Opinion Paper

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Overview of laboratory diagnostics for immediate management of patients presenting to the emergency department with acute bleeding

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Abstract: Acute, life-threatening bleeding is a relatively common but critical presentation in the emergency department (ED), needing immediate assessment and intervention to reduce morbidity and mortality. Rapid identification of the bleeding source, evaluation of hemostatic function, and timely initiation of resuscitation are essential components of early management. Laboratory diagnostics plays a central role in this process, enabling clinicians to stratify the risk, guide therapeutic decisions, and predict outcomes. This opinion paper summarizes current evidence supporting the use of a core panel of laboratory tests in the initial evaluation of patients with emergency bleeding admitted to the ED. The leading characteristics of these initial tests encompass elevated diagnostic sensitivity, high precision and reproducibility, broad analytical measurement range, minimal turnaround time, low sample volume requirements, continuous availability, accessible measurement uncertainty, and proven clinical impact. The hypothetical core tests may include hemoglobin, blood lactate, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, platelet count, viscoelastic assays, specific tests for measuring direct oral anticoagulants (DOACs), cardiac troponins and other organ-specific tests in patients with signs and symptoms of hypovolemic shock-induced organ failure. We believe that early implementation of a targeted, evidence-based initial laboratory diagnostic strategy in patients presenting to the ED with severely acute bleeding may support more effective resuscitation and transfusion protocols, reduce unnecessary interventions, and improve clinical outcomes.

Keywords: bleeding; laboratory testing; diagnosis; emergency department

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Introduction

The hemostatic system is traditionally described as a finely tuned balance between forces that maintain blood fluidity within intact vessels and those that prevent excessive blood loss following vascular injury (Figure 1). Effective hemostasis – the process of arresting bleeding from damaged vessels – requires the activation and coordinated function of a complex system involving two principal phases: platelet-vessel interaction and blood coagulation. The first phase, known as primary hemostasis, primarily involves the formation of a transient platelet plug, consisting mainly of platelets adhering to the exposed subendothelial matrix (“adhesion”) and linking to one another (“aggregation”), in part mediated by the plasma protein von Willebrand factor (VWF). The second phase, or secondary hemostasis, entails a cascade of coagulation factor-mediated reactions that culminate in the generation of fibrin, which stabilizes the initial platelet plug [1]. These processes are tightly regulated by inhibitory mechanisms that prevent inappropriate or prolonged clot formation. Like other physiological systems governed by a balance of opposing forces, hemostasis can be

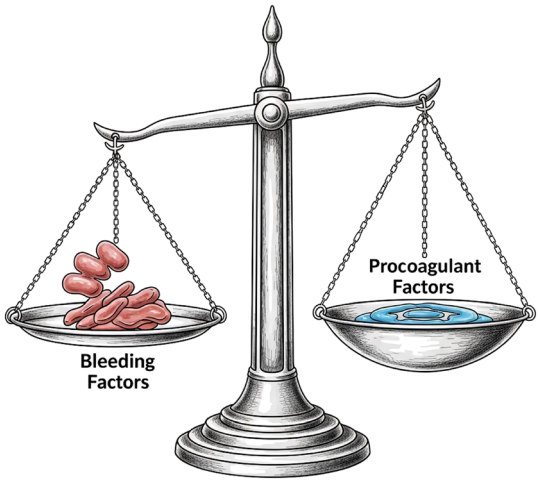

Figure 1: The delicate hemostatic balance: Interplay between procoagulant and anticoagulant forces.

pathologically shifted toward a procoagulant state, resulting in venous or arterial thrombosis, or toward a hemorrhagic state, predisposing individuals to bleeding complications of varying severity depending on the hemostatic response and the magnitude of the insult (Figure 1) [2].

Emergency bleeding is a clinical condition characterized by rapid and severe blood loss that poses a life-threatening risk if not rapidly controlled. This bleeding can manifest externally, through visible wounds or natural body openings, or internally, where blood loss occurs within the body without immediate external signs [3]. In the absence of visible external bleeding, significant internal hemorrhage must be actively sought, particularly in the thorax and abdomen, as well as from fractures of the pelvis or long bones. Multiple etiologies may coexist and interact synergistically to precipitate or exacerbate bleeding severity (Table 1). For instance, patients with minor bleeding triggers such as peptic ulcers or hemorrhoids may develop clinically significant hemorrhages when concurrently receiving anticoagulant or antiplatelet therapy. Key features defining emergency bleeding include: (i) severity, characterized by substantial blood loss often described as heavy, continuous flow or arterial spurting; (ii) persistence, indicating protracted bleeding that continues unless effectively managed; and (iii) lack of control, whereby bleeding does not cease or diminish with initial pressure or standard first aid measures [4].

The most widely used system for classifying the severity of emergency bleeding is the American College of Surgeons (ACS) Advanced Trauma Life Support (ATLS) classification, which stratifies patients into four classes based primarily on estimated blood loss: Class I (<15 %), Class II (mild; 15 %–30 %), Class III (moderate; 31 %–40 %), and Class IV (severe; >40 %) [4]. Additional clinical parameters used within the ATLS framework to refine bleeding severity classification include heart rate, blood pressure, pulse pressure, respiratory rate, urine output, Glasgow Coma Scale, base deficit, and requirements for blood product transfusion.

Epidemiology and initial approach to emergency bleeding

The prevalence of patients presenting with emergency bleeding in the emergency department (ED) varies according to patient demographics, hemorrhage source, and healthcare setting. Non-traumatic bleeding events represent approximately 1.4 % of all ED visits, most commonly due to epistaxis and gastrointestinal bleeding [5], whereas post-traumatic bleeding severe enough to be classified as “major” accounts for 0.5 %–1 % of ED visits [3]. Regardless of etiology, patients presenting with emergency bleeding require immediate clinical management through a multidisciplinary approach. As emphasized in the European guidelines on the management of major bleeding and coagulopathy [6], initial assessment using the ‘ABCDE check’ (Airway, Breathing, Circulation, Disability, Exposure) should focus on determining the extent of hemorrhage by integrating physiological parameters, anatomical injury patterns, underlying causes, and the patient’s initial response to resuscitation. Several scoring systems have been developed to classify the severity of acute traumatic coagulopathies, including the COAST (COAgulopathy of Severe Trauma) [7], TICCS (Trauma-Induced Coagulopathy Clinical Score) [8], and PACT (Prediction of Acute Traumatic Coagulopathy) [9], which may guide the request for urgent laboratory tests to characterize the clinical severity and therapeutic management (Table 2).

