Trauma-Induced Coagulopathy

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Review Article

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Abstract

Keywords

- trauma
- coagulopathy
- trauma-induced coagulopathy
- bleeding

Zusammenfassung

Schlüsselwörter

- Trauma
- Koagulopathie
- trauma-induzierte Koagulopathie
- Blutung

Trauma-induced coagulopathy (TIC) is a heterogeneous entity that contributes to a significant morbidity and mortality following trauma. The activated protein C system, endotheliopathy and platelet dysfunction have been implicated in the pathogenesis of TIC, although there are still controversies on the exact pathogenesis. TIC can be modified by hypoperfusion, acidosis, hypothermia, haemodilution, underlying disease conditions, preinjury medications as well as genetic predispositions. Current definition of this syndrome is based on laboratory abnormalities that do not easily allow a distinction between adaptive and maladaptive changes of the haemostatic system. The management of the coagulopathy in the early phase of trauma focuses on the treatment of bleeding. The improving quality in the early damage control following trauma has led to a marked reduction in morbidity and mortality. In the later phase, hypercoagulopathy and inflammation contribute to organ dysfunction, venous thromboembolism and poor outcome. Despite considerable advances in trauma management, TIC remains a diagnostic and therapeutic challenge both in the early and late phases of trauma. This review mainly focuses on the pathogenesis of TIC, with a very short discussion on diagnostic and therapeutic principles.

Trauma-induzierte Koaqulopathie ist eine heterogene Entität, die zu einer signifikanten Morbidität und Mortalität nach Trauma beiträgt. Das aktivierte Protein C System, Endotheliopathie und Plättchendysfunktion wurden in der Pathogenese der Trauma-induzierten Koaqulopathie diskutiert. Dennoch gibt es weiterhin Kontroversen über die Pathogenese. Trauma-induzierte Koaqulopathie kann durch Hypoperfusion, Azidose, Hypothermie, bereits vorliegende Erkrankungen, Vormedikation und genetische Prädisposition weiter modifiziert werden. Die aktuelle Definition dieses Syndroms basiert auf abnorme Laborparameter, die eine Unterscheidung zwischen adaptiven und maldaptiven hemostatischen Veränderungen nicht ohne weiteres erlauben. Die Behandlung der Koagulopathie in der Frühphase fokussiert auf die Therapie der Blutung. Die Qualitätssteigerungen in der Frühbehandlung nach Trauma haben zur erheblichen Senkung der Morbidität und Mortalität beigetragen. In der Spätphase tragen Hyperkoagulopathie und Inflammation in der Entstehung der Organdysfunktion und der venösen Thromboembolie und zu einer schlechten Prognose bei. Trotz den erheblichen Fortschritten im Trauma-Management stellt die Trauma-induzierte Koaqulopathie nach wie vor sowohl in der Früh- als auch Spätphase eine diagnostische und therapeutische Herausforderung dar. Diese Übersicht fokussiert hauptsächlich auf die Pathogenese der Trauma-induzierten Koagulopathie, mit einer sehr kurzen Diskussion über diagnostische und therapeutische Prinzipien.

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Introduction

Trauma is one of the major global public health challenges. For the year 2013, it was estimated that 973 million people suffered injuries that warranted some type of medical service and 4.8 million people died. Injuries accounted for 10.1% of the global disease burden in 2013, mainly affecting the younger age group. Although advances in trauma and intensive care as well as the widespread implementation of damage control principles resulted in a decline in death rates, the death toll due to trauma is still high. According to a recent retrospective analysis of a large cohort, the prevalence of trauma death has declined since 1983, but the majority of deaths (56%) still occur within the first 24 hours after injury.

Uncontrolled post-traumatic bleeding, which is a major concern in the early phase of trauma resuscitation, is the leading cause of potentially preventable death.^{4–6} There are two mechanisms of bleeding following an injury: anatomical bleeding as a result of blood vessel damage and bleeding due to coagulopathy. Anatomical bleeding can be frequently managed through damage control strategies, which resulted in a decline in the mortality rate attributed to haemorrhage.⁷ However, the coagulopathy following the injury may lead to a haemostatic dysfunction that can significantly contribute to further bleeding, organ dysfunction and poor clinical outcome.

