Pathophysiology of Trauma-Induced Coagulopathy

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Abstract

Trauma-induced coagulopathy (TIC) is a complex hemostatic disturbance that can develop early after a major injury. There is no universally accepted definition of TIC. However, TIC primarily refers to the inability to achieve sufficient hemostasis in severely injured trauma patients, resulting in diffuse microvascular and life-threatening bleeding. Endogenous TIC is driven by the combination of hypovolemic shock and substantial tissue injury, resulting in endothelial damage, glycocalyx shedding, upregulated fibrinolysis, fibrinogen depletion, altered thrombin generation, and platelet dysfunction. Exogenous factors such as hypothermia, acidosis, hypokalemia, and dilution due to crystalloid and colloid fluid administration can further exacerbate TIC. Established TIC upon emergency room admission is a prognostic indicator and is strongly associated with poor outcomes. It has been shown that patients with TIC are prone to higher bleeding tendencies, increased requirements for allogeneic blood transfusion, higher complication rates such as multi-organ failure, and an almost fourfold increase in mortality. Thus, early recognition and individualized treatment of TIC is a cornerstone of initial trauma care. However, patients who survive the initial insult switch from hypocoagulability to hypercoagulability, also termed “late TIC,” with a high risk of developing thromboembolic complications.

Keywords
- trauma-induced coagulopathy
- endotheliopathy
- hyperfibrinolysis
- altered thrombin generation
- platelet dysfunction

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Zusammenfassung

Die trauma-induzierte Koagulopathie (TIC) ist eine komplexe hämostatische Störung, die sich früh nach einer schweren Verletzung entwickeln kann. Bisher gibt es keine allgemein anerkannte Definition von TIC. TIC bezeichnet in erster Linie die Unfähigkeit, schwer verletzter Traumapatienten eine suffiziente Blutstillung zu erreichen, was zu diffusen mikrovaskulären und somit lebensbedrohlichen Blutungen führen kann. Die TIC ist eine „endogene Gerinnungsstörung" die durch die Kombination aus hypovolämischem Schock und erheblicher Gewebeschädigung verursacht wird. Dadurch kommt es zu substanziellen Endothelschäden, Glykokalyxablösungen, einer hochregulierten Fibrinolyse, Fibrinogenmangel, veränderter Thrombinbildung und einer Plättchenfunktionsstörung. „Exogene Faktoren" wie Hypothermie, Azidose, Hypokaliämie und Verdünnung aufgrund der Verabreichung von Kristalloiden und Kolloiden können eine TIC weiter verschlimmern. Eine bestehende TIC bei Schockraum-Aufnahme ist ein prognostischer Indikator und eng mit einem schlechten Outcome assoziiert. Es hat sich gezeigt, dass Patienten mit TIC eine höhere Blutungsneigung aufweisen, einen erhöhten Bedarf an allogenen Bluttransfusionen unterliegen, signifikant mehr Komplikationen wie etwa ein Multiorganversagen zeigen und eine fast vierfach höhere Mortalität aufweisen als gerinnungkompetente Traumapatienten. Daher ist die Früherkennung und individuelle Behandlung einer bestehenden TIC essenziell in der initialen Versorgung von schwerverletzten Patienten. Trauma Patienten, die das initiale Trauma überleben, wechseln von einer Hypokoagulabilität in einen hyperkoagulablen Zustand, der auch als „späte TIC" bezeichnet wird. Damit erhöht sich das Risiko für die Entwicklung thromboembolischer Komplikationen.

Schlüsselwörter

- traumainduzierte Koagulopathie
- Endotheliopathie
- Hyperfibrinolyse
- eingeschränkte Thrombinbildung
- Plättchenfunktionsstörung

Current Understanding of the Pathophysiology of Trauma-Induced Coagulopathy

Hemorrhage is the second leading cause of death following trauma, exceeded only by traumatic brain injury.[1] If severe blood loss after trauma remains uncontrolled, it leads to pronounced hemorrhagic shock, which has been identified as an important driver of trauma-induced coagulopathy (TIC). Historically, coagulopathy after severe trauma was assumed to be a result of hemodilution due to fluid replacement therapy, consumption of coagulation factors at the side of injury, and additional confounders, such as hypothermia and acidosis.[2] Intensive research over the past 15 years has found that TIC is an endogenous dysregulation of the hemostatic system, primarily driven by tissue trauma, shock-related hypoperfusion, endotheliopathy, altered thrombin generation (TG), and platelet dysfunction, which can be further complicated by exogenous factors, such as hypothermia, acidosis, hypocalcemia, and dilution.[3] Early TIC is characterized by a hypocoagulative state and the inability to form sufficient clots, resulting in uncompressible diffuse microvascular bleeding. Studies have revealed that TIC starts early after trauma and can be detected in the most severely injured patients, already at the scene of the accident.[4] The presence of a TIC upon emergency room (ER) admission is associated with higher blood loss, increased allogeneic blood product requirements, higher rates of multi-organ failure, and an almost fourfold increase in mortality compared with trauma patients with hemostatic competence.[5–7] When bleeding and shock-related hypoperfusion is controlled and patients survive the initial first 24 hours, a transition from an early hypocoagulable to a later hypercoagulable and prothrombotic state occurs.[8] Thus, thromboprophylaxis should be initiated as soon as possible.[9] The purpose of this review is to provide current evidence on the potential drivers and mechanisms resulting in "early" TIC.

Definition, Incidence, and Diagnosis of TIC

So far, no universally accepted definition of TIC has been established. The term TIC describes an abnormal hemostatic response following a major injury, which results in an inefficient clot formation process, diffuse microvascular bleeding, and an increased risk of exsanguination.

The diagnosis of TIC still relies on standard coagulation tests, such as prothrombin time and international normalized ratio (INR).[10–12] However, the correlation between INR and TG is poor. Dunbar and Chandler[77] demonstrated that TG parameters in severely injured patients with an INR of greater than 1.5—by definition TIC—were upregulated. Moreover, a single parameter, such as INR, cannot display the complexity of coagulation abnormalities related to TIC.