Characteristics of laboratory tests for management of emergency bleeding

For a laboratory test to be effective and appropriate in managing emergency bleeding in patients presenting to the ED, it must satisfy several critical analytical and practical criteria (Table 3). These criteria include high sensitivity for detecting even subtle bleeding disorders or coagulopathies, as well as high precision and reproducibility to ensure consistent results during repeated testing for patient monitoring. A low measurement uncertainty (which integrates

Table 1: Major causes of acute and emergency bleeding.

1. Traumatic causes
   a. Blunt traumas (e.g., motor vehicle collisions, falls, crush injuries)
   b. Penetrating traumas (e.g., gunshot wounds, stab wounds, impalement injuries)
   c. Severe external wounds (e.g., deep lacerations, amputations, avulsions)
   d. Internal organ injuries (e.g., splenic or hepatic rupture, pelvic and long bone fractures)
2. Non-traumatic (medical) causes
   a. Gastrointestinal (GI) bleeding (e.g., peptic ulcers, esophageal varices, gastritis or esophagitis, diverticulosis/diverticulitis, inflammatory bowel diseases, hemorrhoids anal fissures, GI malignancies
   b. Intracranial hemorrhage (e.g., hemorrhagic stroke, subarachnoid hemorrhage, subdural or epidural hematoma
   c. Upper and lower respiratory tract causes (e.g., massive hemoptysis and epistaxis)
3. Obstetric and gynecological causes
   a. Postpartum hemorrhage
   b. Placental abnormalities (e.g., placenta previa, placental abruption)
   c. Uterine atony
   d. Retained placental tissue/fragments
   e. Ectopic pregnancy rupture
   f. Abortion-related hemorrhage (e.g., incomplete abortion, septic abortion)
4. Vascular disorders
   a. Ruptured aneurysms (e.g., aortic aneurysm, cerebral aneurysm)
   b. Arteriovenous malformations
   c. Vascular tumors (e.g., hemangiomas, angiosarcoma)
   d. Spontaneous vessel rupture (e.g., in connective tissue disorders like Ehlers-Danlos)
5. Hematologic and coagulation disorders
   a. Coagulopathies
      – Inherited: Hemophilia A/B, von Willebrand disease (VWD)
      – Acquired: Disseminated intravascular coagulation (DIC), acquired hemophilia A, other clotting factor inhibitors (e.g., factors II, V), acquired von Willebrand syndrome (AVWS), thrombotic microangiopathies (e.g., thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS))
   b. Medication-induced
      – Anticoagulants (e.g., warfarin, heparins, direct oral anticoagulants)
      – Antiplatelet agents (e.g., aspirin, clopidogrel)
   c. Thrombocytopenia (e.g., autoimmune disorders, sepsis, heparin-induced thrombocytopenia)
6. Neoplastic causes
   a. Tumor erosion into vasculature
   b. Hematologic malignancies
7. Iatrogenic and periprocedural causes
   a. Post-surgical hemorrhage
   b. Bleeding from invasive procedures (e.g., biopsies, catheterizations)
   c. Dialysis-related bleeding
   d. Anticoagulation complications during procedures

preanalytical variability, analytical variability–bias and imprecision–and intra-individual variation) is needed for dichotomy assays (e.g., those associated with a cut-off) and should be integrated in the interpretation of the test [10, 11]. The assay should exhibit broad linearity, given that patients with severe bleeding may present with extreme values (either very low or high). A very short turnaround time (TAT) is essential, as results must be available within min to guide urgent therapeutic decisions. Additionally, tests should require minimal sample volume to avoid iatrogenic anemia and exacerbation of blood waste. Availability around the clock (24/7) and, importantly, the capacity to influence immediate clinical decision-making based on predefined threshold-based action criteria are also indispensable.

With these general considerations in mind, in the following sections we will discuss some urgent laboratory tests that we consider the most relevant for the rapid management of emergency bleeding in the ED. It is important to note that the European guideline on the management of major bleeding and coagulopathy [6] recommends a limited panel of tests, including hemoglobin (as a marker of bleeding), blood lactate (to estimate and monitor bleeding severity, access, tissue hypoperfusion and help determine prognosis), prothrombin time (PT)/international normalized ratio (INR),

Table 2: Comparison of clinical prediction tools for early identification of acute traumatic coagulopathy.

	COAST score (COAgulopathy in severe trauma)			**Trauma induced coagulopathy clinical score, TICCS**			**Prediction of acute coagulopathy of trauma, PACT**		
Number of items	5			3			6		
	Criteria	Classification	Points	Criteria/Classification/Points	Classification	Points	Criteria	Classification	Points by unit
	Entrapment (e.g. in vehicle)	Yes	1	General severity	Critical (to be admitted in resuscitation room)	2	Prehospital Shock index≥1	Yes/no	90
		No	0		Non critical (regular ED room)	0			
	Systolic blood pressure, mmHg	>100	0	Systolic blood pressure, mmHg	Always>90	0	Age	Years to nearest decade	1
		90–100	1		At least once<90	5			
		<90	2						
	Temperature, °C	>35	0				Mechanism of injury not motor vehicle, motorcycle or bicycle crash	Yes/no	50
		32–35	1						
		<32	2						
	Major chest injury likely to require intervention (e.g. decompression, chest tube)	Yes,	1	Extent of significant injuries	Head and neck	1	Number of GCS points below 15	15-GCS	7
		No	0		Left upper extremity	1			
					Right upper extremity	1			
					Left lower extremity	1			
					Right lower extremity	1			
					Torso	2			
					Abdomen	2			
					Pelvis	2			
	Likely intra-abdominal or pelvic injury	Yes,	1				Prehospital CPR	Yes/no	120
		No	0						
							Prehospital intubation	Yes/no	50
Total possible score			0 to 7			0 to 18			394 + age
Reference	[7]			[8]			[9]		

ED, emergency department; Shock index, heart rate/systolic blood pressure; GCS, Glasgow Coma Scale; CPR, cardiopulmonary resuscitation.