During further course of trauma management, particularly in patients with severe injuries, hypercoagulopathy can ensue, which is associated with thromboembolic events and multiple organ dysfunction. Trauma induces local and systemic inflammation, similar to that described in sepsis. Inflammation, in turn, leads to initiation and propagation of the coagulation cascade, while coagulation also influences inflammation. Although their incidence has declined as a result of improved trauma management, multiple organ dysfunction and sepsis are frequent causes of late death following trauma.⁸

Depending on the criteria applied and the severity of injury, coagulopathy can be detected in up to 56% of trauma patients in the early phase of trauma (**Table 1**). However, defining a coagulopathy based on laboratory abnormalities alone does not necessarily translate into a clinically relevant coagulopathy. 18

Mechanisms of Trauma-Induced Coagulopathy

Haemostasis is a complex process at the centre of the body's defence and wound healing system. Physiologic haemostasis is a balance between pro- and anti-coagulation as well as fibrinolysis and anti-fibrinolysis. This process takes place on the surface of endothelial cells and platelets. The intact endothelium is anti-thrombotic, this property being maintained by several mediators, including tissue factor pathway inhibitor, endothelial protein C receptors, endothelial glycocalyx layer (EGL), thrombomodulin, nitric oxide, and tissue plasminogen activator. The EGL is a matrix of macromolecules, which is not only anti-coagulant but also important to maintain microvascular integrity. The most prominent among these molecules are heparan sulfates, accounting for 50 to 90% of the total pool, the rest being mainly chondroitin sulfates and hyaluronic acid. The EGL is a sort of endothelial gatekeeper.

An injury to a vessel wall exposes the subendothelial collagen that provides an adhesion platform for circulating platelets as well as for the interplay between the cellular and humoral components of the haemostatic system. This procoagulant activity is controlled by counter-regulatory anticoagulant cascades. The net effect of these two opposing systems may be generation of pro-coagulation at the site of endothelial injury, while preventing uncontrolled microvascular thrombosis and tissue hypoperfusion by means of endogenous anti-coagulation and fibrinolysis. Thrombin plays a central role in this process by activating both coagulation and anti-coagulation as well as contributing to the crosstalk with the inflammatory response.²²

The activated protein C (APC) system has been considered as a major player in the development of trauma-induced coagulopathy (TIC). APC is a physiologic anti-coagulant that irreversibly inactivates the pro-coagulant factors Va and VIIIa. It is also profibrinolytic by inhibiting plasminogen activator inhibitor-1 (PAI-1). APC is also cytoprotective through anti-inflammatory and anti-apoptotic mechanisms. Results from a mouse model indicated the role of APC in the endogenous coagulopathy following trauma.²³ In a single-centre study in 203 patients

 Table 1 Prevalence of trauma-induced coagulopathy (TIC)

Ref.	N	TIC criteria	Prevalence (%)
Brohi et al ⁹	1,088	PT or aPTT or TT	24.4
MacLeod et al ¹⁰	10,790	PT	28.0
Maegele et al ¹¹	8,724	PT or platelet count	34.2
Hess et al ¹²	15,728	INR, aPTT, platelet count, or fibrinogen concentration	5.5 up to 43.1, depending on injury severity
Floccard et al ¹³	45	ISTH DIC score	56.0
Cohen et al ¹⁴	1,198	INR	41.6
MacLeod et al ¹⁵	701	PT	16.3
Hagemo et al ¹⁶	808	INR	11.0
Fröhlich et al ¹⁷	61,212	PT and/or platelet count	24.5

Abbreviations: aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; PT, prothrombin time; TT, thrombin time.