More advanced technologies, such as viscoelastic test (VET) methods, have discovered more trauma patients with abnormal test results compared with prothrombin time or activated

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partial thromboplastin time.[10–17] This partly explains the wide variation of reported TIC incidences ranging from 25 to 43% of all severely injured patients.[6,14]

In contrast to VET methods, a general accepted "gold standard" for point-of-care platelet function testing has not been established so far.[18] Both the applied technologies and the composition of platelet agonists used to activate thrombocytes differ considerably between the different platelet function analyzer.[19] Moreover, platelet function analyzers were initially developed to assess the impact of platelet inhibitors, such as aspirin or adenosin diphosphate (ADP) antagonists, on thrombocytes rather than to detect potential bleeding related to trauma-induced platelet dysfunction.[20]

Importantly, the laboratory definition of TIC differs from clinically evident coagulopathy with diffuse microvascular bleeding. Chang et al reanalyzed data from the PROHS study and reported that clinically evident coagulopathy was rare (4%) compared with laboratory-defined coagulation abnormalities (39%) but was associated with substantially higher mortality (59 vs. 22%).[21]

Pathophysiology of Trauma-Induced Coagulopathy

Clinical outcomes following traumatic injury depend on the severity of blood loss, the degree of shock on admission, the extent of tissue injury, injury patterns, and the elapsed time from injury to clinical control of the bleeding source.[11,22,23] Initially, after tissue trauma, TG is upregulated, platelets are activated, and clot formation is enhanced to establish rapid bleeding control. Moreover, the release of antifibrinolytic molecules from platelet granules protects the established clot from premature lysis. Nevertheless, if blood loss remains uncontrolled, it results in hypovolemic shock, with devastating consequences.

Shock as a Driver of Trauma-Induced Coagulopathy

An isolated massive tissue injury without shock induces a prothrombotic phenotype of TIC associated with an increased risk of thromboembolic complications.[3] In contrast, the bleeding type of TIC requires both shock-related hypoperfusion with a corresponding low-flow state and tissue trauma.[8] Frith et al demonstrated that the severity of TIC strongly correlated with the combined degree of both injury and shock.[11] A prolongation of the prothrombin time ratio and activated partial thromboplastin time (aPTT) was only detected in shocked patients, defined as an admission base deficit of greater than 6 mmol/L. In contrast, when base deficit remained within normal limits, prothrombin time and aPTT also remained within the reference ranges.[11]

Endotheliopathy of Trauma

The vascular endothelium and its anticoagulant intraluminal layer, the glycocalyx, are a huge, often underestimated organ, with a large surface area of approximately 5,000 m^2 and a weight of approximately 1 kg.[24] The endothelium plays an essential role in coagulation and inflammation, serving as a semipermeable barrier between the fluid phase and the tissue.[25] Endotheliopathy of trauma describes a state of endothelial cell damage and glycocalyx shedding with the release of specific serum biomarkers such as soluble thrombomodulin, syndecan-1, heparan sulfate, chondroitin sulfate, hyaluronic acid, and many more.[24,26–28] Endotheliopathy of trauma is primarily driven by inflammation and shock-related hypoperfusion with the release of high amounts of catecholamines (e.g., adrenalin) and vasoactive hormones such as vasopressin[24] (►Fig. 1). In a rat model of hemorrhagic traumatic shock, chemical sympathectomy suppressed the release of inflammatory cytokines, decreased profibrinolytic activation, and was associated with less endothelial damage compared with sham animals.[29] In another experimental study, Hofmann et al demonstrated an independent association between shock severity and the intensity of endotheliopathy and sympathoadrenal activation.[27] This aligns with the findings in trauma patients, which also showed a strong association between sympathoadrenal activation and the release of markers of endothelial cell and glycocalyx damage.[30] Both adrenalin concentration and endotheliopathy were identified as independent predictors of poor outcomes in trauma patients.[31]

Importantly, a breakdown of the glycocalyx results in capillary leakage and a significant loss of intravascular volume, which additionally worsens hypovolemia in already shocked patients, further intensifying tissue hypoperfusion and shock severity.[8]

Moreover, the release of heparinlike substances, such as heparan sulfate or chondroitin sulfate, as a consequence of glycocalyx shedding was proposed as a potential additional driver of TIC due to an endogenous autoheparinization process.[32] Whether and to what extent autoheparinization plays a role as an additional anticoagulant mechanism that increases bleeding tendency is currently under debate. A recent study investigating potential autoheparinization with different VET assays in severely injured trauma patients did not indicate that the release of heparan sulfate plays a significant role in the pathogenesis of TIC.[33]

Taken together, endotheliopathy of trauma is driven by shock-related release of adrenalin and vasopressin into the bloodstream, which promotes hypocoagulability, hyperfibrinolysis (HF), increased bleeding risk, transfusion requirements, and mortality.

Hyperfibrinolysis

HF has been identified as a predominant driver of TIC, which is strongly associated with poor outcomes in trauma patients.[34–37]

Two mechanisms have been proposed as potential activators of profibrinolytic pathways after a major injury. Brohi et al suggested that hypovolemic shock stimulates the endothelial synthesis of thrombomodulin, which binds thrombin. This complex, in turn, activates protein C. Activated protein C, the main anticoagulant protein of the body, promotes HF by inhibiting plasminogen activator inhibitor-1 (PAI-1), which is the most important antagonist of the profibrinolytic enzyme tissue plasminogen activator (tPA).[38]

