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# Thromboelastography for Diagnosing Coagulopathy and Guiding Blood Transfusion

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Received: 9 May 2024; Accepted: 28 August 2024; Available online: 30 December 2024

**ABSTRACT:** Timely response to coagulopathy could provide the best objective evidence to guide therapies, predict bleeding and thrombotic risk, reduce the cost of care, and improve outcomes. This review sought to identify the diagnostic characteristics of Thromboelastography (TEG) in bleeding and hypercoagulability populations and the guiding principle for blood components transfusion. We reviewed the research studies of TEG in bleeding diseases (trauma, cardiac surgery, and liver surgery) and hypercoagulability populations (obstetric patients, older patients, and infection patients). We also summarized its guiding principle for blood components transfusion (whole blood, platelet, plasma, and cryoprecipitate). Overall, TEG can diagnose surgical bleeding and hypercoagulability population by recognizing the alterations of the coagulation system, e.g., long R, flat α angle, thin maximum amplitude (MA), and increased LY30 in initial severe bleeding trauma patient; shortened R, increased α and MA, shortened K when patient with endothelial injury; decrescent K, increscent α angle, MA and coagulation index (CI) in people over 50 years. TEG can also guide blood transfusion. For example, TEG MA < 55 mm can be a threshold for platelet transfusions for thrombocytopenia patients; one unit of FFP shortens the R time by 5 minutes with a ratio of 5 mins/U of FFP for high-responder surgical patients. TEG can help diagnose coagulopathy and guide blood transfusion. However, there are still challenges and prospects for the clinical applications of TEG, such as achieving faster results and developing realistic blood flow detection environments. We expect that advances in mathematics, physics, and medical analysis will be integrated into patient blood management.

**Keywords:** Thromboelastography; Coagulopathy; Hemorrhage; Hypercoagulability; Blood transfusion



## 1. Introduction

Blood coagulation is an important physiological function that prevents bleeding, while anticoagulation mechanisms precisely control coagulation. Under normal physiologic conditions, anticoagulation is superior to procoagulation [1]. Inherited or acquired factors may destroy the natural balance between anticoagulant and procoagulant systems, which results in coagulopathies [2,3]. Coagulopathies are complex, in part because hypo- and hypercoagulability can coexist in the same patient. They may present either sequentially, as in patients with major trauma [4], or simultaneously, as in patients with liver disease [5].

Timely response to this imbalance could provide the best objective evidence to guide therapies, predict bleeding and thrombotic risk, reduce the cost of care, and improve outcomes. Accumulating evidence showed that thromboelastography (TEG) exhibited robust stability and desirable timeliness and guided hemostasis and anticoagulant therapy timely and successfully, which makes it ideal as a reporter for the process of whole blood (WB) coagulation and fibrinolysis [6–8]. Conventional coagulation tests (CCTs) such as prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), activated clotting time of whole blood (ACT),

platelets, and fibrinogen have been available at most hospitals [9], which measures the time required to form a clot and reflects the concentration and function of the individual component of blood. Compared to CCTs, TEG proves the synergistic process of blood coagulation contributed by plasma and cellular components. Moreover, it is the only detection method to capture information about thrombus formation and fibrinolysis and visualize the process. A detailed comparison between TEG and the main CCTs is shown in Table 1.

Although several reviews exist on the topic of TEG application in clinical treatments, there is still a lack of a comprehensive review on the diagnostic characteristics of TEG associated with various hemorrhage diseases and its guiding principle of blood transfusion. In this study, we reviewed the test principles of TEG and its current applications in clinical practice, ranging from the diagnostic characteristics of TEG in bleeding diseases (trauma, cardiac surgery, and liver surgery) to hypercoagulability populations. We also summarized the guiding principle of blood components transfusion (WB, platelet, plasma, and cryoprecipitate). Finally, we pointed out existing challenges and prospects for the clinical applications of TEG and future directions of precision diagnosis for the disturbances between procoagulant and anticoagulant systems.