with major trauma (mean injury severity score [ISS]: 25.2), a marked increase in APC was observed in those with an ISS > 15 and a base deficit >6. The same study showed a correlation between protein C depletion in the first 12 hours and increased risk of ventilator-associated pneumonia.²⁴ A subsequent publication using data from the Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study supported the assumption that APC may have an important role in the development of TIC. In the PROMMTT study, which included 1,245 severely injured patients (mean ISS: 26.2), acute traumatic coagulopathy identified on arrival to the emergency department was associated with a depletion of the pro-coagulant factors I, II, V, VII, VIII, IX and X on the one hand and activation of the protein C system on the other. 14 A recent study by Davenport et al also showed that elevated APC concentration was associated with excess mortality and morbidity following TIC. In the second part of the same study using a murine model, mortality rate following trauma haemorrhage in transgenic mice with 1,000-fold reduced capacity to activate protein C was almost half that of wild-type mice, suggesting a central role of the protein C pathway in early TIC.²⁵ However, the data on APC in trauma are inconsistent. A recent study comparing 25 trauma patients with hyperfibrinolysis identified using thromboelastography with 14 healthy controls showed a significant early increase in tissue plasminogen activator but not PAI-1 following a severe injury. ²⁶ This finding thus challenges the apparent role of APC-mediated hyperfibrinolysis. A recent systematic literature review concluded that there may not be a direct causeeffect relationship between APC and increased fibrinolysis.²⁷ This contradiction is not surprising, taking into consideration the complexity of the haemostatic system and the crosstalk with the myriad of mediators released following a trauma. 14

Trauma activates the neurohumoral system that results in a catecholamine surge. This increase in catecholamine levels leads to an endothelial damage and glycocalyx degradation, generally known as endotheliopathy. A prospective study using blood samples from adult trauma patients directly admitted to a trauma centre showed that adrenaline level was increased in non-survivors, and this was independently associated with an increase in syndecan-1, which is a marker of glycocalyx degradation. The increase in adrenalin also correlated with biomarkers of endothelial damage and hyperfibrinolysis.²⁸ A recent study confirmed that high adrenaline levels and glycocalyx damage are associated with hypocoagulopathy and hyperfibrinolysis.²⁹ A high level of syndecan-1 in trauma patients was also associated with increased inflammation and endothelial damage. 30 Shedding of EGL components may also contribute to autoheparinization, which was observed in approximately 5% of trauma patients, and this was associated with a high ISS. 31 Endotheliopathy may also contribute to a capillary leak following trauma. 32 A secondary analysis of the data from 512 patients included in the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial showed that, after adjusting for ISS and transfusion requirements, elevated serum syndecan-1 levels were independently associated with the development of sepsis during hospitalization.³³ In a recent prospective observational study in 424 trauma patients, Johansson

et al showed that both adrenaline and syndecan-1 were independent predictors of <24 hours, 7-day and 28-day mortality.³⁴ An animal study using male Sprague-Dawley rats showed that sympathetic denervation was anti-inflammatory, anti-fibrinolytic and endothelial protective in rats with acute traumatic coagulopathy, confirming the role of catecholamines in TIC.35

Hypofibrinogenemia as a consequence of TIC is frequently observed in the early phase of trauma. In a multicentre observational study from the United States,³⁶ including 1.133 trauma patients who arrived in a hospital within 180 minutes post-injury, a fibrinogen concentration <2 g/L measured by the Clauss method was identified in 19.2% of the patients. In another observational study on major trauma patients from Australia, 12.9% of the patients had fibrinogen levels < 1.9 g/L during the initial resuscitation. 37 Low fibrinogen level was in both studies associated with a poor outcome. The age-associated increase in fibrinogen level should be kept in mind when interpreting results.³⁸

Platelets contain a plethora of proteins involved in coagulation and fibrinolysis. It is not yet clear how these contradictory platelet secretions are exactly affecting TIC. Data on platelet function testing in trauma patients are scant, because platelet sample handling and availability of specific assays are complicated. One older small prospective observational study using thromboelastography (TEG)-based platelet functional analysis in whole blood samples collected from trauma patients at risk of TIC immediately after injury and before blood or substantial fluid administration showed a significantly impaired platelet aggregation in response to adenosine diphosphate (ADP) and arachidonic acid, whereby the ADP inhibition was more pronounced.³⁹ Another study on 101 trauma patients using multiple-electrode impedance aggregometry also showed platelet dysfunction in response to ADP, arachidonic acid, collagen and thrombin receptor activating peptide (TRAP), with response to the first three agonists markedly reduced within the first 24 hours. 40 In that study, platelet dysfunction was observed in 45.5% of trauma patients on admission and 91.1% at some time during their intensive care unit (ICU) stay. In another small more recent study on 40 trauma patients, a significantly decreased ADPand TRAP-mediated platelet aggregation was observed, suggesting that thrombin receptor pathway plays an important role in trauma-induced platelet dysfunction.⁴¹ Platelet dysfunction seems to be ubiquitous even in minor trauma. In a recent study, platelet dysfunction identified with TEG-platelet mapping was reported on 459 patients with minor trauma (median ISS: 5).42 However, the mechanisms and the implication of this finding are not clear. Anaemia, be it due to haemorrhage or dilutional, can also affect platelet adhesion. In vitro experiments have shown the dependence of platelet adhesion on haematocrit. 43 Considering the available evidence, endotheliopathy and anaemia may be the triggers for platelet dysfunction in trauma.