Table 3: Essential characteristics of laboratory tests for immediate management of bleeding patients in the emergency department.

Characteristic	Scientific rationale
High diagnostic sensitivity	Detection of subtle coagulation abnormalities or hemostatic defects
High precision and reproducibility	Consistent results across repeated measurements, supporting reliable monitoring
Wide analytical measurement range	Accurate detection across the full spectrum of normal to pathological values.
Minimal turnaround time, TAT	Facilitates rapid clinical decision-making in time-critical scenarios
Low sample volume requirement	Prevent iatrogenic anemia
Continuous availability (24/7)	Aligning with the unpredictable nature of emergencies
Available measurement uncertainty	To assure the right interpretation and utilization of laboratory information
High clinical impact	Provides actionable results that can directly influence urgent diagnostic and therapeutic decisions.

fibrinogen levels, platelet count, and viscoelastic assays for guiding resuscitation and therapeutic interventions.

A recent 2025 consensus document [12] expands the recommended hemostasis assays for this clinical context. In addition to standard coagulation tests such as activated partial thromboplastin time (APTT), it incorporates specialized assays targeting specific hemorrhagic conditions. Notably, the diluted thrombin time (dTT) and anti-factor Xa (anti-Xa) assays are emphasized for their relevance in quantifying concentrations of direct oral anticoagulants (DOACs) in bleeding patients receiving these therapies. The following part of this article is hence focused on some informative laboratory test for patients presenting with acute bleeding in the ED. Intracranial hemorrhages will not be discussed here as they require a specific diagnostic and therapeutic approach that is outside the scope of the present article.

Hemoglobin/hematocrit

Hemoglobin is an iron-containing protein located within red blood cells (RBCs) that plays a critical physiological role in transporting oxygen from the lungs to peripheral tissues and facilitating carbon dioxide removal [13]. Hematocrit is instead defined as the proportion or percentage of volume of packed erythrocytes compared to the total volume of blood [14]. Tissue oxygenation is primarily dependent on hemoglobin concentration, and it is therefore unsurprising that reductions in hemoglobin levels have consistently been associated with adverse clinical outcomes, including increased mortality, across a wide range of clinical conditions [15]. In emergency bleeding scenarios, hemoglobin levels variably drop, with timing and extent that depend on the baseline levels, severity of hemorrhage and clinical setting, so that monitoring hemoglobin trends has become a central aspect for managing bleeding patients, as also clearly endorsed by the ATLS [4]. Important evidence supports this recommendation. In a seminal study conducted by Knottenbelt [16] and including 1,000 trauma patients [16], hemoglobin levels<80 g/L at admission were associated with 48.4 % mortality compared to 2.6 % deaths in patients with admission hemoglobin levels≥80 g/L or more, accounting for an over 35-fold higher risk of mortality (odds ratio [OR]: 35.4; 95 % CI: 15.8–79.5).

Ryan et al. conducted a retrospective observational study on 198 trauma patients requiring emergency management [17], and found that lower hematocrit values at admission (i.e., ≤0.40) were significantly associated with severe hypotension, metabolic acidosis, impaired mental status, injury severity score (ISS), revised trauma score (RTS), blood loss, usage of packed RBCs, fresh frozen plasma, crystalloid and vasopressors. In a following study, Thorson et al. investigated the relationship between admission hematocrit levels and the need for packed RBC transfusion in 1,492 consecutive patients admitted to a Level I trauma center [18]. Admission hematocrit was inversely correlated with the likelihood of packed RBC transfusion ($r = -0.45$) and predicted transfusion requirements with an accuracy of 71 %, a sensitivity of 0.45, and a specificity of 0.94. Lower admission hematocrit values were also significantly associated with greater blood loss, hypotension, and severe shock. Notably, additional evidence from the same group suggested that serial hematocrit measurements may offer superior predictive value for monitoring active bleeding compared to a single baseline measurement. In a follow-up study of 232 trauma patients (72 % non-bleeding, 28 % bleeding), hematocrit was measured twice during initial resuscitation to evaluate its utility in dynamic bleeding assessment [19]. A change in hematocrit (Δ hematocrit) ≥6 % was associated with the highest predictive accuracy for active bleeding, yielding an area under the curve (AUC) of 0.921, a sensitivity of 0.89 and a specificity of 0.95. However, it is important to recognize that both the type and volume of resuscitation fluids administered can significantly influence hemoglobin and hematocrit values, particularly during serial measurements, potentially confounding their interpretation [20].

Important, initial hemoglobin measurements in trauma patients with active bleeding should be interpreted cautiously, as relatively high hemoglobin thresholds (i.e., of 100 g/L in women and 120 g/L in men) in association with significant hemorrhages have been associated with the need

for massive transfusions, defined as least 4 units of packed RBCs in the first 6 h and/or death related to uncontrolled bleeding in the first 24 h following injury [21].

