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Uncovering hypercoagulation status using rotational thromboelastometry in patients with sepsis presented with hypocoagulation based on conventional coagulation tests: an observational study

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Abstract. – OBJECTIVE: Conventional coagulation tests (CCTs) cannot identify hypercoagulation, despite being common in patients with sepsis. Moreover, CCTs overdiagnose hypocoagulation, which increases unnecessary blood transfusion. Therefore, we aimed to use rotational thromboelastometry (ROTEM) to classify the coagulation status of patients with sepsis with abnormal CCTs and to identify the main coagulation components that affect coagulation status.

PATIENTS AND METHODS: This study was part of an observational study to investigate ROTEM use in 161 patients with sepsis with the Sepsis-3 criteria. They underwent concurrent CCTs and ROTEM assessments within 24 hours of Intensive Care Unit admission at the University Medical Center Ho Chi Minh City, from June 2020 to December 2021. This study only extracted data from patients with sepsis with abnormal CCTs, including activated partial thromboplastin time ratio, international normalized ratio (INR), platelet count, and fibrinogen concentration.

RESULTS: A total of 158 patients with sepsis with abnormal CCTs had a median age of 69, and 48.7% were women. Of 34 patients with INR ≥1.6, ROTEM identified 11.8% with hypercoagulation and 20.6% with normal coagulation. Of 29 patients with platelet counts <100 (10^3/mm^3), ROTEM identified 3.5% with hypercoagulation and 24.1% with normal coagulation. In the ROTEM-based hypercoagulability group, an increase in maximum clot firmness was observed in 95.1% of cases; also, this group had significantly higher plasma fibrinogen concentrations than other groups (p<0.005).

CONCLUSIONS: ROTEM can reveal hypercoagulability in patients with sepsis with hypocoagulation based on CCTs. Hyperfibrinogenemia causes hypercoagulation in patients with sepsis.

Key Words:
Coagulopathy, Conventional coagulation test, Hypocoagulation, Hypercoagulation, Rotational thromboelastometry, ROTEM, Hyperfibrinogenemia, Sepsis, Thrombocytopenia.

Abbreviations

aPTT, activated partial thromboplastin time; aPTTr, activated partial thromboplastin time ratio; CCT, conventional coagulation test; CFT, clot formation time; CI, confidence interval; CT, clotting time; EXTEM, assessment of extrinsic coagulation pathway based on rotational thromboelastometry; ICU, intensive care unit; PLT, platelet count; INR, international normalized ratio; INTEM, assessment of intrinsic coagulation pathway based on rotational thromboelastometry; IQR, interquartile range; MCF, maximal clot firmness; PT, prothrombin time; ROTEM, rotational thromboelastometry; TEG, thromboelastography; SOFA, sequential organ failure assessment.

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Introduction

Sepsis is a life-threatening organ dysfunction caused by the dysregulation of the host's response to infection[1,2]. There were 48.9 million sepsis cases and 11 million sepsis-related deaths, accounting for 19.7% of global deaths in 2017[3]. In Vietnam, sepsis represented 16.2% of Intensive Care Unit (ICU) admissions, of which 30% resulted in deaths[4]. The occurrence of sepsis-induced hemostatic disturbances, which have a complex pathogenesis linked to disease severity and play a crucial role in organ dysfunction progression, ranges from 43% to 100%[5,6]. The clinical manifestations of these coagulation disturbances range from mild, subtle activation of the coagulation system to markedly life-threatening disseminated intravascular coagulation[7]. Thus, accurately identifying the coagulation status of patients with sepsis is essential to guide treatment, including antithrombotic therapy or blood product transfusion, to prevent hemorrhage before invasive procedures, thereby contributing to an improved prognosis.

Conventional coagulation tests (CCTs) include international normalized ratio (INR), activated partial thromboplastin time (aPTT), platelet count (PLT), and plasma fibrinogen concentration. CCTs have been widely used in clinical practice for an extended period; however, they have some limitations[6,8,9]. One of the concerning drawbacks of CCTs is that they are performed using plasma components, which do not account for platelets and tissue-bearing cells, thereby leading to an inaccurate reflection of *in vivo* hemostasis[8]. In addition, previous studies[9,10] have demonstrated that CCTs are insufficiently predictive of bleeding in critically ill patients, resulting in suboptimal treatment guidance or blood transfusion monitoring based on the results of CCTs.