While hyperfibrinolysis has been discussed as a major event in early TIC, a trauma-induced fibrinolytic shutdown is also demonstrated.⁴⁴ A study by Moore et al showed that there is a U-shaped distribution of mortality related to

fibrinolysis in response to a major trauma, warning that inadvertent exogenous inhibition of fibrinolysis may have an adverse effect on survival. 45 Fibrinolysis shutdown may even be an adaptive physiologic response to trauma. 46

Shock is an independent risk factor for trauma coagulopathy. 14,47,48 The true incidence of shock in trauma is not clear, since systolic blood pressure was frequently used in several studies as a determinant of hypoperfusion. Traumatic brain injury further hampers the use of blood pressure measurements as a sign of hypoperfusion.⁴⁹

Hypothermia, acidosis and haemodilution are also associated with the development of TIC. Hypothermia can ensue following a trauma as a result of heat loss, reduced heat production and administration of fluids. Clinically significant reduction in platelet function and coagulation factor activity ensues at a core body temperature below 33°C. 50-52

Metabolic acidosis, mostly associated with shock, leads to a reduction in the activity of coagulation factors. 50,53 In a swine model, acidosis, but not hypothermia, resulted in a decrease in plasma fibrinogen concentration by 18%.⁵⁴ Acidosis accelerated fibrinogen consumption, while it did not affect fibrinogen production.⁵⁵ The administration of bicarbonate to correct acidosis is not associated with a reversal of the coagulopathy.⁵⁶ Finally, pre-clinical fluid administration also contributes to the development of a dilutional coagulopathy, 11,14,57 with the incidence of coagulopathy rising with increasing amount of fluid administered. 11

In summary, the pathogenesis of early coagulopathy is multifactorial, with the balance between pro- and anti-coagulation influenced by injury severity, hypoperfusion, acidosis, hypothermia, underlying disease conditions, medication history and genetic predispositions as well as emergency treatment (►Fig. 1).

Late Coagulopathy

The haemostatic reaction following trauma returns to baseline during recovery in patients without complications, while

patients with severe injury may suffer from the sequelae of massive coagulopathy. Recovery of the coagulopathy after severe trauma may be delayed in such patients.⁵⁸ There is a massive reorganization of the human genome following trauma, which leads to a multitude of changes in innate immunity and inflammation. 59,60 Trauma also results in an uncontrolled local and systemic release of damage-associated molecular patterns (DAMPs) that trigger an inflammatory response.⁶¹

Similar to the haemostatic response, it remains difficult to distinguish between adaptive and maladaptive systemic inflammatory responses to injury. From clinical viewpoint, the feasible means to identify maladaptive systemic inflammation is at present the identification of organ dysfunction, in analogy to the current definition of sepsis.⁶² Almost 30% of severely injured patients develop a multiple organ dysfunction syndrome (MODS) and this is associated with a high risk for nosocomial infections. 60,63 Similar to TIC, inflammation and infection result in a chain of coagulopathies that may culminate into a disseminated intravascular coagulopathy (DIC),⁶⁴ which is associated with a significantly high mortality rate. 65 The late hypercoagulopathy following trauma also contributes to an increased risk of venous thromboembolism (Fig. 2).66-70

Diagnosis of Trauma-Induced Coagulopathy

The diagnosis of TIC is still based on laboratory abnormalities that may not necessarily correspond to a distinct clinical phenotype. Despite significant advances in coagulation research, there is no adequately valid test to predict and identify a clinically relevant acquired coagulopathy. Published reports on TIC have been mostly based on the evidence of abnormal laboratory findings of prothrombin time, activated partial thromboplastin time, plasma fibrinogen concentration, platelet count, either alone or in combination. However, an important caveat in this regard is comparing data from patients with those of the healthy population without due consideration of the physiological adaptive changes of the haemostatic system in trauma.