**Table 1.** Comparison of TEG with conventional coagulation tests.

| Test way | aPTT | PT/INR | ACT | TEG |
|---|---|---|---|---|
| Monitor pathway | Intrinsic | Extrinsic | Intrinsic | Intrinsic, extrinsic |
| Test principle | Coagulation cascade/ colorimetric | Coagulation cascade/ colorimetric | Coagulation cascade/ colorimetric | Cellular base model/shear stress electromagnetic induction |
| Coagulation factors | XII, XI, IX, VIII, X, V, II | VII, X, V, II | XII, XI, IX, VIII, X, V, II | Clotting factors, platelets, fibrinogen, and initiators of fibrinolysis |
| Sample | Plasma | Plasma | Plasma | Whole blood |
| Volume | 3 mL | 3 mL | 3 mL | 360 μL |
| Activators | Elliagic acid, kaolin, micronized silica | Calcium, TF, phospholipid | Diatomaceous earth, glass beads, kaolin | Kaolin, calcium |
| End point | Clot formation | Clot formation | Clot formation | Fibrinolysis |
| LMWH monitoring | No | No | Yes | Yes |
| Heparin sensitivity | 0.1–1 U/mL | 0.1–1 U/mL | 1–5 U/mL | 0.005 U/mL |
| Monitor range | Speed of fibrin strand formation | | | Kinetics of all stages in thrombus formation, clot stability and firmness, as well as fibrinolysis |
| Sensitivity and specific | Highly variable, less sensitivity | | | Minor shifts can be monitored |
| Time | 50 minutes | | | 30 minutes |

TEG: thromboelastography; aPTT: activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; ACT: activated coagulation time.

## 2. Test Principles of TEG

TEG was developed in Germany by Dr. Hartert in the late 1940s. TEG parameters are related to the formation and lysis of a clot, which can represent the formation rapidity, strength and stability of a clot [10]. Studying the characteristics of TEG parameters may help analyse different coagulopathy mechanisms to make a precise clinical diagnosis. Reaction time (R) is defined as the time from the start of the reaction to the detection of a measurable clot. K is the time from R to reach a certain firmness of the clot. The α angle reflects the clot formation rate. The clot elasticity maximum amplitude (MA) reflects the contribution of fibrin and platelets to clot strength. LY30 is the percentage decrease in amplitude 30 minutes after MA, which measures the degree of fibrinolysis. Coagulation index (CI) gives information about the overall coagulation process, which is calculated by the equation: $CI = -0.1227R + 0.0092K + 0.1655MA - 0.024\alpha$. Hypercoagulable, hypocoagulable and fibrinolytic states can be interpreted by TEG tracing. A brief explanation of TEG parameters and various examples of TEG traces are provided in Figure 1.

As a point-of-care (POC) testing technique for monitoring dynamic changes from clot formation to fibrinolysis, TEG provides a comprehensive assessment of blood coagulation. Five different tests are now available for TEG (Table 2): a standard test (kaolin activator, k-TEG), a heparinase test (kaolin activator and heparinase, heparinase-TEG), a platelet mapping test (adenosine diphosphate (ADP) or arachidonic acid (AA), TEG-PM), a functional fibrinogen TEG (tissue factor and abciximab, ff-TEG), and a rapid test (kaolin and tissue factor, r-TEG) [11–14].

