study of coagulation factors have significantly progressed the treatment of trauma patients. Fujiwara *et al* (90), employing a rat model of controlled cortical impact, demonstrated that daily intravenous injections of 350 mg/kg of a synthetically derived activated peptide of factor IX (termed F9-AP) significantly mitigated adjacent neuronal loss associated with secondary brain injury, markedly reducing both the volume of brain injury and associated edema. Moreover, recombinant activated factor VII, which exhibits lesser dependence on platelet function, appears to offer distinct advantages for patients with severely compromised platelet function or severe thrombocytopenia, effectively diminishing the risk of intracranial hemorrhage (91). Prothrombin complex concentrate (PCC), an inactivated blend comprising of factors II, IX, VII and X, has been proven to be highly efficacious in managing refractory bleeding to conventional treatment methods and in correcting elevated international normalized

ratio (INR) levels (92). In TBI, where fibrinogen levels can be depleted, it is imperative to restore these levels to within normal ranges to alleviate inflammation and reduce endothelial permeability (93). The supplementation of factor XIII plays equally a critical role in inhibiting hyperfibrinolysis, stabilizing clot formations and minimizing surgical blood loss (94,95). However, compared with plasma, PCC may reduce hematoma expansion, yet shows no significant difference in 90-day mortality or Glasgow Coma Scale scores (96).

Reversal agents for direct oral anticoagulants (DOACs). With an aging population, the number of patients with TBI concurrently taking oral anticoagulants is increasing. To ameliorate adverse outcomes including bleeding in patients undergoing surgery or those suffering from TBI while on these therapies, the development of antidotes for the reversal of DOACs has emerged as a crucial area of research. In 2015, publication of the first study demonstrating the safety and efficacy of idarucizumab, a targeted monoclonal antibody fragment for the acute reversal of dabigatran, a direct thrombin inhibitor, marked a significant advancement in anticoagulation management (97). This was followed by the introduction of Andexanet alfa, an antagonist of the facto Xa inhibitors, into clinical practice (98). Protamine sulfate is employed for the reversal of both unfractionated heparin and low molecular weight heparin (LMWH). However, its routine administration for reversing prophylactic subcutaneous heparin is not recommended unless there is a significantly prolonged activated partial thromboplastin time (aPTT) (99).

Notably, non-specific hemostatic agents such as PCC and activated prothrombin complex concentrate may also serve to reverse the effects of DOACs. However, FDA-approved reversal agents are not applicable to all DOACs or all clinical scenarios where reversal may be considered. Furthermore, the complexity of clinical use is compounded by factors such as cost, preparation and the lack of standardized protocols (97).

Potential therapies. Research underscores the complex and heterogeneous nature of TBI progression, necessitating exploration beyond conventional treatments toward interventions that may confer additional benefit to patients. This section delineates several promising potential therapeutic avenues post-TBI, aiming to foster groundbreaking advancements in the management during process.

It has been demonstrated that elevated levels of matrix metalloproteinase-9 (MMP-9) following brain injury contributes to the dysfunction of the BBB (100). Encouragingly, administration of MMP inhibitors in rodent models of brain injury has led to improved outcomes (101), indicating that MMP inhibition may represent a viable therapeutic strategy for patients with TBI. Moreover, the integration of medical science and nanotechnology has facilitated the development of platelet-mimicking nanovesicles, which incorporate the biological characteristics of platelet membranes into a lipid-based nanostructure. Through bioengineering manipulations, these particles can partially or fully emulate the hemostatic functions of natural platelets to varying extents (102), thus offering a promising alternative to platelet transfusion therapy. Additionally, novel resuscitative agents, known as platelet-derived extracellular vesicles (103), have surfaced, exhibiting remarkable hemostatic potency in patients with TBI via multiple mechanisms. However, current investigational agents remain in the experimental phase and additional research and data are required before they can advance to clinical application. As research advances and technology evolves, it is anticipated that additional mechanisms will be elucidated and applied to strategies aimed at ameliorating the outcomes for TBI survivors.