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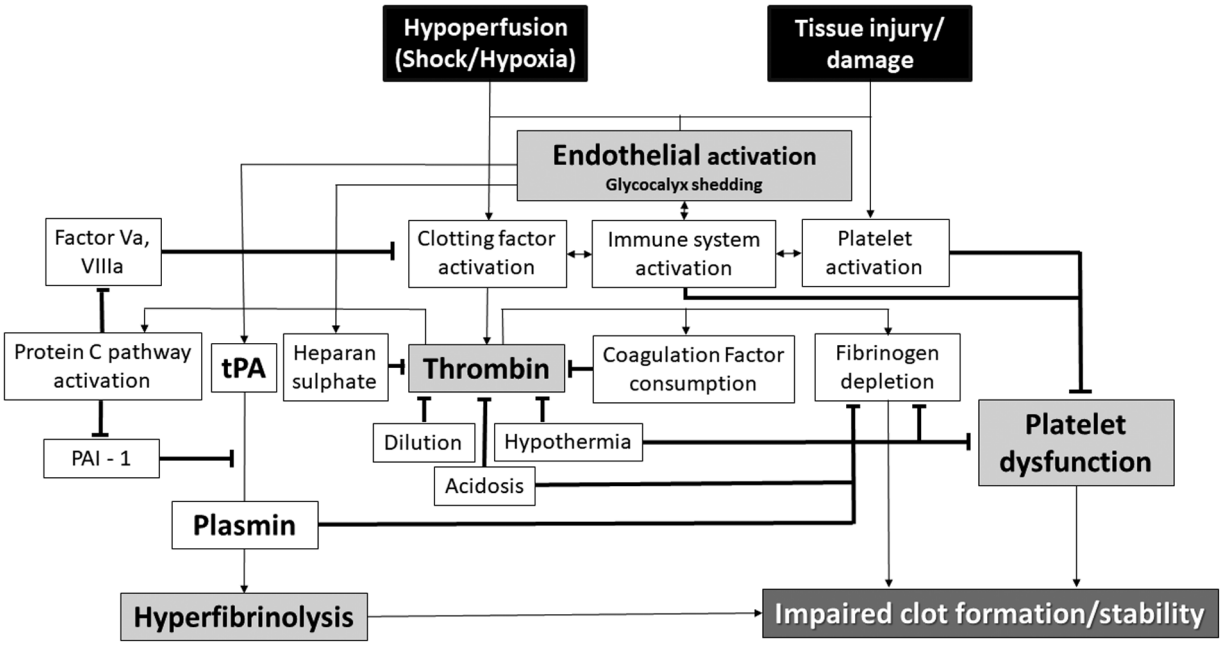

Fig. 1 Schematic overview of potential drivers of trauma-induced coagulopathy. t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1. Activators; inhibitors.

Another hypothesis suggests that hypoxemia, in conjunction with high concentrations of adrenalin, vasopressin, and thrombin, powerfully activates endothelial cells. In turn, significant amounts of tPA are released from the Weibel–Palade vesicles into the bloodstream.[39] This hypothesis is supported by the finding that HF has also been demonstrated in other nontraumatic low-flow states, such as life-threatening anaphylactic shock or out-of-hospital cardiac arrest.[40,41]

Independent of the suggested mechanism, tPA cleaves plasminogen to plasmin, which dissolves fibrin and—if available in high amounts—fibrinogen. Thus, upregulated plasmin generation promotes premature clot dissolution and hypofibrinogenemia.

With the implementation of VET methods in modern trauma care, HF has been identified as an important contributor to TIC.[35,36,42–44] However, there is no uniform definition of HF based on VET results. For the ROTEM/ClotPro devices, HF is defined as a breakdown of greater than 15% of the maximum clot firmness. For TEG, a reduction of greater than 3% 30 minutes (LY30) after reaching the maximum amplitude of the clot is by definition HF.

However, not only the percentage of decreased clot firmness but also the speed of clot dissolution is linked to poor outcomes. Fulminant lysis, defined as a complete breakdown of the clot within 30 minutes (ROTEM) or the so-called diamond of death shape of the clot (TEG), is associated with an almost 100% mortality.[37,45,46] Thus, the pattern of clot lysis seems to be crucial for clinical outcomes (►Fig. 2). It is essential to note that the absence of lysis signs in VETs does not rule out profibrinolytic activation. Raza et al reported in a cohort of trauma patients that, despite normal maximum lysis (ML) in ROTEM, high plasmin–antiplasmin complexes (>1,500 µg/L) were detected, suggestive of fibrinolytic activation.[47] Moreover, currently available VET assays are designed to detect systemic lysis only. Thus, local lysis might take place but remain unnoticed by VET methods.

From an evolutionary point of view, HF counteracts shock-related microvascular stasis, microthrombosis, tissue hypoperfusion, and hypoxemia to maintain blood flow, even at the cost of an increased bleeding rate due to the dissolution of already established clots[48] (►Fig. 3).

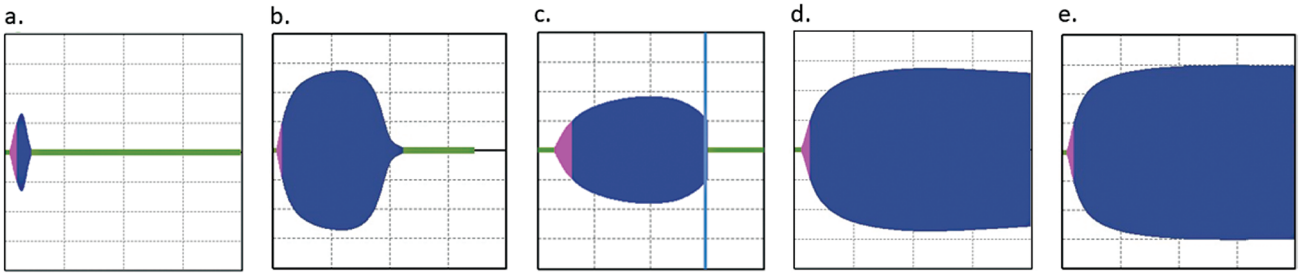

Fig. 2 Different lysis patterns measured by rotational viscoelastometry. (**a**) Fulminant lysis or so-called diamond of death shape. (**b**) Intermediate type of clot lysis. (**c**) Late lysis. (**d**) Physiologic lysis. (**e**) Fibrinolytic shutdown.