Unlike CCTs, viscoelastic testing, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), uses whole blood to analyze the coagulation status at all stages of coagulation and comprehensively assesses *ex vivo* hemostasis, including clot formation, amplification, and dissolution[8]. ROTEM is a newer generation device than TEG, able simultaneously analyze four channels, whereas TEG can only analyze two channels[11]. TEG and ROTEM have similar operational techniques; however, the principal distinction between them lies in the rotating element: the TEG rotates the cup, whereas the ROTEM rotates the pin. ROTEM delivers valuable clinical information, such as clot strength, fibrinolysis, hypercoagulability, and platelet function during clot formation[8,9]. Moreover, ROTEM can yield several results within 5 min, whereas CCTs take approximately an average of 88 min[12]. ROTEM has been validated as an accurate, repeatable technique approved and registered in Europe and the Food and Drug Administration as a legal and reliable method[13,14].

ROTEM detects fluctuating hemostasis in patients with sepsis, ranging from hypercoagulability to hypocoagulability, which is linked to increased mortality rate[6,15-17]. CCTs overdiagnose hypocoagulability in patients with cirrhosis[18] and polytrauma[19]. Moreover, hypocoagulability, detected by ROTEM, is associated with increased mortality in patients with sepsis with a normal INR and aPTT[15]. Conversely, patients with sepsis and thrombocytopenia may reveal hypercoagulability on TEG[16]. Muzaffar et al[20] reported that 80% of patients with sepsis with INR ≥1.6 upon admission had either hypercoagulation or normal coagulation. In patients with cirrhosis with hypocoagulable trends identified by CCTs, the TEG-guided blood product transfusion strategy before invasive procedures significantly reduces the required amount of blood products to be transfused without an increased risk of bleeding compared with the CCT-guided approach[18]. ROTEM testing has been widely applied and demonstrated to reduce the demand for blood transfusions, lower transfusion-related complications, and enhance prognosis in critically ill patients with trauma, cardiac surgery, and liver transplantation[9,18]. In Vietnam, promising ROTEM results were obtained in studies[21,22] involving patients with immune thrombocytopenic purpura and pediatric septic shock. However, studies on the role of ROTEM in evaluating coagulation status, implementation of ROTEM-based transfusion guidelines for invasive procedures, and the use of ROTEM for predicting bleeding risk in patients with sepsis are limited, especially in Vietnam. Therefore, the effectiveness and efficiency of ROTEM in diagnosing hemostasis in patients with sepsis and predicting prognosis, particularly in those with abnormal CCT results, are unclear. We aimed to use ROTEM and CCTs to assess coagulation status and classify hypocoagulation, hypercoagulation, and normal coagulation in patients with sepsis with abnormal CCTs, and to identify which coagulation components significantly affect coagulation status.

Patients and Methods

Study Settings and Design

This study was part of an observational, single-centre study conducted at the 30-bed non-COVID-19 Medical-Surgical-ICU, the University Medical Center, University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam. The University Medical Center is a teaching and referral hospital with 910 beds.

Data were collected from June 2020 to December 2021. All eligible patients or their legal representatives were fully informed about the study and signed written consent forms before data collection. The Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City approved the study (reference number: IRB-VN01002/IRB00010293/FWA00023448, 349/HĐĐĐ-ĐHYD date May 26th, 2020).

Sampling and Participants

Participants were recruited if they (i) were 18 years or older, (ii) were diagnosed with sepsis upon admission, and (iii) presented with abnormal CCTs results. Sepsis diagnosis was established when there was an acute increase in the total sequential organ failure assessment (SOFA)[23] score of ≥2 points due to infection[24]. A baseline SOFA score of 0 points was assumed in cases without prior information about organ dysfunction[24]. Abnormal CCT results were identified if the CCT results [INR, aPTT ratio (aPTTr), platelet count, and plasma fibrinogen concentration] were beyond the normal laboratory ranges. The normal laboratory ranges for CCTs included INR: 0.8-1.2, aPTTr: 0.8-1.2, PLT: 150-450 (10^3/mm^3), and plasma fibrinogen concentration: 2-4 g/L. CCTs and ROTEM were concurrently performed within 24 h of ICU admission.