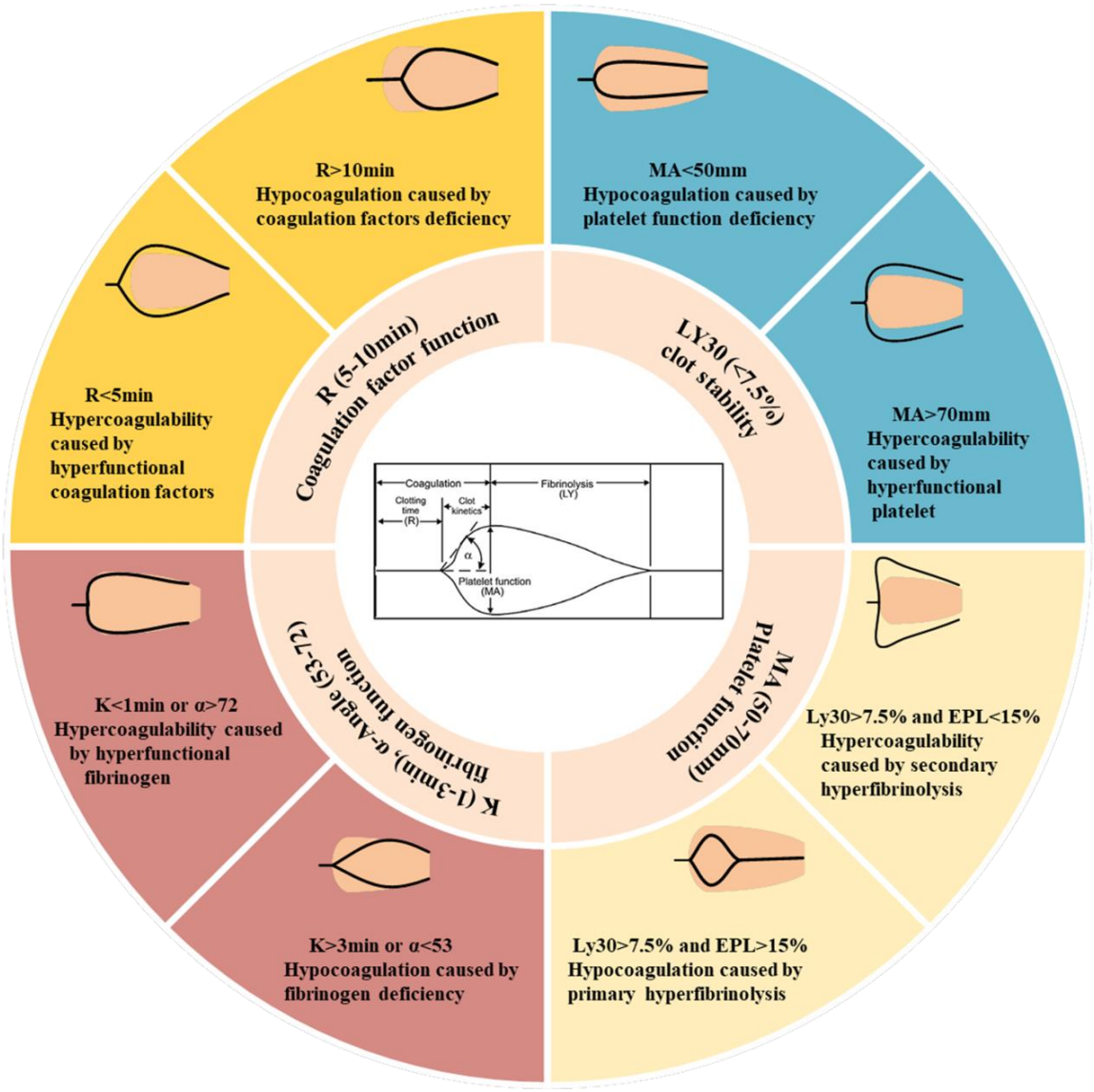
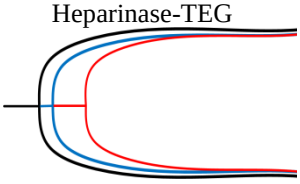
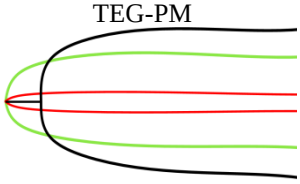
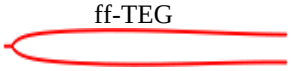



**Figure 1.** Major parameters and typical examples of TEG traces. R is the time from the start of the reaction to measurable clot formation; MA is the maximum amplitude of clot elasticity, which reflects the properties of fibrin and platelets; K is the time from R to reach a certain firmness of the clot; α angle reflects the clot formation rate; LY30 measures persistent lysis 30 minutes after reaching MA.