Regarding the transfusion thresholds, the ACS recommends initiating packed RBC transfusion when hemoglobin levels fall below 100 g/L, whereas European guidelines recommend that if erythrocyte transfusion is necessary, treatment should aim to achieve a target hemoglobin concentration of 70 g/L–90 g/L [6]. For bleeding situations unrelated to trauma, the 2023 AABB (Association for the Advancement of Blood and Biotherapies) International Guidelines recommend restrictive transfusion strategies, typically with a threshold of 70 g/L for both adult and pediatric patients [22]. The panel also recognizes important additional considerations, including signs, symptoms, comorbid conditions, and patient values and preferences, that will differ between patients. The recommendation is strong, based on moderate certainty evidence for most patients, but conditional, based on lower certainty evidence subgroups that include hematologic and oncologic disorders in adults and cyanotic cardiac conditions in infants [22]. Beyond the transfusion threshold, in cases of severe bleeding, implementing a rapid transfusion strategy is crucial for improving survival outcomes, with optimal blood product delivery times ideally maintained under 8 min [23]. To further expedite clinical management, the use of point-of-care testing (POCT) by clinicians at the patient's bedside represents a practical approach. However, a recent meta-analysis has demonstrated that hemoglobin measurements obtained via POCT should not be considered interchangeable with central laboratory values. Caution is therefore warranted when using POCT to guide intraoperative transfusion decisions [24].

Blood lactate

Blood lactate, commonly referred to as lactate or lactic acid, is a metabolic byproduct of anaerobic glycolysis. It is produced when oxygen availability is limited, resulting in the conversion of pyruvic acid into lactate during glucose metabolism [25]. Consequently, it is well established that lactate concentrations tend to increase proportionally with the degree of blood loss and the severity of tissue hypoperfusion.

A systematic literature review conducted by Baxter et al. [26], which included 15 studies, showed consistently higher blood lactate levels among non-survivors compared to survivors in trauma patients admitted to the ED [26]. Moreover, both elevated lactate concentrations and reduced lactate clearance were identified as significant predictors of hemorrhage in this patient population. Supporting this evidence, a recent study involving 270 trauma patients admitted to the ED found that baseline and 2-h blood lactate concentrations were approximately 2- and 3-fold higher, respectively, in non-survivors than in survivors [27]. In addition, lactate clearance was substantially lower (approximately 45 %) in non-survivors; multivariate analysis confirmed that reduced lactate clearance was significantly associated with unfavorable outcomes (OR: 0.89; 95 % confidence interval: 0.84–0.93).

In a separate meta-analysis involving 11 studies with sample sizes ranging from 104 to 1,644 patients, the prognostic value of blood lactate for mortality prediction in acute and severe upper gastrointestinal bleeding was assessed [28]. The pooled diagnostic accuracy was 0.79 (95 % CI: 0.72–0.85), with a sensitivity of 0.72 (95 % CI: 0.57–0.83) and specificity of 0.75 (95 % CI: 0.61–0.85). Importantly, the lactate thresholds used across the studies ranged from 1.85 to 4.3 mmol/L.

Accumulating evidence suggests that specific lactate values can hence guide the clinical decision-making in patients with acute bleeding. A lactate concentration≥3–3.5 mmol/L may be useful for early triage due to its high sensitivity for risk stratification; values≥4 mmol/L are associated with poor prognosis due to high specificity for adverse outcomes; values≥7 mmol/L are indicative of extreme risk and may necessitate urgent intervention; and a lactate clearance<10 % at 6 h after admission may reflect inadequate resuscitation. These thresholds are supported by several studies [29–32].

Coagulation testing

According to European clinical guidelines [6], hemostasis testing is an essential component in the management of patients presenting with emergency bleeding, serving two critical purposes: identifying the underlying cause of bleeding when not immediately apparent, and guiding the monitoring of resuscitation and therapeutic interventions. Conventionally, a prothrombin time ratio (PT/r) exceeding 1.2 is indicative of moderate traumatic coagulopathy, whereas values above 1.5 reflect severe coagulopathy and are associated with markedly increased risk of hemorrhagic complications. Additionally, hypofibrinogenemia, defined as fibrinogen levels<1.3 g/L, correlates strongly with elevated mortality rates in this patient population [33]. Fibrinogen concentrate or cryoprecipitate should be administered if major bleeding is accompanied by a plasma fibrinogen level≤1.5 g/L. The possibility to get a short TAT (<30 min) was demonstrated for many hemostasis assays following assays [34], using short centrifugation or adapted protocols [35].

Prothrombin time (PT)

Frith et al. conducted a retrospective cohort study involving 5,693 trauma patients admitted to five international trauma centers [36]. Their findings demonstrated a progressive increase in mortality risk correlated with PT/r values. Specifically, mortality was 7 % in patients with PT/r ≤ 1.2, rising significantly to 22.7 % in those with PT/r > 1.2 ($p < 0.001$), and further increasing to 27.8 % in patients with PT/r > 1.5 ($p < 0.001$). The median admission PT/r value remained below 1.2 in patients without hypoperfusion, regardless of injury severity. Moreover, the requirement for blood product transfusion was significantly associated with PT/r values exceeding 1.2. PT/r also showed a significant positive correlation with Injury Severity Score (ISS) ($r = 0.38$; $p < 0.001$) and with hypoperfusion, as indicated by base deficit ($r = 0.31$; $p < 0.001$). In an animal study, reported in this same article, the authors used Wistar rats randomly assigned to control, trauma, hemorrhagic shock, or combined trauma and hemorrhagic shock groups, reporting that both PT/r and APTT were significantly elevated in the hemorrhagic shock and combined groups, with statistical significance achieved in the latter.

Deras et al. [37] performed a retrospective study of 522 trauma patients [37], demonstrating that the severity of coagulopathy increased in parallel with rising PT/r values measured via a POCT device. They identified optimal PT/r cutoffs for predicting moderate and severe coagulopathy as 1.2 (sensitivity 0.80, specificity 0.87) and 1.4 (sensitivity 0.81, specificity 0.97), respectively. Patients with PT/r>1.4 had a markedly higher incidence of massive transfusion requirements (32 % vs. 4 %; $p < 0.05$) and were more frequently diagnosed with organ failure (78 vs. 28 %; $p < 0.05$) compared to those with PT/r < 1.2. Beyond its clinical utility in assessing the severity of acute coagulopathy, prolonged PT values may be used as an indicator of overdose of vitamin K antagonists (VKAs). The sensitivity of PT for detecting the presence of various classes of DOACs remains instead limited [38], and should not be used in this context. Prolonged PT is also a non-reliable predictor of bleeding risk in patients with liver disease [12], and current guidelines do not recommend the use of blood components (fresh frozen plasma, prothrombin complex, fibrinogen) to correct those abnormalities for management of periprocedural bleeding [39, 40]. Physicians should also be aware of the artefactual factors leading to both shortened and extended coagulation times [41]. In addition, the PT/r is unable to account for the different responsiveness of commercial thromboplastins to different factor deficiencies [42].