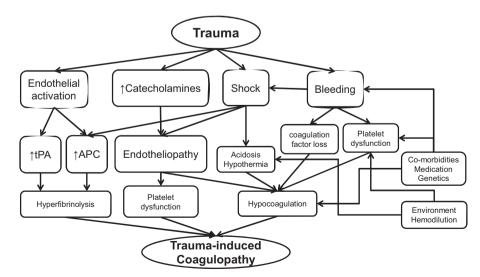


Fig. 1 Mechanisms of early trauma-induced coagulopathy (TIC). Patient factors (medication, comorbidities, genetic polymorphism) as well as environmental factors (heat loss) or iatrogenic injury (e.g. haemodilution) modify TIC.

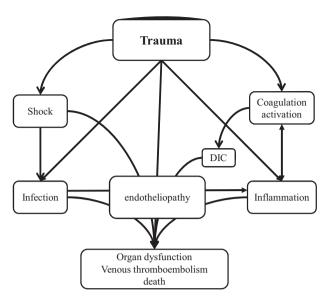


Fig. 2 Consequences of late coagulopathy in trauma. Damage to the endothelium plays a crucial role in inflammation and infection.

Viscoelastic point-of-care tests are increasingly used to diagnosis and manage TIC-associated bleeding. However, published data are mostly retrospective and/or observational. 71–74 Despite these drawbacks, viscoelastic point-of-care tests can help trauma caregivers to establish algorithms for rapid diagnosis of relevant bleeding diathesis and appropriate use of haemostatic drugs. Nevertheless, the extra-haemostatic effects of coagulation, such as its role in inflammation and immune modulation, are still difficult to characterize, let alone identify with routine laboratory assays.

Treatment of Trauma-Induced Coagulopathy

Changes in the haemostatic system following a trauma should be viewed in two ways. First, the urgent need in the early phase of trauma is to treat and avoid bleeding. The second issue, which is even more difficult to diagnose as well as manage, is the role and the dynamics of haemostasis in the development of organ dysfunction following trauma. There are limitations regarding conclusions derived from available evidence, because data from published studies show considerable heterogeneity in study design, study population and outcome measures.⁷⁵ Evidence for clinically meaningful modification of the haemostatic system in relation to inflammation and organ dysfunction is still lacking.

Early appropriate damage control contributes to the reduction of the incidence of TIC. Beyond the mechanical management of bleeding, hyperfibrinolysis during the early phase of TIC has been the subject of research and treatment strategies. The CRASH-2 trial has shown that early administration of tranexamic acid in adult trauma patients with, or at risk of, significant bleeding was associated with a reduced risk of death. Guidelines for transfusion of red blood cells and platelets as well as administration of pro-coagulant factors in the management of bleeding have been developed based on available evidence. Although such algorithms may help standardize the use of blood products, there are still several

controversial issues to be considered. First, the use of fresh frozen plasma (FFP) in TIC is declining. While FFP may be a better volume replacement than a crystalloid solution during trauma management, it is not efficient in correcting a coagulopathy. Second, platelet count does not necessarily correlate with platelet function. There is still a lack of appropriate routine laboratory assays to test for platelet function during trauma, so that treatment recommendations are still mainly empirical. Third, current management strategies do not address the role of the coagulation system in inflammation due to lack of appropriate diagnostic tools. For instance, a very important lesson from the CRASH-2 trial is that administration of tranexamic acid later than 3 hours after trauma was associated with a poor outcome.⁷⁶ This underscores the dynamics of the coagulation system and the role of every coagulation step in the inflammation and wound healing process. Both hyperfibrinolysis and fibrinolysis shutdown are part of this adaptive system, so that inadvertent exogenous manipulation of these steps may be harmful.

Conclusion

TIC is a complex heterogeneous syndrome with a multitude of pathogenetic factors, which include both adaptive and maladaptive changes in the haemostatic system. Comparing differences in laboratory parameters between trauma patients and healthy controls is not an ideal design to differentiate between adaptive and maladaptive changes following trauma. Based on available data, it is difficult to discern between simple association and cause–effect relationships. More high-quality research is still required to better define TIC both in the early and late phases and establish optimal treatment targets.