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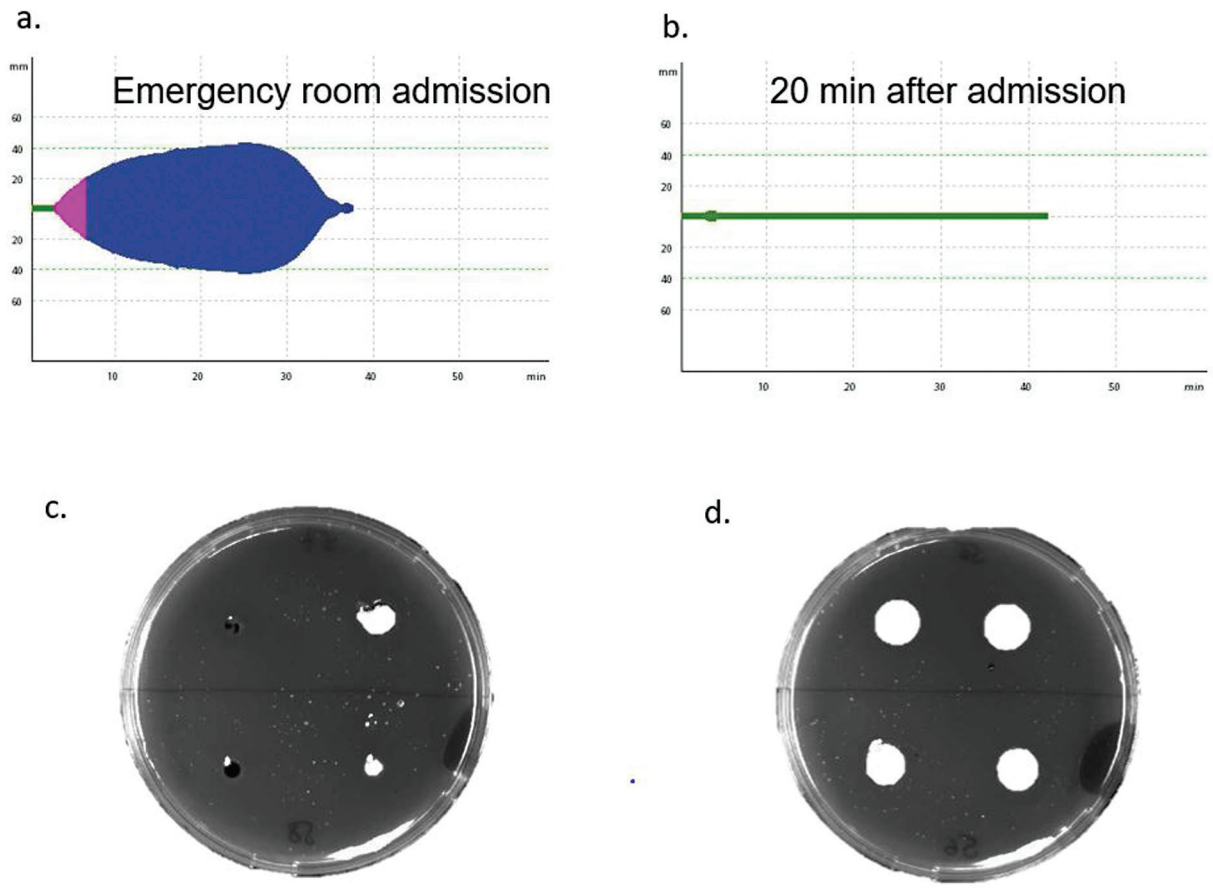

Fig. 3 Hyperfibrinolysis detected by EXTEM (ROTEM) upon (**a**) emergency room admission. (**b**) Twenty minutes after admission, no clot formation in the ROTEM analysis could be detected any more. (**c**) Plasma (200 µL) collected upon admission and (**d**) after 20 minutes was spiked on fibrin plates. Substantial increase in the fibrinolytic area after 20 minutes corresponds to increased lysis observed in EXTEM.[42]

Fibrinolytic Shutdown

Lysis and HF are strongly inhibited by PAI-1, which starts its upregulation approximately 2 hours after the initial trauma and may result in complete inhibition of clot lysis, a condition known as "fibrinolytic shutdown."[49,50] Numerous studies demonstrated that mortality in patients with fibrinolytic shutdown, defined as LY30 < 0.8% in TEG or as ML < 5% in ROTEM, was higher than in patients with physiologic lysis.[51–56]

However, whether VET methods accurately define fibrinolysis phenotypes is still under discussion.[47,53,56,57] To diagnose lysis and HF, D-dimers and plasmin–antiplasmin complexes are potentially more sensitive parameters than VETs. Gall et al identified a cohort of trauma patients with high D-dimer levels and increased blood product consumption and mortality despite low ML in ROTEM.[56] Cardenas et al analyzed blood samples from trauma patients with TEG and measured the plasmin–antiplasmin complexes and D-dimers. A total of 89% of the shutdown patients had moderate to high fibrinolytic activation by the plasmin–antiplasmin complexes. Thus, low TEG LY30 does not reflect hypercoagulability, but a TIC with moderate fibrinolysis and fibrinogen consumption associated with poor outcomes.[57] Similar findings using ROTEM have been reported by David et al, who observed in the ROTEM shutdown group lower fibrinogen concentrations and higher levels of fibrin degradation products than in the patients with physiologic lysis. The authors suggested that fibrinolytic shutdown probably reflects a moderate form of coagulopathy and fibrinolysis rather than hypercoagulopathy.[53]

Currently, it remains to be elucidated which is the optimal way to identify fibrinolytic shutdown in major trauma patients, as the measurement of the plasmin–antiplasmin complexes is not feasible in routine clinical practice.[58]

In summary, the endothelium reacts uniformly to hypoxic stress and sympathoadrenal hyperactivation, with an early and robust release of tPA and cleavage of plasminogen to plasmin. PAI-1 starts to increase 2 hours after endothelial cell activation, resulting in an endogenous inhibition of lysis.[59,60] This delayed PAI-1 expression promotes a shift toward a hypofibrinolytic state and may lead to microvascular thrombosis and multi-organ failure.