Fibrinogen

Hypofibrinogenemia is a key component of coagulopathy encountered in bleeding situations such as trauma, postpartum hemorrhage, and gastrointestinal bleeding [43]. Robust evidence supporting the current recommendations of the European guidelines – namely, that low fibrinogen concentrations are associated with adverse outcomes in patients experiencing emergency bleeding – has been provided by data from a prospective, statewide trauma registry in Victoria, Australia [44]. This registry included 4,773 trauma patients and demonstrated a significant association between plasma fibrinogen levels and both the extent of hemorrhage and transfusion requirements. Specifically, patients stratified by fibrinogen levels (>1.0, 1.0–1.5, 1.6–2.0, 2.1–4.0, and > 4.0 g/L) exhibited progressively higher hemoglobin concentrations (86, 102, 121, 134, and 131 g/L, respectively; p for trend<0.01). Correspondingly, the proportion of patients receiving≥1 unit of packed RBCs decreased across these strata (85.1, 71.7, 52.5, 26.5, and 18.5 %; p for trend<0.01), as did the rate of massive transfusion (55.3, 32.9, 16.9, 4.1, and 1.6 %; p for trend<0.01). These findings were further corroborated by a subsequent large retrospective study involving 7,063 patients with major bleeding (94 % survivors and 6 % non-survivors) [45]. In this analysis, non-survivors demonstrated significantly prolonged prothrombin time/international normalized ratio (PT/INR) (2.12 vs. 1.48; $p < 0.001$) and APTT (35.5 s vs. 19.0 s; $p < 0.001$). Importantly, patients with fibrinogen concentrations>1.3 g/L exhibited a 35 % reduction in 28-day mortality (OR: 0.65; 95 % CI: 0.48–0.87). Using restricted cubic spline analysis, the authors identified an optimal post-treatment fibrinogen target range of 2.0 g/L–2.5 g/L.

Consistent with these findings, the ACS has set a threshold for the administration of cryoprecipitate or fibrinogen concentrate at plasma fibrinogen levels<1.8 g/L, as outlined in their updated Massive Transfusion in Trauma Guidelines. According to the other recent guidelines, fibrinogen concentrate or cryoprecipitate should be administered if major bleeding is accompanied by hypofibrinogenemia (i.e., plasma fibrinogen level≤1.5 g/L, or<2 g/L for postpartum hemorrhage) [6, 46]. Finally, it should also be noted that fibrinogen measurement depends on the instrument and reagent [47], and that thrombin inhibitors such as dabigatran may interfere with the measurement [48].

Activated partial thromboplastin time (APTT)

Although not explicitly referenced in the European guidelines [6], APTT testing may still hold significant clinical

relevance in the management of patients with emergency bleeding. This is supported by the American College of Surgeons, which recommends consideration of plasma transfusion when APTT values exceed 35 s. Evidence from previously reviewed studies reinforces the utility of APTT as a prognostic marker, as APTT prolongation has been shown to correlate with bleeding severity and adverse clinical outcomes [36, 45], providing further justification for its inclusion in the routine assessment of critically bleeding patients.

Unlike PT, which primarily evaluates the "extrinsic" and "common" coagulation pathways, APTT assesses the "intrinsic" and "common" pathways [1]. While this classical division of the coagulation cascade has been revised – recognizing that the intrinsic pathway plays a limited role in physiological hemostasis and is now more accurately conceptualized as the "thrombin burst" – this framework remains clinically relevant in emergency settings. In particular, APTT retains diagnostic utility in patients with unexplained bleeding, serving as a critical clue for underlying coagulation disorders [1]. One such disorder is acquired hemophilia, a rare but potentially life-threatening condition caused by the development of autoantibodies against coagulation factors (especially factor VIII, but also factors II, V and IX may be involved) [49], in patients without an inherited deficiency. The clinical presentation is highly variable and depends on the inhibitor titer and degree of factor activity suppression. Patients often present with spontaneous, severe, and sometimes unexplained bleeding – typically involving soft tissues, muscles, mucous membranes, and occasionally retroperitoneal or gastrointestinal sites – while hemarthrosis, common in congenital hemophilia, is less frequently observed [49].

Laboratory evaluation may reveal isolated APTT prolongation as the only abnormal coagulation parameter; PT, platelet count, and fibrinogen levels might be within normal limits, except for patients with antibodies against factor V and factor II, where PT will also be abnormal. Importantly, for acquired hemophilia A, the extent of APTT prolongation does not always correlate with the clinical severity or antibody titer [50]. Also, exclusion of a lupus anticoagulant is important, although this is more typically associated with thrombosis unless also associated with factor II deficiency [51]. Nevertheless, prompt recognition of an isolated prolonged APTT in the appropriate clinical context is essential, as delays in initiating immunosuppressive therapy are associated with increased mortality in these patients [49]. Finally, physicians should be aware of the artefactual factors leading to both shortened and extended coagulation times [51].

Testing for direct oral anticoagulants (DOACs)

DOACs represent a distinct class of anticoagulant agents designed to combine the therapeutic advantages of both VKAs and heparins – namely, oral administration, fixed dosing, and reduced need for routine laboratory monitoring [52]. These features have significantly contributed to their widespread adoption in clinical practice, progressively replacing VKAs and heparins in various therapeutic settings. However, despite their favorable pharmacokinetic profiles, DOACs are not devoid of adverse effects, the most clinically significant being an increased risk of bleeding.