**Table 2.** Five TEG tests.

| Tests | Reagents | Parameters | Advantages |
|---|---|---|---|
| k-TEG | Kaolin | R, K, Angle, MA, LY30, EPL | A global haemostasis assessment<br>Useful in estimating platelet function, thrombus formation, clot tensile strength, and fibrinolysis |
| r-TEG | Kaolin, tissue factor | ACT, K, Angle, MA | Clotting accelerated by activation of extrinsic and intrinsic pathways<br>Useful in trauma |

| | | | |
|---|---|---|---|
| Heparinase-TEG  | Kaolin, heparinase | ΔR<br>$\Delta R=R_{CKH}-R_{CK}>2$, with heparin effect<br>$\Delta R=R_{CKH}-R_{CK}\leq 2$, without heparin effect | Determining residual heparin effect<br>Useful in monitoring the effects of heparin and protamine |
| TEG-PM  | ADP or AA | PRI (%)=100%-[($MA_{ADP/AA}$-$MA_{fibrin}$)/($MA_{thrombin}$-$MA_{fibrin}$)]×100 | Reflecting the inhibition effect of antiplatelet drugs<br>P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) decrease $MA_{ADP}$; TXA2 inhibitors (aspirin) decrease $MA_{AA}$; GPIIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide) decrease both $MA_{ADP}$ and $MA_{AA}$ |
| ff-TEG  | Tissue factor, abciximab | R, MA, FLEV | Assessing fibrinogen function directly<br>Useful in judging low fibrinogen levels in trauma patients |

TEG: thromboelastography; k-TEG: kaolin-TEG; r-TEG: rapid-TEG; ff-TEG: TEG functional fibrinogen; TEG-PM: TEG platelet mapping; ACT: activated coagulation time; R: reaction time; $R_{CK:}$ reaction time in citrated kaolin TEG assay; $R_{CKH:}$ reaction time in citrated kaolin with heparinase TEG assay; AA: arachidonic acid; ADP: adenosine diphosphate; PRI: platelet receptor inhibition; MA: maximum amplitude; $MA_{fibrin}$: fibrin MA; $MA_{thrombin}$: thrombin MA; $MA_{ADP/AA}$: MA-adenosine diphosphate/arachidonic acid.

### *2.1. TEG for Diagnosing Hemorrhage*

Severe bleeding can lead to death in patients who undergo trauma or surgery [15]. Multiple factors, such as vascular injuries, ongoing blood loss, and platelet dysfunction, can cause persistent bleeding [16]. Accurate differentiation of these factors is the key to successful treatment. Recent developments showed that TEG can diagnose surgical and non-surgical bleeding by recognizing alterations in the coagulation system [17,18].

(1) Trauma: The patients with severe bleeding trauma initially presented with hypocoagulability, manifested with long R, flat α angle, thin MA, and increased LY30 [19,20]. For acute traumatic coagulopathy, up to 25% of severely injured trauma patients arrived at the hospital with a prolonged clotting time and excessive fibrinolysis [21]. The ACT of r-TEG is available within 5 minutes, followed by the MA and α angle results within 15 minutes. According to the percent lysis (cutoffs of LY30 from 3% to 15%), r-TEG can diagnose the existence of primary fibrinolysis after trauma occurs, even within 1 hour [22]. Hypercoagulable state is another important manifestation of trauma, which is characterized by endothelial injury, excessive thrombin generation, hyperfibrinogenemia, platelet hyperactivity, anticoagulant pathways impairment, and fibrinolysis shutdown. Correspondingly, TEG could trace the changes, such as shortened R for coagulation factors hyperfunction, increased α angle and shortened K for fibrinogen hyperfunction, increased MA for platelet hyperfunction, and reduced LY30 (< 0.8%) for fibrinolysis shutdown [23–25]. The specific phenotype of trauma-induced coagulopathy has corresponding TEG trace characteristics. For pediatric trauma patients, there were no differences in TEG characteristics between males and females in younger children (<10 years). Still, for older children (11–18 years), males had greater K time, reduced α angle, and lower MA than females [26]. For blunt and penetrating pediatric trauma patients, MA and α angle decreased in patients with shock [6,27]. For severely injured children, fibrinolysis shutdown (LY30 < 0.8%) occurred 1 hour after injury [16].