Fibrinogen Deficiency

Fibrinogen has a molecular weight of 350 kDa and is synthesized solely in the liver.[61] The circulating levels range between 2 and 4 g/L in a healthy adult but can be upregulated 20-fold, mediated by infection, inflammation, and IL-6 release.[62] Thrombin cleaves fibrinogen to fibrin fibers, cross-linked by activated factor XIII, which increases mechanical

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strength and resistance to premature fibrinolytic degradation.[63] Moreover, fibrinogen binds with high affinity to glycoprotein IIb/IIIa receptors expressed on the surface of activated platelets, thereby facilitating further platelet aggregation.[64] Thus, fibrinogen plays an essential role in both primary and secondary hemostasis.[65]

In a severely injured bleeding patient, fibrinogen is the first coagulation factor to reach critically low levels.[4,66] Moreover, hypofibrinogenemia upon ER admission is associated with higher bleeding rates, increased allogenic blood transfusion requirements, and increased mortality.[67–69] A critical fibrinogen level associated with a tendency toward increased bleeding is assumed to be less than 1.5 g/L.[67,70] Consequently, current guidelines recommend early fibrinogen substitution, particularly when levels decline below 1.5 g/L.[71]

Hypofibrinogenemia in trauma patients is driven by blood loss, hemodilution, hyperfibrinogenolysis, and consumption due to clot formation at the site of injury.[65] Moreover, experimental studies demonstrated that hypothermia, which is common in severely injured patients, impairs fibrinogen synthesis, and acidosis accelerates fibrinogen breakdown.[72,73] Schlimp et al observed that fibrinogen levels upon ER admission were strongly associated with shock severity in trauma patients. If base deficit exceeded 6 mmol/L, fibrinogen plasma concentrations decreased to less than 200 mg/dL in 81% of the patients and less than 150 mg/dL in 63% of the patients.[74] Interestingly, the acute-phase response of fibrinogen is not downregulated by early exogenous fibrinogen substitution during initial trauma care.[75]

Taken together, fibrinogen is the most vital and vulnerable coagulation factor, and it reaches critically low levels earlier than other coagulation proteins. Low fibrinogen upon admission is strongly associated with poor outcomes.

Altered Thrombin Generation

Thrombin cleaves fibrinogen to fibrin and activates factor XIII (FXIII), platelets, endothelial cells, and leucocytes. When bound to thrombomodulin, thrombin activates the protein C pathway and becomes an anticoagulant factor.[38] Immediately after initial tissue trauma, TG is strongly upregulated to create sufficient clots for quick termination of blood loss.[76,77]

TG can be altered by several trauma-related mechanisms, such as loss and consumption of coagulation factors, dilution, hypothermia, and acidosis (►Fig. 1).[78,79] Studies in severely injured patients demonstrated that factor V, factor VII, and factor IX are predisposed to low levels.[66,80,81] Nevertheless, experimental and clinical studies have demonstrated that TG remains unaffected.[80,82]

Cardenas et al reported that trauma patients upon ER admission had significantly higher TG parameters than uninjured subjects.[76] Only 17% of the patients demonstrated a peak TG of less than 250 nM. However, these patients required more allogeneic blood products, had a fourfold increased risk of massive transfusion, and a threefold increased risk of mortality.[76] Coleman et al also observed high-volume blood transfusion in trauma patients with compromised TG.[83]

Hypercoagulability was also reported by Schreiber et al in 62% of the investigated trauma patients in the first 24 hours after injury, with a female predilection.[84] Hypercoagulability might be related to tissue factor exposure and the additional release of procoagulant microparticles and damage-associated molecular patterns.[85] Thus, it is highly questionable whether an initial augmentation of TG should be considered a primary goal of early hemostatic management in major traumas.[86]

In summary, major tissue trauma creates an initial procoagulant environment driven by tissue factor exposure and the release of procoagulants, resulting in a substantial upregulation of TG. At a later stage, TG can be altered by shock-related activation of the protein C pathway, dilution and consumption of the coagulation factors, hypothermia, and acidosis.

Platelet Dysfunction

Platelets play a vital role in initial clot formation. Activated platelets adhere to the subendothelial collagen of damaged tissues and provide the surface for the assembly of clotting factors to further amplify TG.[87] Moreover, platelets are involved in inflammation and wound healing by recruiting immune cells from the circulation in a P-selectin-dependent mechanism.[88]

There is a growing body of evidence that severe trauma not only affects plasmatic coagulation factors but also compromises platelet function. Platelet dysfunction occurs early after initial tissue injury despite a normal platelet count.[15]

Numerous studies have demonstrated that even mildly impaired platelet aggregation in response to different platelet agonists, such as thrombin and adenosine diphosphate receptor stimulation, is associated with poor outcomes.[15,16,89–92] In a retrospective study, Solomon et al analyzed platelet function in major trauma patients after ER admission. Decreased platelet aggregation assessed by Multiplate was associated with increased mortality.[90] Kutcher et al also measured platelet function by Multiplate aggregometry in severely injured patients on admission and during their hospital stay. Despite a normal platelet count, platelet dysfunction was observed in 45% of patients on admission and in 91% during their hospital stay.[15]

The exact mechanism that promotes platelet dysfunction following trauma remains to be elucidated. Verni et al spiked healthy platelets with plasma collected from trauma patients and detected a significantly diminished response to multiple platelet agonists. The authors suggested that soluble plasma species may downregulate various platelet activation pathways.[91] Another hypothesis suggested that platelets are captured by leukocytes, which was linked to impaired platelet function detected by Multiplate.[17] Vulliamy et al observed a ballooning of platelets induced by histone H4, a damage-associated molecular pattern, which is released in massive quantities after severe injury.[93]

Taken together, platelet dysfunction occurs early after severe trauma independently of platelet count. This initial inhibition of platelet function has been linked to adverse outcomes. Interestingly, recent studies in major trauma

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patients could not demonstrate a clear clinical benefit of early estimation of platelet dysfunction by Multiplate or TEG platelet mapping to improve outcome.[94–96]

Conclusion

TIC is a heterogeneous, dynamic, and complex coagulation disorder that starts early after the initial injury. Many different potential drivers, of which shock-related hypoperfusion seems to be the most critical, have been identified. Advanced understanding of the pathophysiology of TIC, in alliance with innovative coagulation monitors, which allow individualized guidance of hemostatic therapy, has the potential to improve a patient's outcome.