Participants were excluded if they (i) received blood product transfusions (excluding packed red blood cells) within the last 24 h, (ii) had a medical history of coagulation disorders or hematology, (iii) concurrently used anticoagulant or antiplatelet agents, (iv) were diagnosed with cirrhosis Child-Pugh C (Child-Pugh score ≥10 points), (v) were at the end-stage renal disease on intermittent dialysis, (vi) were diagnosed with cancer or (vii) were pregnant.

ROTEM Tests

The ROTEM instrument comprises a pin suspended in a cup filled with blood. Its movement is recorded by a device in non-contact with the pin, thereby allowing for the assessment of changes in viscoelasticity during coagulation. Fibrin formation between the cup and pin influences the pin's movement, resulting in a trace that reflects the distinct phases of the clotting process through mechanical impedance, which is detected and displayed as a diagram on the computer screen. ROTEM instruments have several separate channels that allow simultaneous or sequential running of samples and provide different

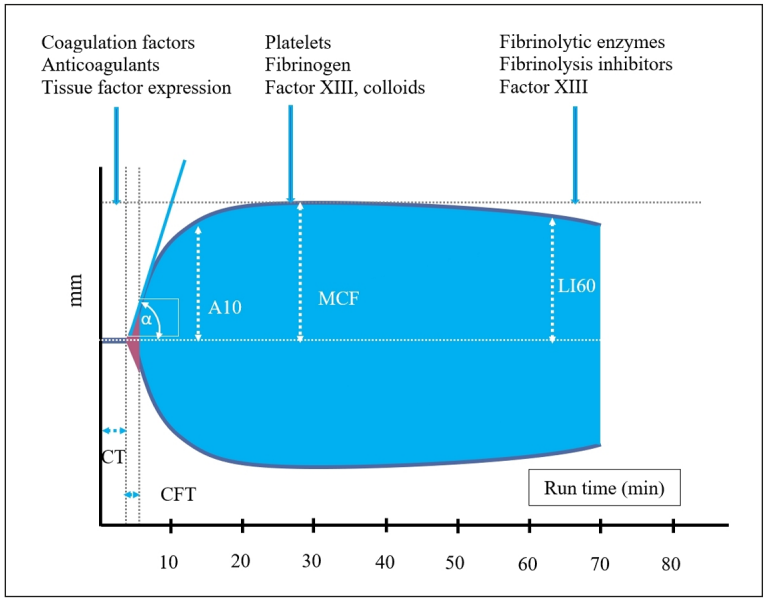

Figure 1. Important parameters on rotation thromboelastometry. CT, clotting time; CFT, clotting formation time; A10, amplitude 10 min after CT; MCF, maximum clot firmness; LI60, lysis index 60 min after CT.

meanings depending on the reagents used[25]. We used ROTEM® delta (TEM International GmbH, Germany) in this study.

The assessment of extrinsic coagulation pathway based on rotational thromboelastometry (EXTEM) channel was used to evaluate the extrinsic coagulation pathway by adding tissue factors. The assessment of intrinsic coagulation pathway based on rotational thromboelastometry (INTEM) channel was used to evaluate the intrinsic coagulation pathway by adding ellagic acid[25].

The following ROTEM parameters were collected: (i) clotting time (CT), the period from initiation of the test to the formation of the clot with an amplitude of 2 mm; (ii) clot formation time (CFT), the duration from the blood clot at 2 mm amplitude until the amplitude reached 20 mm; and (iii) maximum clot firmness (MCF), the maximum amplitude of clot[25] (Figure 1).

ROTEM Results

ROTEM parameters were considered abnormal if they exceeded the normal range based on the manufacturer's instructions[25]. The reference values for $CT\text{-}_{INTEM}$ (100-240 s), $CFT\text{-}_{INTEM}$ (30-110 s), $MCF\text{-}_{INTEM}$ (50-72 mm), $CT\text{-}_{EXTEM}$ (38-79 s), $CFT\text{-}_{EXTEM}$ (34-159 s), $MCF\text{-}_{EXTEM}$ (50-72 mm) were used in this study[25]. Based on the ROTEM results, hypocoagulation was defined as having one or more of the following criteria: prolonged CT, CFT, or decreased MCF of the INTEM or EXTEM channels[6]. Conversely, hypercoagulation was defined as one or more of the following criteria: shortened CT, CFT, or increased MCF of the INTEM or EXTEM channels[6]. Normal coagulation was determined if neither the hypo nor hypercoagulation criteria were met.