4. Complications

TBI can be accompanied by a wide array of complications, including but not limited to epilepsy, cerebral herniation, hydrocephalus and cerebrocardiac syndrome (104-106). These concomitant complications are intimately associated with a diminished quality of life and heightened mortality rates. Specifically, in the period following the initial day post-TBI, the emergence of multiple organ dysfunction and thrombotic events become the predominant causes of mortality among critically ill patients (107). Besides emphasizing early preventive strategies, it is equally essential to unravel the mechanisms that underlie the initiation and progression of these complications is equally indispensable. This underscores the imperative for a thorough comprehension and the formulation of precise intervention strategies.

Multiple organ dysfunction syndrome (MODS). Post-traumatic MODS is widely recognized as a consequence of deregulated responses to trauma. The primary pathogenic mechanism likely involves the activation of both coagulation and inflammatory cascades (108,109). Furthermore, MODS is intimately associated with extracellular histones, HMGB1 and S100A8/9, among other factors. Notably, elevated levels of HMGB1 contribute to organ injury (109). Additionally, the dynamic interaction between platelets and leukocytes facilitates leukocyte recruitment to sites of injury, facilitating tissue repair (110). Nevertheless, an excessive immune response appears to inflict organ damage (111). Fortunately, proactive management of coagulopathy exhibits promising potential in ameliorating the incidence of organ failure (112).

Thrombosis. Thromboembolic events play a significant cause in increasing morbidity and disability rates among patients, particularly those who have suffered TBI and are severely injured or unable to mobilize independently. Considering TBI as an established independent risk factor for venous thromboembolism (VTE) (113,114). The present discussion predominantly focuses on VTE, extending beyond traditional triggers to explore the pivotal role played by the interaction between platelets and monocytes in the initiation and propagation of VTE (115). Moreover, factors including NETs, platelet-derived microparticles and protein C depletion (38) are intimately associated with VTE development. In intensive care units, the occurrence of VTE among critically ill trauma patients is notably elevated, with an estimated incidence of up to 35% (116). Even with the implementation of mechanical prophylaxis measures for deep vein thrombosis (DVT), residual DVT and pulmonary embolism (PE) rates remain substantial at 31 and 3% (114), respectively. A recent large comprehensive observational

study emphasized that *de novo* pulmonary thrombi are more prevalent than PEs originating from DVT, often manifesting early in the clinical course (117). In animal models of TBI, microthrombi are predominantly observed in the pericontusional cortex (118), composed of fibrin, platelets and other components. LMWH has demonstrated superior efficacy in preventing thromboembolism compared to unfractionated heparin (119), indicating that, following a thorough patient evaluation and confirmation of no contraindications, early initiation of LMWH for thromboprophylaxis is recommended. Apart from LMWH, factor XI inhibitors, such as Abelacimab, have shown effectiveness in preventing VTE (120), offering an alternative preventive strategy in managing thrombotic risks.

Consequently, early detection, prevention and management of MODS and thrombotic events assume paramount importance. Identification and assessment of disease severity, as well as prediction of risks in patients, are facilitated through monitoring vital signs, imaging changes, laboratory parameters and scoring systems such as APACHE II, SOFA and qSOFA (121,122). Management of these patients should be viewed as a dynamic process, necessitating close surveillance and prompt adjustment of therapeutic strategies as needed. Given the unique nature of each patient's condition, treatment plans should be individualized, with the overarching goals of maximizing organ function recovery, preventing thrombosis and enhancing quality of life.

5. Diagnostic tools for coagulopathy following TBI

Laboratory assessments aimed at detecting coagulopathy and techniques reflecting brain injury are crucial in diagnosing and managing coagulation disorders that arise following TBI (Table II). Conventional coagulation assays, routinely employed in clinical settings to evaluate hemostatic function, encompass prothrombin time, aPTT and INR (123,124), which aid in prognostication post-cranial injury. Nonetheless, these tests fail to capture the full complexity of coagulation processes and have limitations in accurately representing thrombin generation and precision in hemostatic evaluation (125,126).