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References

1 Oyeniyi BT, Fox EE, Scerbo M, Tomasek JS, Wade CE, Holcomb JB. Trends in 1029 trauma deaths at a level 1 trauma center: impact of a bleeding control bundle of care. Injury 2017;48(01):5–12
2 Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. J Trauma 1997;42(05):857–861, discussion 861–862
3 Duque P, Mora L, Levy JH, Schöchl H. Pathophysiological response to trauma-induced coagulopathy: a comprehensive review. Anesth Analg 2020;130(03):654–664
4 Floccard B, Rugeri L, Faure A, et al. Early coagulopathy in trauma patients: an on-scene and hospital admission study. Injury 2012; 43(01):26–32
5 MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma 2003;55 (01):39–44
6 Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003;54(06):1127–1130
7 Maegele M, Lefering R, Yucel N, et al; AG Polytrauma of the German Trauma Society (DGU) Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury 2007;38(03):298–304
8 Moore EE, Moore HB, Kornblith LZ, et al. Trauma-induced coagulopathy. Nat Rev Dis Primers 2021;7(01):30
9 Rappold JF, Sheppard FR, Carmichael Ii SP, et al. Venous thromboembolism prophylaxis in the trauma intensive care unit: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document. Trauma Surg Acute Care Open 2021;6(01):e000643
10 Baksaas-Aasen K, Gall LS, Stensballe J, et al. Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial. Intensive Care Med 2021;47(01):49–59
11 Frith D, Goslings JC, Gaarder C, et al. Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. J Thromb Haemost 2010;8(09):1919–1925
12 Bouzat P, Charbit J, Abback PS, et al; PROCOAG Study Group. Efficacy and safety of early administration of 4-factor prothrombin complex concentrate in patients with trauma at risk of massive transfusion: the PROCOAG randomized clinical trial. JAMA 2023;329(16):1367–1375
13 Davenport R, Manson J, De'Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med 2011;39(12):2652–2658
14 Khan S, Brohi K, Chana M, et al; International Trauma Research Network (INTRN) Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage. J Trauma Acute Care Surg 2014;76(03):561–567, discussion 567–568
15 Kutcher ME, Redick BJ, McCreery RC, et al. Characterization of platelet dysfunction after trauma. J Trauma Acute Care Surg 2012; 73(01):13–19
16 Vulliamy P, Montague SJ, Gillespie S, et al. Loss of GPVI and GPIbα contributes to trauma-induced platelet dysfunction in severely injured patients. Blood Adv 2020;4(12):2623–2630
17 Zipperle J, Altenburger K, Ponschab M, et al. Potential role of platelet-leukocyte aggregation in trauma-induced coagulopathy: ex vivo findings. J Trauma Acute Care Surg 2017;82(05):921–926
18 Zipperle J, Schmitt FCF, Schöchl H. Point-of-care, goal-directed management of bleeding in trauma patients. Curr Opin Crit Care 2023;29(06):702–712
19 Connelly CR, Yonge JD, McCully SP, et al. Assessment of three point-of-care platelet function assays in adult trauma patients. J Surg Res 2017;212:260–269
20 Schriner JB, George MJ, Cardenas JC, et al. Platelet function in trauma: is current technology in function testing missing the mark in injured patients? Shock 2022;58(01):1–13
21 Chang R, Fox EE, Greene TJ, et al; PROHS Study Group. Abnormalities of laboratory coagulation tests versus clinically evident coagulopathic bleeding: results from the prehospital resuscitation on helicopters study (PROHS). Surgery 2018;163(04):819–826
22 Chang R, Kerby JD, Kalkwarf KJ, et al; PROPPR Study Group. Earlier time to hemostasis is associated with decreased mortality and rate of complications: Results from the Pragmatic Randomized Optimal Platelet and Plasma Ratio trial. J Trauma Acute Care Surg 2019;87(02):342–349
23 Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J Trauma 2006;60(6, Suppl): S3–S11