Conflict of Interest

The author received research grant from CSL Behring and Bayer Vital as well as honoraria and/or travel reimbursements over the last three years for lectures on topics of coagulation, but not related to trauma, from CSL Behring and Boehringer Ingelheim.

References

- 1 Haagsma JA, Graetz N, Bolliger I, et al. The global burden of injury: incidence, mortality, disability-adjusted life years and time trends from the Global Burden of Disease study 2013. Inj Prev 2016;22(01):3–18
- 2 Bardes JM, Inaba K, Schellenberg M, et al. The contemporary timing of trauma deaths. J Trauma Acute Care Surg 2018;84(06): 893–899
- 3 Valdez C, Sarani B, Young H, Amdur R, Dunne J, Chawla LS. Timing of death after traumatic injury-a contemporary assessment of the temporal distribution of death. J Surg Res 2016;200(02):604-609
- 4 Evans JA, van Wessem KJ, McDougall D, Lee KA, Lyons T, Balogh ZJ. Epidemiology of traumatic deaths: comprehensive populationbased assessment. World J Surg 2010;34(01):158–163
- 5 Holcomb JB, del Junco DJ, Fox EE, et al; PROMMTT Study Group. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a timevarying treatment with competing risks. JAMA Surg 2013;148 (02):127–136

- 6 Saar S, Lomp A, Laos J, et al. Population-based autopsy study of traumatic fatalities. World J Surg 2017;41(07):1790–1795
- 7 Jochems D, Leenen LPH, Hietbrink F, Houwert RM, van Wessem KJP. Increased reduction in exsanguination rates leaves brain injury as the only major cause of death in blunt trauma. Injury 2018;49(09):1661–1667
- 8 Sobrino J, Shafi S. Timing and causes of death after injuries. Proc Bayl Univ Med Cent 2013;26(02):120–123
- 9 Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003;54(06):1127–1130
- 10 MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma 2003;55 (01):39–44
- 11 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
- 12 Hess JR, Lindell AL, Stansbury LG, Dutton RP, Scalea TM. The prevalence of abnormal results of conventional coagulation tests on admission to a trauma center. Transfusion 2009;49(01):34–39
- 13 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
- 14 Cohen MJ, Kutcher M, Redick B, et al; PROMMTT Study Group. Clinical and mechanistic drivers of acute traumatic coagulopathy. J Trauma Acute Care Surg 2013;75(01, Suppl 1):S40–S47
- 15 MacLeod JB, Winkler AM, McCoy CC, Hillyer CD, Shaz BH. Early trauma induced coagulopathy (ETIC): prevalence across the injury spectrum. Injury 2014;45(05):910–915
- 16 Hagemo JS, Christiaans SC, Stanworth SJ, et al. Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study. Crit Care 2015;19:97
- 17 Fröhlich M, Mutschler M, Caspers M, et al; TraumaRegister DGU. Trauma-induced coagulopathy upon emergency room arrival: still a significant problem despite increased awareness and management? Eur J Trauma Emerg Surg 2017 (e-pub ahead of print)
- 18 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
- 19 Hoffman M, Monroe DM III. A cell-based model of hemostasis. Thromb Haemost 2001;85(06):958–965
- 20 Weinbaum S, Tarbell JM, Damiano ER. The structure and function of the endothelial glycocalyx layer. Annu Rev Biomed Eng 2007; 9:121–167
- 21 Reitsma S, Slaaf DW, Vink H, van Zandvoort MA, oude Egbrink MG. The endothelial glycocalyx: composition, functions, and visualization. Pflugers Arch 2007;454(03):345–359
- 22 Crawley JT, Zanardelli S, Chion CK, Lane DA. The central role of thrombin in hemostasis. J Thromb Haemost 2007;5(Suppl 1):95–101
- 23 Chesebro BB, Rahn P, Carles M, et al. Increase in activated protein C mediates acute traumatic coagulopathy in mice. Shock 2009;32 (06):659–665
- 24 Cohen MJ, Call M, Nelson M, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. Ann Surg 2012;255(02):379–385
- 25 Davenport RA, Guerreiro M, Frith D, et al. Activated protein C drives the hyperfibrinolysis of acute traumatic coagulopathy. Anesthesiology 2017;126(01):115–127
- 26 Chapman MP, Moore EE, Moore HB, et al. Overwhelming tPA release, not PAI-1 degradation, is responsible for hyperfibrinolysis in severely injured trauma patients. J Trauma Acute Care Surg 2016;80(01):16–23, discussion 23–25
- 27 Gando S, Mayumi T, Ukai T. Activated protein C plays no major roles in the inhibition of coagulation or increased fibrinolysis in acute coagulopathy of trauma-shock: a systematic review. Thromb J 2018; 16:13