(2) Cardiac Surgery: Bleeding complications are common in patients undergoing cardiac surgery, which are attributed to significant fibrinolysis, coagulation factor deficiency, and platelet dysfunction. In adult cardiac surgery, postoperative TEG variables R, K, α angle, MA and clot elasticity (G) changed significantly compared to preoperative TEG variables (preoperative vs 1 hour postoperatively, R: 8 ± 2.1 vs 10 ± 2.6, $P < 0.05$; K: 2 ± 0.6 vs 3 ± 0.7, $P < 0.001$; α angle: 61 ± 6.1 vs 56 ± 7.5, $P < 0.001$; MA: 63 ± 4.3 vs 58 ± 4.9, $P < 0.001$; G: 9 ± 1.7 vs 7 ± 1.4, $P < 0.001$) [28]. Some researchers concluded that TEG parameter cannot estimate perioperative total blood loss [29]. However, for pediatric intensive care unit (ICU) patients, TEG MA can reflect blood loss in the first hour as it is correlated with platelet count and fibrinogen concentration [30]. The children with congenital heart disease had significantly impaired thrombin production, which TEG can diagnose but not by aPTT and PT. At the same time, TEG R revealed that coagulopathy lasted 12 hours after surgery in these patients [31]. TEG CI was

significantly lower for patients with left ventricular assist device implantation, in patients with suspected pump thrombosis starting at the sixth month post-implantation compared to the patients with no pump thrombosis [32].

(3) Liver Surgery: Liver surgery can affect both the pro- and anticoagulant systems and induce disturbances of hemostasis balance [33]. In liver transplant patients, the blood coagulation system was altered during the perioperative period and these changes can be reflected by TEG [9,34]. Prior to liver transplant, TEG values were not correlated with the clinical picture [17]. Intraoperatively, the R value began to prolong in the early stages of the post-reperfusion of the graft liver and it was remarkable during reperfusion. Still, it returned to preoperative value about 2 hours after the graft. The CI gradually decreased from the beginning of the operation, with the lowest value tested in the middle of the anhepatic stage [35]. Krzanicki et al. also found prolonged R is measured at reperfusion, which can be reversed on the heparinase-TEG [36]. During the first 24 hours after transplantation, TEG data showed a change from a hypercoagulable to a hypocoagulable state, objectively revealing the real dynamic nature of hemostasis [37]. For pediatric liver transplantation, MA and α angle decreased. At the same time, R time increased throughout the perioperative period, which also showed a transition from a hypercoagulable state to a slow clot formation and fibrinolysis [38].

(4) Non-surgical Bleeding: Heparin can cause non-surgical bleeding, which can be monitored by heparinase-TEG [39], and a k-TEG (no heparinase) can be tested simultaneously. ΔR, defined as differences between the R-time of k-TEG and heparinase-TEG, is proportional to the degree of heparinization. Hypercoagulability may decline heparin response in patients with congenital heart disease. Some researchers concluded that preoperative TEG K<1.3 minutes suggests decreased heparin response [40]. Besides exogenous heparin residual, endogenous heparin-like substances are also responsible for non-surgical bleeding, which can be monitored by heparinase-TEG. Patients with liver disease or hepatic injury have a decreased elimination rate of endogenous heparin-like substances, causing increased heparinoid levels, especially in patients undergoing orthotopic liver transplantation [41]. In 41 patients treated with extracorporeal membrane oxygenation (ECMO), Ranucci et al. found that ΔR became progressively more pronounced from the start of ECMO until day 5, then declined and disappeared after 10 days [42]. One study reported a case with severe postpartum hemorrhage (PPH) caused by endogenous heparin-like substances, whose ΔR significantly exceeded the detection limit and the bleeding was successfully stopped after protamine treatment by the guidance of TEG [18].

### *2.2 TEG for Diagnosing Hypercoagulability*

Hypercoagulability is a major concern in populations such as obstetric patients, older patients, and infection patients, which can result in venous thromboembolism and acute coronary syndromes [7,43]. Insert the illustrations and their captions where it was mentioned at the first time in the text. In addition, you may still need to provide figures and their captions, and tables within a single file or individual illustration and table files in a zip folder.

(1) Obstetric Population: TEG was more recently used in pregnancy and puerperium [7,44]. Compared with males, pregnant women had a shorter R and K and a larger α angle and MA [45]. Similarly, a significant increase in coagulation after cesarean delivery was observed, as indicated by shorter R and K times and a larger α angle in the postoperative period [46]. Preeclampsia is the most common medical complication of pregnancy, which is usually associated with hypercoagulability due to increased coagulation factors [47]. TEG-CI is significantly greater in women with preeclampsia, thus, it can be used for the early prediction of severe preeclampsia [48].