More advanced global hemostasis assessments, including rotational thromboelastometry (ROTEM), thromboelastography (TEG) and thrombin generation tests, may offer a superior real-time analysis of hemostatic status. These provide swift feedback for therapeutic intervention and enable more precise predictions treatment outcomes (127). These methodologies further facilitate goal-directed transfusion strategies (128) and guide heparin administration for thromboembolism prophylaxis (129), with TEG particularly unaffected by the administration of TXA (130). A fibrinogen level concentration 2.0 g/l is recognized as a risk factor for coagulopathy and associated complications post-TBI. Both ROTEM and TEG have proven effective in swiftly and precisely measuring fibrinogen levels (127). Moreover, recent research involving bleeding adult and pediatric patients has demonstrated that transfusion strategies guided by viscoelastic tests improve survival rates, decrease blood product usage and reduce the incidence of renal failure when compared with other methods (131). Point-of-care platelet function testing (POC-PFT), exemplified by systems including VerifyNow, Plateletworks, PFA-100/200, show promise in identifying platelet dysfunction or guiding antiplatelet therapy (6,20). However, the absence of a gold standard for POC-PFT and substantial variation among available analyzers in terms of implementation technique and platelet agonists utilized hinder widespread acceptance. Consequently, current European guidelines on massive hemorrhage and coagulation management in trauma do not advocate for the routine use of POC-PFT (132).

6. Neurocritical care monitoring tools

For patients suffering from moderate to severe brain injuries, the mere reliance on conventional blood tests is insufficient, Conventional coagulation tests measure only ~4% of total thrombin generation and do not assess the overall hemostatic state. Furthermore, these tests do not reflect the interactions between multiple coagulation pathway mechanisms (133-135). Therefore, the incorporation of cutting-edge neurocritical care monitoring instruments is of utmost importance. In this context, multimodal monitoring (MMM) encompasses a range of techniques, including intracranial pressure (ICP)-monitoring, cerebral microdialysis (CMD), cerebral tissue oxygenation monitoring and continuous electroencephalography (EEG) (3), amongst others. Through the amalgamation of these diverse monitoring modalities, MMM provides a comprehensive, real-time evaluation of the patient's cerebral pathophysiology. This significantly bolsters the management of brain disorders, elevates patient outcomes and propels clinical research forward.

Primarily, ICP monitoring stands as a pivotal component, as elevated ICP can diminish cerebral perfusion [cerebral perfusion pressure=mean arterial pressure (MAP)-ICP], subsequently augmenting the peril of ischemia and herniation (136,137). In accordance with the established guidelines, maintaining ICP at 20-25 mmHg (138), with MAP kept at 60-70 mmHg in severe patients with TBI, is paramount in effectively mitigating adverse outcomes. Furthermore, CMD emerges as an invasive yet invaluable technique. It involves hourly sampling and analysis of cerebral extracellular fluid metabolites, offering an unprecedented glimpse into the biochemical shifts within the brain (139). Complementing this, cerebral tissue oxygenation monitoring employs near-infrared spectroscopy for a non-invasive, continuous assessment of regional concentrations of oxygenated and deoxygenated hemoglobin in the brain (140). This, in turn, aids in evaluating the risk of cerebral hypoxia and shaping individualized therapeutic strategies. However, it's worth noting that its application remains primarily confined to superficial areas such as the frontal cortex, owing to technological limitations.

In the realm of severe TBI, post-traumatic seizures affect roughly one in ten patients, with asymptomatic seizure activity prevalence potentially escalating to 20-25% (141). Continuous EEG enables the early detection of these cerebral pathologies and guides antiepileptic therapy. As previously reported, the successful management of a 25-year-old comatose patient following a car accident was achieved through the utilization of the MMM monitoring and management system. This

Table II. Advantages and disadvantages of various diagnostic tools.