Statistical Analysis

Data were entered using Epidata 3.1 (available at: https://www.epidata.dk) and analyzed using Intercooled Stata version 17 (College Station, TX, USA). Sex, vasopressor use, mechanical ventilation support, in-hospital mortality, and source of infection were described as frequencies and percentages. Age, SOFA score, NR, aPTTr, platelet counts, fibrinogen concentrations, $CT\text{-}_{INTEM}$, $CFT\text{-}_{INTEM}$, $MCF\text{-}_{INTEM}$, $CT\text{-}_{EXTEM}$, $CFT\text{-}_{EXTEM}$ and $MCF\text{-}_{EXTEM}$ were described as medians and interquartile ranges (IQRs). The Wilcoxon-Mann-Whitney U test was used to compare the INR, aPTTr, platelet counts, and fibrinogen levels between the hypocoagulation, hypercoagulation, and normal coagulation groups. All statistical tests were performed using two-tailed tests at 5% significance. Statistical significance was set at a two-sided *p*-value of 0.05.

Results

Patient Characteristics

We recruited 158 participants with a median age of 69 years [IQR 60-81], and 48.7% were women. The median SOFA score was 6.5 [IQR 4-9]. The percentage of patients with septic shock was 44.3%. The percentages of patients using vasopressors and mechanical ventilation support were 53.2% and 53.8%, respectively. The in-hospital mortality rate was 20.4%. Approximately 50% of patients with sepsis had a pulmonary source of infection. The median values for INR, aPTTr, platelet counts, and plasma fibrinogen concentrations in the study population were 1.32 [1.15-1.55], 1.06 [0.93-1.2], 200 [127-273] and 5.51 [4.15-6.71], respectively. Further details are presented in Table I.

Coagulation Status Classification Based on Rotem Results

In the patients with sepsis, the percentage of patients with abnormal CCTs was extremely high; 98.1% (158/161). Among the 158 patients with sepsis with abnormal CCTs, ROTEM revealed 55.7% (88/158) had hypocoagulation, 25.9% (41/158) had hypercoagulation, and 32.3% (51/158) had normal coagulation.

ROTEM revealed 27.2% hypercoagulation, 27.2% normal coagulation, and 62.1% hypocoagulation among patients with INR ≥1.2. Similarly, among patients with INR ≥1.6, ROTEM revealed 11.8% hypercoagulation, and 20.6% normal coagulation (Figure 2).

In the patients with INR ≥1.2, ROTEM classified 27.2% with hypercoagulation, 27.2% with normal coagulation, and 62.1% with hypocoagulation. Among the patients with INR ≥1.6, ROTEM classified 11.8% with hypercoagulation and 20.6% with normal coagulation (Figure 2). Among 12 patients with aPTTr <0.8, ROTEM classified 58.3% with hypocoagulation, 33.3% with normal coagulation, and 8.3% with hypercoagulation (Figure 3).

ROTEM classified 55.6% of patients with platelet counts ≥450 ($10^3/mm^3$) and 42.9% of those with platelet counts ≥500 ($10^3/mm^3$) as having hypocoagulation. Among the patients with

Table I. Baseline, laboratory, and clinical characteristics of the study population (n = 158).

Variables	Normal value	N (%)	Median [IQR]
Age (years)			69 [60-81]
Sex, n (%)			
Male		81 (51.3)	
Female		77 (48.7)	
Sepsis subgroups, n (%)			
Sepsis without shock		88 (55.7)	
Septic shock		70 (44.3)	
SOFA score			6.5 [4-9]
Vasopressor, n (%)		84 (53.2)	
Mechanical ventilation, n (%)		80 (53.8)	
In-hospital mortality, n (%)		29 (20.4)	
Source of infection, n (%)			
Lung		67 (42.4)	
Others		91 (57.6)	
INR	0.8-1.2		1.32 [1.15-1.55]
aPTTr	0.8-1.2		1.06 [0.93-1.2]
PLT (10^3/mm^3)	150-450		200 [127-273]
Fibrinogen (g/L)	2-4		5.51 [4.15-6.71]
CT-INTEM (s)	100-240		212 [184-253]
CFT-INTEM (s)	30-110		72 [59-96]
MCF-INTEM (mm)	50-72		65.5 [60-71]
CT-EXTEM (s)	38-79		73 [63-86]
CFT-EXTEM (s)	34-159		74 [60-98]
MCF-EXTEM (mm)	50-72		67 [62-72]

IQR, interquartile range; SOFA, sequential organ failure assessment; SD, standard deviation; INR, international normalized ratio; aPTTr, activated partial thromboplastin time ratio; PLT, platelet counts; CT, clotting time; CFT, clot formation time; MCF: maximum clot firmness.