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24 Johansson PI, Stensballe J, Ostrowski SR. Erratum to: Shock induced endotheliopathy (SHINE) in acute critical illness: a unifying pathophysiologic mechanism. Crit Care 2017;21(01): 187
25 Cardenas JC, Dong JF, Kozar RA. Injury-induced endotheliopathy: what you need to know. J Trauma Acute Care Surg 2023;95(04): 454–463
26 Haywood-Watson RJ, Holcomb JB, Gonzalez EA, et al. Modulation of syndecan-1 shedding after hemorrhagic shock and resuscitation. PLoS One 2011;6(08):e23530
27 Hofmann N, Zipperle J, Jafarmadar M, et al. experimental models of endotheliopathy: impact of shock severity. Shock 2018;49(05): 564–571
28 Rahbar E, Cardenas JC, Baimukanova G, et al. Endothelial glycocalyx shedding and vascular permeability in severely injured trauma patients. J Transl Med 2015;13:117
29 Xu L, Yu WK, Lin ZL, et al. Chemical sympathectomy attenuates inflammation, glycocalyx shedding and coagulation disorders in rats with acute traumatic coagulopathy. Blood Coagul Fibrinolysis 2015;26(02):152–160
30 Ostrowski SR, Henriksen HH, Stensballe J, et al. Sympathoadrenal activation and endotheliopathy are drivers of hypocoagulability and hyperfibrinolysis in trauma: a prospective observational study of 404 severely injured patients. J Trauma Acute Care Surg 2017;82(02):293–301
31 Johansson PI, Henriksen HH, Stensballe J, et al. Traumatic endotheliopathy: a prospective observational study of 424 severely injured patients. Ann Surg 2017;265(03):597–603
32 Ostrowski SR, Johansson PI. Endothelial glycocalyx degradation induces endogenous heparinization in patients with severe injury and early traumatic coagulopathy. J Trauma Acute Care Surg 2012; 73(01):60–66
33 Zipperle J, Oberladstätter D, Weichselbaum N, et al. Thromboelastometry fails to detect autoheparinization after major trauma and hemorrhagic shock. J Trauma Acute Care Surg 2022;92(03): 535–541
34 Chapman MP, Moore EE, Ramos CR, et al. Fibrinolysis greater than 3% is the critical value for initiation of antifibrinolytic therapy. J Trauma Acute Care Surg 2013;75(06):961–967, discussion 967
35 Cotton BA, Harvin JA, Kostousouv V, et al. Hyperfibrinolysis at admission is an uncommon but highly lethal event associated with shock and prehospital fluid administration. J Trauma Acute Care Surg 2012;73(02):365–370, discussion 370
36 Ives C, Inaba K, Branco BC, et al. Hyperfibrinolysis elicited via thromboelastography predicts mortality in trauma. J Am Coll Surg 2012;215(04):496–502
37 Schöchl H, Frietsch T, Pavelka M, Jámbor C. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. J Trauma 2009;67(01):125–131
38 Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg 2007;245 (05):812–818
39 Cap A, Hunt BJ. The pathogenesis of traumatic coagulopathy. Anaesthesia 2015;70(1, Suppl 1):96–101, e32–e34
40 Schöchl H, Cadamuro J, Seidl S, et al. Hyperfibrinolysis is common in out-of-hospital cardiac arrest: results from a prospective observational thromboelastometry study. Resuscitation 2013; 84(04):454–459
41 Koami H, Sakamoto Y, Furukawa T, Imahase H, Iwamura T, Inoue S. Utility of rotational thromboelastometry for the diagnosis of asymptomatic hyperfibrinolysis secondary to anaphylaxis. Blood Coagul Fibrinolysis 2016;27(04):450–453
42 Schöchl H, Voelckel W, Maegele M, Solomon C. Trauma-associated hyperfibrinolysis. Hamostaseologie 2012;32(01):22–27
43 Taylor JR III, Fox EE, Holcomb JB, et al; PROPPR Study Group. The hyperfibrinolytic phenotype is the most lethal and resource intense presentation of fibrinolysis in massive transfusion patients. J Trauma Acute Care Surg 2018;84(01):25–30
44 Theusinger OM, Wanner GA, Emmert MY, et al. Hyperfibrinolysis diagnosed by rotational thromboelastometry (ROTEM) is associated with higher mortality in patients with severe trauma. Anesth Analg 2011;113(05):1003–1012
45 Farrell MS, Moore EE, Thomas AV, et al. “Death diamond” tracing on thromboelastography as a marker of poor survival after trauma. Am Surg 2022;88(07):1689–1693
46 Moore EE, Moore HB, Thomas SG, et al. Serial “death diamond” TEGs are a bedside indicator of futile resuscitation during massive transfusion. J Trauma Acute Care Surg 2023;95(03):e19–e21
47 Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. J Thromb Haemost 2013;11(02):307–314
48 Johansson PI, Ostrowski SR. Acute coagulopathy of trauma: balancing progressive catecholamine induced endothelial activation and damage by fluid phase anticoagulation. Med Hypotheses 2010;75(06):564–567
49 Moore HB, Moore EE, Neal MD, et al. Fibrinolysis shutdown in trauma: historical review and clinical implications. Anesth Analg 2019;129(03):762–773
50 Shimono K, Ito T, Kamikokuryo C, et al. Damage-associated molecular patterns and fibrinolysis perturbation are associated with lethal outcomes in traumatic injury. Thromb J 2023;21; (01):91
51 Moore HB, Moore EE, Liras IN, et al. Acute fibrinolysis shutdown after injury occurs frequently and increases mortality: a multicenter evaluation of 2,540 severely injured patients. J Am Coll Surg 2016;222(04):347–355
52 Moore HB, Moore EE, Huebner BR, et al. Fibrinolysis shutdown is associated with a fivefold increase in mortality in trauma patients lacking hypersensitivity to tissue plasminogen activator. J Trauma Acute Care Surg 2017;83(06):1014–1022
53 David JS, Lambert A, Bouzat P, et al. Fibrinolytic shutdown diagnosed with rotational thromboelastometry represents a moderate form of coagulopathy associated with transfusion requirement and mortality: a retrospective analysis. Eur J Anaesthesiol 2020;37(03):170–179
54 Liu B, Yang C, Deng Y, et al. Persistent fibrinolysis shutdown is associated with increased mortality in traumatic pancreatic injury. Injury 2023;54(05):1265–1270
55 Meizoso JP, Karcutskie CA, Ray JJ, Namias N, Schulman CI, Proctor KG. Persistent fibrinolysis shutdown is associated with increased mortality in severely injured trauma patients. J Am Coll Surg 2017;224(04):575–582
56 Gall LS, Vulliamy P, Gillespie S, et al; Targeted Action for Curing Trauma-Induced Coagulopathy (TACTIC) partners. The S100A10 pathway mediates an occult hyperfibrinolytic subtype in trauma patients. Ann Surg 2019;269(06):1184–1191
57 Cardenas JC, Wade CE, Cotton BA, et al; PROPPR Study Group. TEG lysis shutdown represents coagulopathy in bleeding trauma patients: analysis of the PROPPR cohort. Shock 2019;51(03): 273–283
58 Duque P, Calvo A, Lockie C, Schöchl H. Pathophysiology of trauma-induced coagulopathy. Transfus Med Rev 2021;35(04):80–86
59 Popescu NI, Lupu C, Lupu F. Disseminated intravascular coagulation and its immune mechanisms. Blood 2022;139(13):1973–1986
60 Schöchl H, Solomon C, Schulz A, et al. Thromboelastometry (TEM) findings in disseminated intravascular coagulation in a pig model of endotoxinemia. Mol Med 2011;17(3–4):266–272
61 Lowe GD, Rumley A, Mackie IJ. Plasma fibrinogen. Ann Clin Biochem 2004;41(Pt 6):430–440
62 Mosesson MW. Fibrinogen and fibrin structure and functions. J Thromb Haemost 2005;3(08):1894–1904
63 Dorgalaleh A, Rashidpanah J. Blood coagulation factor XIII and factor XIII deficiency. Blood Rev 2016;30(06):461–475