Diagnostic tools	Content	Advantages	Disadvantages	Clinical application
CCAs	Tests such as prothrombin time, activated partial thromboplastin time and international normalized ratio	It can indirectly predict the prognosis of patients with coagulopathy	It is unable to provide real-time information on coagulation changes; it does not assess the levels of thrombin or the extent of clot formation involved in the reaction	Conventional methods
ROTEM	Detailed kinetics of blood coagulation such as clot initiation time, fibrin formation velocity, clot firmness and fibrinolysis activity	It allows for real-time assessment of hemostatic status, rapid feedback on test results and prediction of treatment efficacy; it can quickly and accurately evaluate fibrinogen levels; and it can guide therapeutic interventions	It requires stringent technical expertise; interpretation of results still relies heavily on the operator's experience, with lower standardization compared to conventional tests; and it is relatively more costly	Preferred methods
TEG	Reaction time; kinetic time; alpha angle; maximum amplitude; lysis at 30 min	It allows for real-time assessment of hemostatic status, rapid feedback on test results and prediction of treatment efficacy; it can quickly and accurately evaluate fibrinogen levels; and it can guide therapeutic interventions	It demands strict technical requirements; results can be influenced by human factors; and it is time-consuming	Preferred methods
POC-PFT	TEG (TEG 5000/6 s Hemostasis Analyzer System), ROTEM (ROTEM Delta System), platelet reactivity turbidimetry test (VerifyNow System), multiple electrode platelet aggregometry (Multiplate Analyzer) and PFA (PFA-100/200)	It enables real-time monitoring of platelet function: Reducing blood transfusion in cardiac surgery and in predicting the risk of perioperative blood loss in high risk cardiac surgery patients	There is no universally recognized 'gold standard'; it requires stringent technical expertise; and the results can be subject to human-related variables	Not routinely utilized

ROTEM, rotational thromboelastography; TEG, thromboelastography; PFA, platelet function analyzer.

case underscores the practical utility of MMM. The system is capable of providing real-time updates on physiological changes and offering early indications of potential issues before they escalate, thereby guiding preemptive interventions (142). In conclusion, with the progression of technology and the accumulation of clinical experience, the application of MMM is likely to evolve into a more refined and widespread practice. IF so, it would be an indispensable component of modern neurointensive care.

7. Summary and perspectives

TBI triggers swift and substantial modifications in cellular behaviors, thereby amplifying the intricacy of coagulopathy mechanisms and complicating treatment options by altering both intra- and intercellular connections. The diverse changes induced by TBI are still inadequately targeted by current therapeutic approaches. As a result, there is an urgent necessity for deeper investigation to clarify the fundamental mechanisms

underlying coagulopathy of post-TBI and to refine precision therapies accordingly. This involves establishing diagnostic thresholds and developing targeted therapeutic interventions aimed at effectively managing coagulation disorders. Current research lacks prospective diagnostic modalities that can accurately determine the timepoint of hemostatic failure, making it challenging to define the optimal timing for initiating anticoagulation therapy in patients with coagulopathy. The aging population of patients with TBI, coupled with the widespread use of antiplatelet medications and anticoagulants, poses a considerable challenge in comprehending the distinct impacts of various antiplatelet medications and anticoagulants on post-TBI coagulopathy. Tackling these challenges is paramount for improving clinical outcomes and minimizing the morbidity and mortality associated with this condition. Hence, there is a critical need for more expeditious and efficacious techniques to restore coagulation, thereby limiting the progression of brain injury in patients on anticoagulant and antiplatelet medications, with the ultimate aim of improving outcomes. Moreover, future research focusing on the management of coagulopathies in both critically and non-critically ill patients post-TBI should prioritize not just survival rates, but also enhancements in quality of life for patients.

Acknowledgements

The authors are grateful to Ms. Du Pengchao (Binzhou Medical College, Yantai, China) for her insightful suggestions and constructive feedback on the manuscript.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

HH and ZQ performed the literature search and co-wrote the manuscript. RL, BJ, LW and AL participated in the literature search and reviewed the literature and the manuscript. HH, ZQ, RL, BJ, LW and AL made substantial contributions to the conception and revision of the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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