A recent network meta-analysis of randomized controlled trials quantified the risk of major bleeding associated with different anticoagulants. The incidence was reported as 18 per 1,000 patients for warfarin, 53 per 1,000 for apixaban, 26 per 1,000 for dabigatran, 19 per 1,000 for edoxaban, and 31 per 1,000 for rivaroxaban [53]. Given these data, it is not unexpected that patients on DOAC therapy may present to the ED with acute bleeding episodes, which now represent an increasingly significant public health concern. According to U.S. data, ED visits for DOAC-related bleeding rose by 31 % between 2016 and 2020, a trend largely attributed to the growing use of these agents. In contrast, visits for warfarin-related bleeding declined over the same period [54].

In the context of trauma, anticoagulant use is now considered a marker of severity, with prognostic implications comparable to those of the injury mechanism itself [55]. In cases of active bleeding, patients on DOACs should be managed in specialized centers with established protocols for rapid anticoagulation reversal, ensuring timely access to reversal agents and expert care [55]. In such scenarios, current clinical guidelines recommend laboratory assessment of residual anticoagulant activity to guide the optimal therapeutic approach, particularly with regard to the timing and necessity of reversal strategies [56]. Although commonly available global coagulation assays such as PT and APTT are frequently used in emergency settings, they are insufficiently sensitive or specific for accurately quantifying DOAC plasma activity across all agents. To address this limitation, specific assays have been developed and are now recommended in clinical practice [57, 58]. For patients on anti-factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban), anti-Xa assays calibrated for the specific DOAC are considered the preferred method for quantifying plasma drug levels. Heparin-calibrated anti-Xa assays are not recommended to exclude concentration-thresholds of 30 ng/mL to 50 ng/mL [59]. For patients receiving the direct thrombin

inhibitor dabigatran (an anti-IIa agent), the diluted thrombin time assay or ecarin chromogenic assay offer a more precise and reliable measurement of anticoagulant activity [60]. In absence of these specific assays, a normal thrombin time could be useful able to exclude the presence of dabigatran [61].

Viscoelastic measures (VEM)

Viscoelastic testing (VET) methods, especially Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM), have emerged as valuable diagnostic tools for rapid assessment of coagulation status in patients presenting to the ED with acute and massive bleeding. These technologies provide real-time, dynamic information on clot initiation, formation, strength, and lysis, thereby offering critical insights for management of coagulopathy in trauma and surgical patients [62, 63].

In both the Europe and United States, the clinical utility of VET has been increasingly recognized. These tools not only facilitate a better understanding of a patient's hemostatic profile but also support targeted transfusion strategies, including the administration of plasma, cryoprecipitate, RBCs, platelet concentrates, and antifibrinolytic agents in patients with trauma-induced coagulopathy or hemorrhagic shock [4, 6, 64].

Several studies have demonstrated that VET-guided management protocols in trauma care can lead to improved clinical outcomes. A systematic review and meta-analysis by Fahrendorff et al. included 15 randomized controlled trials comprising 1,238 patients, comparing VET-guided transfusion strategies to clinician-guided decisions or standard coagulation test-based protocols [65]. The analysis found that VET-guided interventions were associated with significantly reduced perioperative bleeding (standardized mean difference [SMD]: −1.40; 95 % CI: −2.57 to −0.23), lower transfusion requirements for RBCs (SMD: −0.64; 95 % CI: −1.12 to −0.15), and fresh frozen plasma (SMD: −1.98; 95 % CI: −3.41 to −0.54). While all-cause mortality was also lower in the VET group, the difference did not reach statistical significance (odds ratio [OR]: 0.60; 95 % CI: 0.34–1.07; p = 0.08).

Cochrane et al. [66] conducted a retrospective cohort study to evaluate the clinical and economic impact of implementing TEG-guided therapy in patients with major hemorrhage. The authors compared outcomes from two consecutive one-year periods: pre-TEG (126 patients) and post-TEG implementation (125 patients). The adoption of TEG-guided resuscitation was associated with significantly reduced mortality at both 24 h (5 % vs. 13 %; p = 0.006) and 30 days (11 % vs. 25 %; p = 0.002). Additionally, blood product wastage was significantly lower post-implementation (1.1 vs. 1.8 RBC units; p = 0.002). Although the cost savings did not reach statistical significance (p = 0.41), the study concluded that TEG-guided management was associated with improved survival, reduced blood product waste, and was cost-neutral when compared to conventional coagulation testing. Conversely, results from a subsequent multicenter, randomized controlled trial comparing empiric major hemorrhage protocols based on either VET or conventional coagulation testing revealed no statistically significant superiority of VET-guided therapy. Specifically, the proportion of patients alive and free from massive transfusion was similar between groups (VET: 67 % vs. conventional: 64 %; OR: 1.15; 95 % CI: 0.76–1.73), as was the 28-day mortality rate (25 % vs. 28 %; OR: 0.84; 95 % CI: 0.54–1.31) [67].

Taking together, there is currently no evidence that VEMs are superior to conventional coagulation tests in the management of patients presenting to the ED with acute and massive bleeding. In addition, VEMs do not show the whole coagulation process as they are not sensitive to VWF and minor/moderate fibrinolytic activity as well as natural anticoagulants, and have limited sensitivity to platelet function [12]. The implementation of VEMs in clinical practice remains challenging due to the need for clearly defined action thresholds and adequate clinician training. These factors can considerably impede their routine use in acute care settings. Thus, implementation of POCT or conventional coagulation testing should be based on local laboratory capabilities, institutional protocols, and cost-efficiency considerations. Regardless of the method employed, the overarching goal is to provide rapid test results (ideally within 30 min) to facilitate timely and effective clinical decision-making [6].

Platelet count

The rationale for including platelet count in the diagnostic panel for patients with emergency bleeding in the ED may initially appear counterintuitive, due to their essential role in primary hemostasis [1]. However, its clinical relevance is firmly grounded in basic hemostatic physiology. Platelets are central to primary hemostasis; they rapidly adhere to the site of vascular injury to form the initial hemostatic plug. Consequently, patients with thrombocytopenia or platelet dysfunction are inherently at higher risk of bleeding due to impaired clot formation [1].