- 28 Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR. High circulating adrenaline levels at admission predict increased mortality after trauma. J Trauma Acute Care Surg 2012;72(02): 428–436
- 29 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
- 30 Johansson Pl, Stensballe J, Rasmussen LS, Ostrowski SR. A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis, and increased mortality in trauma patients. Ann Surg 2011;254(02):194–200
- 31 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
- 32 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
- 33 Wei S, Gonzalez Rodriguez E, Chang R, Holcomb JB, Kao LS, Wade CE; PROPPR Study Group. Elevated syndecan-1 after trauma and risk of sepsis: a secondary analysis of patients from the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial. J Am Coll Surg 2018;227(06):587–595
- 34 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
- 35 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
- 36 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
- 37 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
- 38 Ohmori T, Kitamura T, Tanaka K, et al. Admission fibrinogen levels in severe trauma patients: a comparison of elderly and younger patients. Injury 2015;46(09):1779–1783
- 39 Wohlauer MV, Moore EE, Thomas S, et al. Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. J Am Coll Surg 2012;214(05):739–746
- 40 Kutcher ME, Redick BJ, McCreery RC, et al. Characterization of platelet dysfunction after trauma. J Trauma Acute Care Surg 2012; 73(01):13–19
- 41 Ramsey MT, Fabian TC, Shahan CP, et al. A prospective study of platelet function in trauma patients. J Trauma Acute Care Surg 2016;80(05):726–732, discussion 732–733
- 42 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
- 43 Spann AP, Campbell JE, Fitzgibbon SR, et al. The effect of hematocrit on platelet adhesion: experiments and simulations. Biophys J 2016;111(03):577–588
- 44 Barrett CD, Moore HB, Banerjee A, Silliman CC, Moore EE, Yaffe MB. Human neutrophil elastase mediates fibrinolysis shutdown through competitive degradation of plasminogen and generation of angiostatin. J Trauma Acute Care Surg 2017;83(06):1053–1061
- Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. J Trauma Acute Care Surg 2014;77(06):811–817, discussion 817
- 46 Gomez-Builes JC, Acuna SA, Nascimento B, Madotto F, Rizoli SB. Harmful or physiologic: diagnosing fibrinolysis shutdown in a