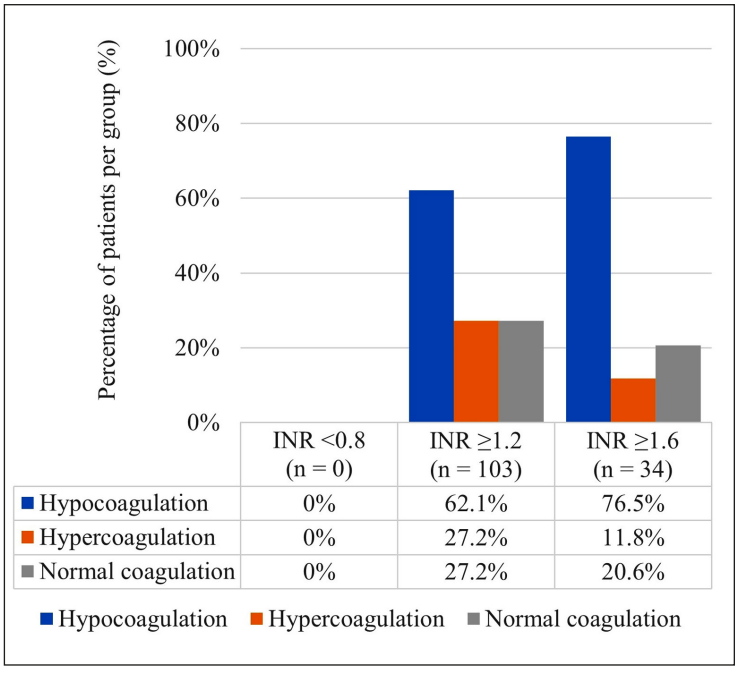

Figure 2. Various coagulation forms defined by ROTEM in patients with abnormal INR. As the groups are not mutually exclusive, the patient numbers can exceed 100%. ROTEM, rotational thromboelastometry; INR, international normalized ratio.

platelet counts <150 (10^3/mm^3) or <100 (10^3/mm^3), ROTEM classified approximately 25% with normal coagulation and 75% with hypocoagulation. Similarly, among those with platelet counts <100 (10^3/mm^3), ROTEM classified 24.1% as having normal coagulation and 3.5% as having hyper-

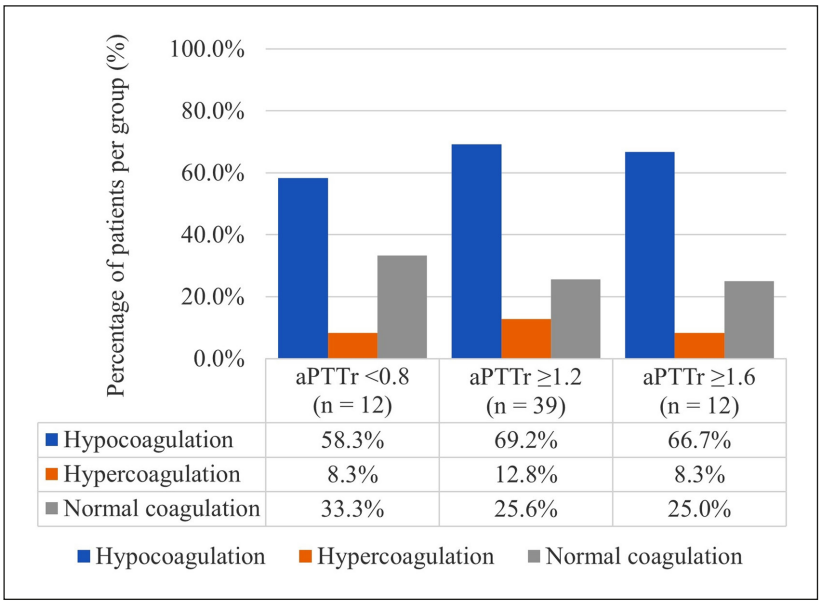

Figure 3. Various coagulation forms defined by ROTEM in patients with abnormal aPTTr. As the groups are not mutually exclusive, the patient numbers can exceed 100%. aPTTr, activated partial thromboplastin time ratio.

coagulation. ROTEM identified all patients with platelet counts of <50 (10^3/mm^3) as having hypocoagulation (Figure 4).