Unlike procedural contexts such as surgery or lumbar puncture, where transfusion thresholds are more clearly established [68], no universal consensus currently exists on platelet transfusion thresholds for patients presenting with

acute bleeding. Furthermore, the European guidelines [6] and the recent 2025 AABB Clinical Practice Guidelines do not offer definitive recommendations in this regard [69], while advocating for restrictive platelet transfusion strategies, as there was no consistent evidence across randomized clinical trials to support the benefit of platelets impacting clinical outcomes. Nevertheless, the ACS provides general guidance, suggesting platelet transfusion when the platelet count falls below 150×10^9/L. According to European guidelines, platelet transfusions should aim to keep the platelet count above 50×10^9/L in trauma patients with ongoing bleeding, and above 100×10^9/L in patients suffering from traumatic brain injury [6].

The evidence supporting routine platelet count assessment in emergency bleeding is substantial. In a retrospective cohort study involving 389 massively transfused trauma patients, Brown et al. demonstrated that each 50×10^9/L increase in admission platelet count was associated with a 17 % reduction in 6 h mortality (odds ratio [OR]: 0.83; 95 % CI: 0.70–0.99) and a 14 % reduction in 24 h mortality (OR: 0.86; 95 % CI: 0.75–0.98) [70]. Additionally, for every 50×10^9/L increase in platelet count, transfusion requirements decreased by 0.7 units in the first 6 h (95 % CI: −1.3 to −0.14) and by 1 unit over the first 24 h (95 % CI: −1.6 to −0.36), respectively. Further corroborating these findings, an observational study based on a multicenter prospective trauma registry of 19,596 patients revealed that lower platelet counts on admission were associated with acute traumatic coagulopathy (correlation coefficient r = 0.31; p < 0.001). Patients with severe bleeding or requiring massive transfusion had significantly lower platelet counts (180 and 158 vs. 231×10^9/L, respectively; both p < 0.01) [71]. Notably, each 50×10^9/L decrement in platelet count was associated with a 61 % increase in 24-h all-cause mortality (OR: 0.39; 95 % CI: 0.36–0.42). In support of platelet transfusion strategies, a meta-analysis including five randomized controlled trials and 1,757 bleeding patients demonstrated that higher platelet-to-RBC transfusion ratios were associated with significantly reduced 24-h (OR: 0.69; 95 % CI: 0.53–0.89) and 30-day (OR: 0.78; 95 % CI: 0.63–0.98) mortality [72].

Cardiac troponins

Although cardiac troponin measurement is not currently included in formal guidelines for management of emergency bleeding, several important considerations support its potential clinical relevance in this setting. According to the Fourth Universal Definition of Myocardial Infarction [73], type 2 myocardial infarction (MI) is caused by an imbalance between myocardial oxygen supply and demand. In the context of acute and severe bleeding, especially when accompanied by a rapid decline in hemoglobin levels, hypotension, or shock, myocardial ischemia may ensue. If this ischemia is sustained, it can lead to cardiomyocyte necrosis and subsequent elevation of cardiac troponin levels.

The prognostic significance of cardiac troponins in patients with acute bleeding has been particularly investigated in those with gastrointestinal hemorrhage. In a retrospective cohort study of 290 patients presenting to the ED with acute gastrointestinal bleeding, Iqbal et al. found that patients with elevated cardiac troponin I (cTnI) had a nearly fourfold increased risk of in-hospital mortality (OR: 3.9; 95 % CI: 1.4–11.2) compared to those without cTnI elevation. Additionally, these patients had a longer hospital stay (6 vs. 5 days; p = = 0.02) [74]. A subsequent study by Kousa et al. examined 172 patients with acute gastrointestinal bleeding and observed that those with elevated cTnI levels underwent more downstream cardiac testing, experienced longer delays before endoscopic evaluation, and had prolonged hospitalizations. Although mortality was higher among patients with elevated troponin (23 % vs. 14 %), the difference did not reach statistical significance (p = 0.18) [75]. Further evidence on this matter has been provided by Iser et al., who prospectively followed 156 patients presenting with hematemesis or melena [76]. Their study demonstrated that elevated cTnI was associated with a significantly higher risk of hypotension (OR: 3.0; 95 % CI: 1.9–4.8), cardiac compromise (OR: 5.4; 95 % CI: 3.1–9.1), and rebleeding (OR: 3.2; 95 % CI: 1.5–6.7).

Taken together, these findings would suggest that the measurement of cardiac troponins may be clinically appropriate in patients with emergency bleeding presenting to the ED, especially in those with signs or symptoms of myocardial ischemia. Although further studies are needed to define precise thresholds and treatment implications, early troponin assessment may aid in risk stratification and guide multidisciplinary management.

Detection of the new anti-factor XI(a) anticoagulants

New anticoagulation strategies have recently been explored to achieve non-inferior efficacy while minimizing the bleeding risk in comparison to DOAC. One of them consists of targeting (activated-) FXI(a), which could decouple thrombosis from hemostasis [77]. Such inhibitors are under exploration for a variety of indications, i.e., reducing thrombotic risk in patients with end-stage renal disease, as well as after ischemic stroke and myocardial infarction, and

preventing post-operative venous thromboembolism [77, 78].