(2) Older Population: The balance between the procoagulant and anticoagulant systems is an age-related dynamic process [43]. Roeloffzen et al. revealed hypercoagulability with aging, which can be reflected by K decrescence, α angle, MA, and CI increscence in people over 50 years [49]. In another multicenter study, TEG results showed that 50 years was regarded as the threshold age for delineating the reference intervals of R, K and α angle and 40 years was the cut-off age for MA and CI [50]. Among a total of 160 patients (70.6 ± 12.3 years), it suggested that a hypercoagulable signal on TEG and a reaction time <5 min was associated with a poorer 90-day outcome [51].

(3) Infection Population: Severe infection can enhance thrombotic complications by activating coagulation, thrombin generation, and hypercoagulation [52]. Sepsis is a serious disease with inflammation and abnormal coagulation disorders. The patients with different degrees of sepsis had different TEG trace characteristics [53]. Compared with sepsis patients without shock, shock patients had significantly longer K time, lower α angle, MA and CI and significantly higher LY30, suggesting a hypocoagulable state with reduced platelet and fiber function and progressive fibrinolysis [54]. SARS-CoV-2 can induce thromboembolic disease by activating coagulation

cascades and thrombin formation [55]. TEG assay was recommended for all severe COVID-19 patients [52], of which the data showed a high MA and α angle and no fibrinolysis at 30 minutes (LY30 = 0%) [56].

## 3. TEG for Guiding Blood Transfusion

Transfusion strategies are critical to control trauma bleeding [57] and increasing evidence supports that TEG can be used to guide hemostatic therapies with fresh-frozen plasma (FFP), platelet concentrates as well as coagulation factor concentrates [17,58–60]. Prolonged R indicates decreased coagulation factors, which can be resuscitated using FFP and prothrombin complex [61]. Prolonged K or decreased α angle indicates fibrinogen deficiency, which can be corrected by cryoprecipitation or lyophilized fibrinogen concentrate. Platelet transfusion can correct decreased MA [62]. Several groups confirmed that using TEG coupled with a transfusion algorithm could decrease blood product transfusion [60,63,64].

(1) WB Transfusion: WB and modified WB transfusion are the preferred resuscitation option after massive blood loss [65]. Reliance on the 1:1:1 (plasma, platelets, and RBC) model with little knowledge of the patient's hemodynamic or coagulation status may increase mortality [66]. TEG monitoring, especially in the far-forward combat environment, allows for personalized and goal-directed blood component transfusions to enhance the WB transfusion protocols [66,67]. In one recent clinical trial of patients with airborne injuries at risk of hemorrhagic shock (NCT03477006), followed by r-TEG-guided resuscitation, it showed that a larger number of WB units transfusion prehospital is safer compared with in-hospital component transfusion (1:1:1) and associates with hemostatic benefits and lower RBC needs in the whole treatment [68]. Meanwhile, ACT>128 seconds predicts a need for a massive transfusion (≥10 blood product units in the first 6 hours) and ACT<105 seconds means that no transfusion is required in the first 24 hours [69].

(2) Platelet Transfusion: Platelet transfusions are commonly administered to prevent or treat bleeding in patients with acquired thrombocytopenia. It is often monitored by methods that approximate the platelet, such as corrective count increment (CCI) and percent platelet recovery (PPR). These methods are based on platelet counts, but the quality of evidence is limited [70]. Thus, research is needed to determine the optimal evaluating indicators better. Evidence suggests that TEG can be a better test than the platelet count to guide platelet transfusion for certain diseases [71]. MA and α angle are related to platelet count and function, which are increased in hypercoaguable states and decreased in thrombocytopenia, platelet dysfunction, and hypofibrinogenemia [72]. Lee et al. concluded that TEG-PM is a powerful method to predict the hemostatic potential for patients with platelet function disorders, at least in mice, and found that K and α angle are two optimal parameters in guiding platelet transfusion [71]. A prospective, observational pilot study of 13 thrombocytopenic and haemato-oncologic patients showed that TEG α angle was correlated better with bleeding than platelet count [73]. Studies revealed that α angle was decreased when platelet count fell below $50 \times 10^9$/L [74]. Compared with the transfusion threshold of PLT < $50 \times 10^9$/L, TEG MA < 55 mm reduced the number of platelet transfusions [75].