According to the ROTEM classification, all patients with plasma fibrinogen concentration <2 g/L had hypocoagulation, whereas, for those with fibrinogen concentrations ≥4 g/L, the hypocoagulability rate was 51.6% and hypercoagulability rate was 30.2% (Figure 5).

The Main Components Affecting Coagulation Status in Patients with Sepsis

In the ROTEM-based hypocoagulation group, a prolonged CT-$_{INTEM}$ and CT-$_{EXTEM}$ were common with rates of 58.0% and 67.0%, respectively, whereas a decreased MCF-$_{INTEM}$ and MCF-$_{EXTEM}$ had low rates of 14.8% and 12.5%, respectively. Conversely, in the ROTEM-based hypercoagulation group, the rates of increased MCF-$_{INTEM}$ and

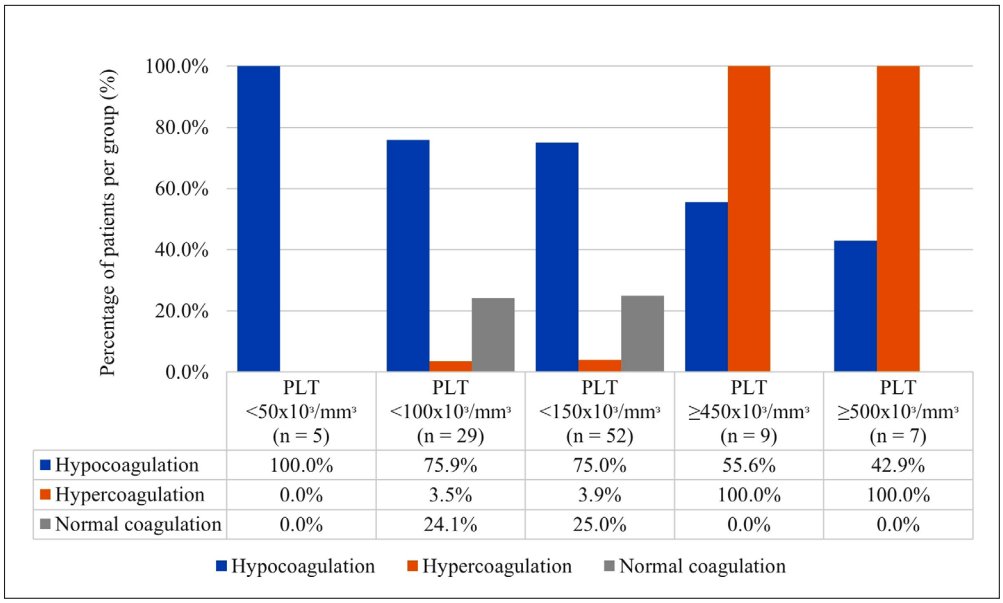

Figure 4. Various coagulation forms defined by ROTEM in patients with abnormal PLT. As the groups are not mutually exclusive, the patient numbers can exceed 100%. PLT, platelet count.

Table II. The prevalence of ROTEM parameter abnormalities (n = 158).

	Criteria	ROTEM-based hypercoagulation n = 41			Criteria	ROTEM-based hypocoagulation n = 88		
		INTEM n (%)	EXTEM n (%)	INTEM/EXTEM n (%)		INTEM n (%)	EXTEM n (%)	INTEM/EXTEM n (%)
CT	Shortened	1 (2.4)	1 (2.4)	2 (4.9)	Prolonged	51 (58.0)	59 (67.0)	81 (92.1)
CFT	Shortened	0 (0)	1 (2.4)	1 (2.4)	Prolonged	26 (29.5)	11 (12.5)	27 (30.7)
MCF	Increased	32 (78.0)	36 (87.8)	39 (95.1)	Decreased	13 (14.8)	11 (12.5)	15 (17.1)

CT, clotting time; CFT, clot formation time; MCF, maximum clot firmness; INTEM, assessment of intrinsic coagulation pathway based on rotational thromboelastometry; EXTEM, assessment of extrinsic coagulation pathway based on rotational thromboelastometry.