Several strategies have been proposed to inhibit FXI and/or FXIa, of which 3 are currently in advanced clinical development: antisense oligonucleotides (ASOs, i.e., Fesomersen), monoclonal antibodies (mABs) (i.e., abelacimab), and small molecules (i.e., asundexian and milvexian) [77]. Importantly, these therapeutic classes differ in their mechanisms of action and pharmacologic properties. While these anticoagulants are not yet available and do not require routine laboratory monitoring, there is a need to address bleeding risk management for patients already enrolled in phase III trials. These patients may face elective or unplanned invasive procedures and bleeding events in anticipation of marketing authorization. Experience from managing patients with inherited FXI deficiency, along with data from early clinical trials, suggests that the bleeding risk associated with anti-FXI(a) is likely to be low but can vary depending on the clinical situation [79]. The French Working Group on Perioperative Haemostasis and the French Society of Thrombosis and Haemostasis have recently made some proposals to guide the management of bleeding and invasive procedures in patients treated with anti-factor XI(a) anticoagulants. First, a normal APTT is unlikely to be associated with high level of anticoagulation and leads to standard management [79]. Conversely, prolonged APTT may indicate the presence of the anticoagulant but does not provide information on concentration of the drug and the level of anticoagulation. A dose-dependent prolongation of APTT was shown, but it differs according to reagents, and the lack of extensive data makes this test difficult to interpret. Moreover, a prolonged APTT may also result from causes other than the presence of anti-XI(a) (bleeding-induced coagulopathy, lupus anticoagulant, etc.) [79]. Measurement of FXI levels is only relevant in case of treatment with antisense oligonucleotides. Finally, there is too limited data to draw any conclusion on the effect of anti-FXI/XIa anticoagulants on viscoelastic tests (TEG and ROTEM) [80].

Conclusions

In this opinion paper, we have attempted to summarize important evidence regarding the clinical usefulness of initial laboratory testing in patients admitted to the ED with acute, life-threatening bleeding (Table 4). While this overview may not be exhaustive, and additional tests could be considered based on local laboratory capabilities, institutional protocols, and resource availability, the selected tests meet fundamental criteria for being considered "emergency" laboratory investigations applicable in the context of "emergency" bleeding.

Table 4: Key laboratory tests for immediate management of bleeding patients in the emergency department.

Test	Clinical significance	Decisional thresholds
Hemoglobin/ hematocrit	Reflect and monitor oxygen-carrying capacity; guide transfusion decision	Trauma-related bleeding: <100 g/L Non-traumatic related bleeding: 70–80 g/L (American college of surgeons) Target hemoglobin concentration of 70–90 g/L for transfusion (European guidelines for trauma)
Blood lactate	Assesses tissue perfusion; prognostic marker of shock severity	>3–3.5 mmol/L (initial triage) >4 mmol/L (worse prognosis) ≥7 mmol/L (high mortality risk)
Prothrombin time, PT	Assess coagulation status; detect warfarin overdose, vitamin K deficiency or trauma-induced coagulopathy; detect acquired factor II or V inhibitors	>1.2 (moderate coagulopathy) >1.4–1.5 (severe coagulopathy)
Fibrinogen	Key factor in clot formation; detect and monitor trauma-induced coagulopathy	< 2 g/L (transfusion threshold in post-partum hemorrhage) <1.5 g/L (transfusion threshold) <1.3 g/L (associated with poor outcome)
Activated partial thromboplastin time, APTT	Screen for intrinsic pathway dysfunction; detect acquired hemophilia A or acquired factor II or V inhibitors	Interpretation depends on the instrument and reagent
Viscoelastic measures, VEM	Real-time assessment of clot formation and fibrinolysis	Interpretation depends on the platform and parameters
Platelet count	Assess thrombocytopenia; guide transfusion and bleeding risk assessment	$<150 \times 10^9$/L (increased bleeding risk) $<50 \times 10^9$/L (in patients with ongoing bleeding)
Cardiac troponins	Detect myocardial injury due to hypoperfusion; prognostic marker in bleeding	>99th percentile upper reference limit (URL)

These criteria include the test's ability to provide rapid, actionable results, its relevance to the pathophysiology of bleeding or coagulopathy, and its demonstrated prognostic or therapeutic implications in emergency care. Importantly, we recognize that this core panel may need to be

complemented by organ-specific laboratory analyses and advanced diagnostic algorithms in critically ill patients who progress to multi-organ dysfunction. Such tests include blood gas analysis (to monitor metabolic status), serum creatinine (for renal function), liver enzymes and bilirubin (for hepatic injury), lipase (for pancreatic injury), and lactate dehydrogenase (for ischemic tissue injury). Notably, in patients with upper gastrointestinal bleeding, blood is digested into proteins, which are subsequently metabolized to blood urea nitrogen through the urea cycle. Therefore, elevated blood urea nitrogen levels have been suggested as another useful test to identify patients with more severe upper gastrointestinal bleeding [81].

Among others, ionized calcium (iCa^{2+}) deserves specific mention due to its direct role in coagulation. A recent retrospective analysis of the Trauma Register DGU (Deutsche Gesellschaft für Unfallchirurgie), which included 30,183 major trauma patients, demonstrated that deviations from the normal iCa^{2+} range – specifically, levels<1.1 or>1.2 mmol/L – were independently associated with increased risks of traumatic coagulopathy and need for transfusion [82]. These findings highlight the importance of early calcium monitoring and correction during massive transfusion protocols.

Nevertheless, while valuable, organ- and system-specific tests should be considered second-line investigations – used to complement, rather than replace, the primary laboratory panel in the acute phase of hemorrhagic shock or trauma at ED admission, as summarized in Table 4. Their utility becomes more pronounced once the immediate bleeding threat is addressed, or when clinical deterioration suggests the development of secondary complications such as shock-induced end-organ failure.

In conclusion, the early and targeted use of laboratory diagnostics in emergency bleeding is fundamental for risk stratification, therapeutic decision-making, and outcome prediction. Standard laboratory tests such as hemoglobin, platelet count, fibrinogen, PT/INR, APTT, and lactate – alongside specialized assays including viscoelastic testing, DOAC-specific assays, and cardiac troponins – form the cornerstone of diagnostic work-up in this setting. When interpreted within a structured clinical algorithm, these tests can enable a rapid and individualized approach to resuscitation and transfusion, potentially improving survival and reducing unnecessary interventions. Future research should aim to validate comprehensive diagnostic pathways that integrate both frontline and advanced laboratory tools to support real-time decision-making in the ED, especially for institutions managing high volumes of trauma and critically bleeding patients.

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