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64 Kononova O, Litvinov RI, Blokhin DS, et al. Mechanistic Basis for the Binding of RGD- and AGDV-peptides to the platelet integrin αIIbβ3. Biochemistry 2017;56(13):1932–1942
65 Schlimp CJ, Schöchl H. The role of fibrinogen in trauma-induced coagulopathy. Hamostaseologie 2014;34(01):29–39
66 Chambers LA, Chow SJ, Shaffer LE. Frequency and characteristics of coagulopathy in trauma patients treated with a low- or high-plasma-content massive transfusion protocol. Am J Clin Pathol 2011;136(03):364–370
67 McQuilten ZK, Wood EM, Bailey M, Cameron PA, Cooper DJ. Fibrinogen is an independent predictor of mortality in major trauma patients: a five-year statewide cohort study. Injury 2017; 48(05):1074–1081
68 Rourke C, Curry N, Khan S, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost 2012;10(07):1342–1351
69 Lv K, Yuan Q, Fu P, et al. Impact of fibrinogen level on the prognosis of patients with traumatic brain injury: a single-center analysis of 2570 patients. World J Emerg Surg 2020;15(01):54
70 Hagemo JS, Stanworth S, Juffermans NP, et al. Prevalence, predictors and outcome of hypofibrinogenaemia in trauma: a multicentre observational study. Crit Care 2014;18(02):R52
71 Rossaint R, Afshari A, Bouillon B, et al. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. Crit Care 2023;27:80
72 Martini WZ, Pusateri AE, Uscilowicz JM, Delgado AV, Holcomb JB. Independent contributions of hypothermia and acidosis to coagulopathy in swine. J Trauma 2005;58(05):1002–1009, discussion 1009–1010
73 Martini WZ, Holcomb JB. Acidosis and coagulopathy: the differential effects on fibrinogen synthesis and breakdown in pigs. Ann Surg 2007;246(05):831–835
74 Schlimp CJ, Voelckel W, Inaba K, Maegele M, Ponschab M, Schöchl H. Estimation of plasma fibrinogen levels based on hemoglobin, base excess and Injury Severity Score upon emergency room admission. Crit Care 2013;17(04):R137
75 Schlimp CJ, Ponschab M, Voelckel W, Treichl B, Maegele M, Schöchl H. Fibrinogen levels in trauma patients during the first seven days after fibrinogen concentrate therapy: a retrospective study. Scand J Trauma Resusc Emerg Med 2016;24:29
76 Cardenas JC, Rahbar E, Pommerening MJ, et al. Measuring thrombin generation as a tool for predicting hemostatic potential and transfusion requirements following trauma. J Trauma Acute Care Surg 2014;77(06):839–845
77 Dunbar NM, Chandler WL. Thrombin generation in trauma patients. Transfusion 2009;49(12):2652–2660
78 Meng ZH, Wolberg AS, Monroe DM III, Hoffman M. The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. J Trauma 2003;55(05):886–891
79 Wolberg AS, Meng ZH, Monroe DM III, Hoffman M. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma 2004;56(06): 1221–1228
80 Woolley T, Gwyther R, Parmar K, et al. A prospective observational study of acute traumatic coagulopathy in traumatic bleeding from the battlefield. Transfusion 2020;60(Suppl 3):S52–S61
81 Rizoli SB, Scarpelini S, Callum J, et al. Clotting factor deficiency in early trauma-associated coagulopathy. J Trauma 2011;71(5, Suppl 1):S427–S434
82 Gangloff C, Mingant F, Theron M, et al. New considerations on pathways involved in acute traumatic coagulopathy: the thrombin generation paradox. World J Emerg Surg 2019;14:57
83 Coleman JR, Moore EE, Samuels JM, et al. Whole blood thrombin generation in severely injured patients requiring massive transfusion. J Am Coll Surg 2021;232(05):709–716
84 Schreiber MA, Differding J, Thorborg P, Mayberry JC, Mullins RJ. Hypercoagulability is most prevalent early after injury and in female patients. J Trauma 2005;58(03):475–480, discussion 480–481
85 Holnthoner W, Bonstingl C, Hromada C, et al. Endothelial cell-derived extracellular vesicles size-dependently exert procoagulant activity detected by thromboelastometry. Sci Rep 2017;7(01):3707
86 Schöchl H, Maegele M, Grottke O. Is “thrombin burst” now the worst option in trauma? Shock 2017;47(06):780–781
87 Monroe DM, Hoffman M. What does it take to make the perfect clot? Arterioscler Thromb Vasc Biol 2006;26(01):41–48
88 Ed Rainger G, Chimen M, Harrison MJ, et al. The role of platelets in the recruitment of leukocytes during vascular disease. Platelets 2015;26(06):507–520
89 Sirajuddin S, Valdez C, DePalma L, et al. Inhibition of platelet function is common following even minor injury. J Trauma Acute Care Surg 2016;81(02):328–332
90 Solomon C, Traintinger S, Ziegler B, et al. Platelet function following trauma. A multiple electrode aggregometry study. Thromb Haemost 2011;106(02):322–330
91 Verni CC, Davila A Jr, Balian S, Sims CA, Diamond SL. Platelet dysfunction during trauma involves diverse signaling pathways and an inhibitory activity in patient-derived plasma. J Trauma Acute Care Surg 2019;86(02):250–259
92 Vulliamy P, Kornblith LZ, Kutcher ME, Cohen MJ, Brohi K, Neal MD. Alterations in platelet behavior after major trauma: adaptive or maladaptive? Platelets 2021;32(03):295–304
93 Vulliamy P, Gillespie S, Armstrong PC, Allan HE, Warner TD, Brohi K. Histone H4 induces platelet ballooning and microparticle release during trauma hemorrhage. Proc Natl Acad Sci U S A 2019;116(35):17444–17449
94 Pommer P, Oberladstätter D, Schlimp CJ, et al. multiplate platelet function testing upon emergency room admission fails to provide useful information in major trauma patients not on platelet inhibitors. J Clin Med 2022;11(09):11
95 Stettler GR, Moore EE, Moore HB, et al. Platelet adenosine diphosphate receptor inhibition provides no advantage in predicting need for platelet transfusion or massive transfusion. Surgery 2017;162(06):1286–1294
96 Cannon JW, Dias JD, Kumar MA, et al. Use of thromboelastography in the evaluation and management of patients with traumatic brain injury: a systematic review and meta-analysis. Crit Care Explor 2021;3(09):e0526

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