(3) Plasma Transfusion: FFP, plasma frozen within 24 hours (PF24), thawed plasma (TP), and liquid plasma (LP) are commonly transfused in clinical practice. Usually, when PT or aPTT is 1.5 to 2 times the upper reference value or an international normalized ratio (INR) is 1.5 to 2.0, plasma should be transfused [76]. However, for the patients with advanced cirrhosis, the TEG-guided transfusion strategy via R > 10 minutes led to a significantly less FFP transfusion [75]. Stettler et al. proposed plasma transfusion for injured patients receiving massive transfusions with an R > 4.45 minutes [76]. In severely injured multi-trauma patients, the optimal R value threshold for diagnosing procoagulant factor deficiency was 3.9 to 4.1 minutes, while 4.3 minutes was used to diagnose severe procoagulant factor deficiency [77]. A single FFP unit decreased the R by 5 minutes with a response ratio of 5 min/U of FFP for high-responder surgical patients [78]. Overall, the TEG-guided strategy reduces FFP transfusion and severe transfusion-related reactions and does not affect bleeding control or survival.

(4) Cryoprecipitate Transfusion: When fibrinogen consumption (e.g., disseminated intravascular coagulation) and/or loss (e.g., due to massive hemorrhage) occur, cryoprecipitate transfusion may be necessary to maintain coagulation potential [79]. The critical point of fibrinogen concentration is 100 mg/dL. Prolonged K or decreased α angle indicates fibrinogen deficiency, which can be corrected by cryoprecipitation or lyophilized fibrinogen concentrates [80]. TEG α angle less than 45° instead of fibrinogen < 80 mg/dL can save cryoprecipitate transfusion in liver cirrhosis patients [75]. In Stettler et al.'s study, fibrinogen products were recommended for trauma activation patients with α angle less than 67° [76]. Savage et al. used the MA/R ratio to describe the patients with a specific risk for traumatic coagulopathy whose mortality decreased as the MA/R ratio increased. Meanwhile, they also

comment on earlier administration of cryoprecipitate, which can increase the MA/R ratios and benefit resuscitation [81].

## 4. Summary and Future Perspectives

In this review, we summarized the diagnostic characteristics of TEG in hemorrhage and hypercoagulability diseases and the guidance for blood transfusion. As a reporter for the process of whole blood coagulation and fibrinolysis, TEG is increasingly used for guiding anticoagulant drug use and coagulopathy identification in other diseases. However, despite the advances achieved in TEG-guided clinical therapy, the distinguishable diagnostic characteristics and blood transfusion threshold for treating patients are not fully understood. In the future, more models simulating the thrombus formation and fibrinolysis processes are needed to study the changes under different physiological and pathological conditions *in vivo*, and more high-quality randomized controlled trials will be developed to reveal the TEG characteristics in patients with different diseases. With these advances, we can further explore its roles in reducing transfusion of blood components, overall mortality, and treatment cost.

## Author Contributions

Conceptualization: S.W. (Shichun Wang) and C.Y.; Methodology: S.W. (Shichun Wang), Q.L., and C.Y.; Visualization: S.W. (Shichun Wang), Q.L., S.W. (Shan Wang), and J.Y.; Writing—Original Draft Preparation: S.W. (Shichun Wang), Q.L., Y.F., and Y.X.; Writing—Review & Editing: S.W. (Shichun Wang) and C.Y.

## Ethics Statement

Not applicable.

## Informed Consent Statement

Not applicable.

## Funding

This research was funded by the Natural Science Foundation of Chongqing (Grant No. cstc2021jcyj-msxmX0702 and cstb2022nscq-msx0974) and the National Natural Science Foundation of China (Grant No. 81700180).

## Declaration of Competing Interest

The authors declared no conflict of interests.

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