- trauma cohort with rotational thromboelastometry. Anesth Analg 2018;127(04):840-849
- 47 Brohi K, Cohen MJ, Ganter MT, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma 2008;64(05):1211-1217, discussion 1217
- 48 Jansen JO, Scarpelini S, Pinto R, Tien HC, Callum J, Rizoli SB. Hypoperfusion in severely injured trauma patients is associated with reduced coagulation factor activity. J Trauma 2011;71(05, Suppl 1):S435-S440
- 49 Lechleuthner A, Lefering R, Bouillon B, Lentke E, Vorweg M, Tiling T. Prehospital detection of uncontrolled haemorrhage in blunt trauma. Eur J Emerg Med 1994;1(01):13-18
- 50 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
- 51 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
- 52 Mitrophanov AY, Rosendaal FR, Reifman J. Computational analysis of the effects of reduced temperature on thrombin generation: the contributions of hypothermia to coagulopathy. Anesth Analg 2013;117(03):565-574
- 53 Engström M, Schött U, Romner B, Reinstrup P. Acidosis impairs the coagulation: a thromboelastographic study. J Trauma 2006;61 (03):624-628
- 54 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
- 55 Martini WZ, Holcomb JB. Acidosis and coagulopathy: the differential effects on fibrinogen synthesis and breakdown in pigs. Ann Surg 2007;246(05):831-835
- 56 Martini WZ, Dubick MA, Pusateri AE, Park MS, Ryan KL, Holcomb JB. Does bicarbonate correct coagulation function impaired by acidosis in swine? J Trauma 2006;61(01):99-106
- 57 Hussmann B, Lefering R, Waydhas C, et al; Trauma Registry of the German Society for Trauma Surgery. Does increased prehospital replacement volume lead to a poor clinical course and an increased mortality? A matched-pair analysis of 1896 patients of the Trauma Registry of the German Society for Trauma Surgery who were managed by an emergency doctor at the accident site. Injury 2013;44(05):611-617
- 58 McCully BH, Connelly CR, Fair KA, et al; PROPPR Study Group. Onset of coagulation function recovery is delayed in severely injured trauma patients with venous thromboembolism. J Am Coll Surg 2017;225(01):42-51
- 59 Tompkins RG. Genomics of injury: the glue grant experience. J Trauma Acute Care Surg 2015;78(04):671-686
- 60 Lord JM, Midwinter MJ, Chen YF, et al. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet 2014;384(9952):1455-1465
- 61 Bortolotti P, Faure E, Kipnis E. Inflammasomes in tissue damages and immune disorders after trauma. Front Immunol 2018;9:1900
- 62 Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(08):801-810

- 63 Minei JP, Cuschieri J, Sperry J, et al; Inflammation and the Host Response to Injury Collaborative Research Program. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. Crit Care Med 2012;40(04):1129-1135
- Levi M, van der Poll T. Coagulation and sepsis. Thromb Res 2017; 149:38-44
- 65 Dhainaut JF, Yan SB, Joyce DE, et al. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. J Thromb Haemost 2004;2(11):1924-1933
- Van Haren RM, Valle EJ, Thorson CM, et al. Hypercoagulability and other risk factors in trauma intensive care unit patients with venous thromboembolism. J Trauma Acute Care Surg 2014;76(02):443-449
- Hamada SR, Espina C, Guedj T, et al. High level of venous thromboembolism in critically ill trauma patients despite early and well-driven thromboprophylaxis protocol. Ann Intensive Care 2017;7(01):97
- Skrifvars MB, Bailey M, Presneill J, et al; EPO-TBI investigators and the ANZICS Clinical Trials Group. Venous thromboembolic events in critically ill traumatic brain injury patients. Intensive Care Med 2017:43(03):419-428
- Van Gent JM, Calvo RY, Zander AL, et al. Risk factors for deep vein thrombosis and pulmonary embolism after traumatic injury: a competing risks analysis. J Trauma Acute Care Surg 2017;83(06): 1154-1160
- Sumislawski JJ, Kornblith LZ, Conroy AS, Callcut RA, Cohen MJ. Dynamic coagulability after injury: is delaying venous thromboembolism chemoprophylaxis worth the wait? J Trauma Acute Care Surg 2018;85(05):907-914
- Hunt H, Stanworth S, Curry N, et al. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding. Cochrane Database Syst Rev 2015;(02):CD010438
- Hanke AA, Horstmann H, Wilhelmi M. Point-of-care monitoring for the management of trauma-induced bleeding. Curr Opin Anaesthesiol 2017;30(02):250-256
- 73 Kelly JM, Rizoli S, Veigas P, Hollands S, Min A. Using rotational thromboelastometry clot firmness at 5 minutes (ROTEM® EXTEM A5) to predict massive transfusion and in-hospital mortality in trauma: a retrospective analysis of 1146 patients. Anaesthesia 2018;73(09):1103-1109
- 74 Mohamed M, Majeske K, Sachwani GR, Kennedy K, Salib M, McCann M. The impact of early thromboelastography directed therapy in trauma resuscitation. Scand I Trauma Resusc Emerg Med 2017;25(01):99
- Balvers K, Wirtz MR, van Dieren S, Goslings JC, Juffermans NP. Risk factors for trauma-induced coagulopathy- and transfusion-associated multiple organ failure in severely injured trauma patients. Front Med (Lausanne) 2015;2:24
- Shakur H, Roberts I, Bautista R, et al; CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376(9734):23-32
- Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care 2016;20:100