MCF-$_{EXTEM}$ were 78.0% and 87.8%, respectively, whereas the proportions of decreased CT-$_{INTEM}$ and CT-$_{EXTEM}$ were extremely low (2.4%, Table II).

In addition, the fibrinogen levels were higher in the ROTEM-based hypercoagulation group than in the normal and hypocoagulation groups. The ROTEM-based hypocoagulation group had a higher INR and aPTTr, lower fibrinogen levels, and lower platelet counts than the ROTEM-based hypercoagulation group (Table III).

Discussion

Our study revealed heterogeneity in the coagulation results between ROTEM and CCTs in patients with sepsis. Specifically, according to the ROTEM classification, patients with INR or aPTTr >1.2 or >1.6 had various coagulation forms, including hypercoagulability, hypocoagulability, and normal coagulation. Similarly, hypercoagulability and hypocoagulability were observed in the thrombocytosis and hyperfibrinogenemia groups.

The pathogenesis of sepsis-induced hemostatic disturbances is complicated and involves activation of the coagulation cascade, platelets, inflammatory cells (such as neutrophils and lymphocytes), and vascular endothelial cell injury. Tissue factors, prothrombotic molecules, and circulating plasma proteins that act as anticoagulants (including antithrombin, protein S, and protein C) also contribute to the coagulation process[5,26]. It

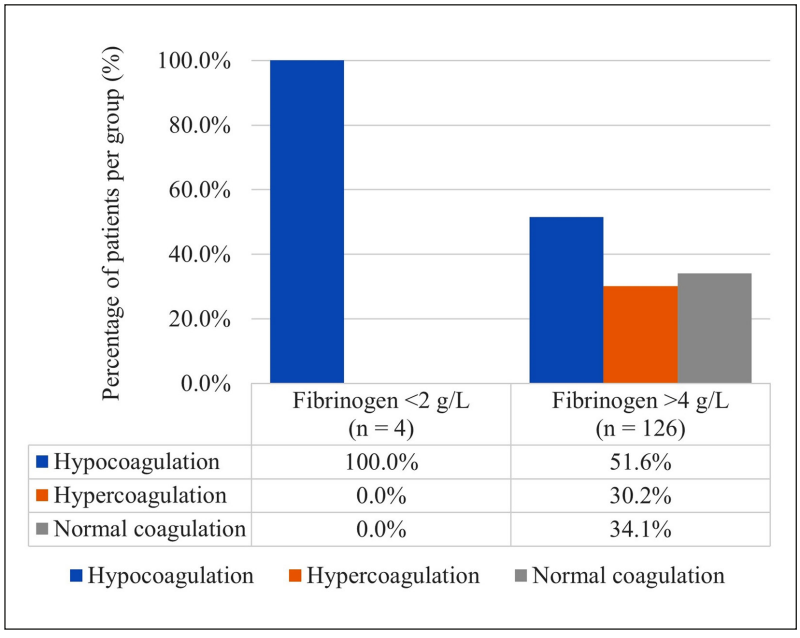

Figure 5. Various coagulation forms defined by ROTEM in patients with abnormal plasma fibrinogen concentration. As the groups are not mutually exclusive, the patient numbers can exceed 100%.

Table III. Comparing results of the conventional coagulation test with different ROTEM-based coagulation status types (n = 136†).

	Normal coagulation (A) n = 51	ROTEM-based pure hypocoagulation (B) n = 66	ROTEM-based pure hypercoagulation (C) n = 19	*p* (AB) n = 117	*p* (AC) n = 70	*p* (BC) n = 85
INR	1.21 [1.08-1.45]	1.43 [1.17-1.8]	1.24 [1.14-1.37]	0.004*	0.942	0.021*
aPTTr	1.02 [0.89-1.16]	1.13 [0.96-1.36]	1.02 [0.91-1.11]	0.023*	0.99	0.099
PLT	207 [147-258]	135 [86-188]	275 [212-419]	< 0.001*	< 0.001*	< 0.001*
Fibrinogen	5.07 [4.28-5.72]	5.205 [3.33-6.66]	6.69 [5.86-7.39]	0.889	< 0.001*	0.002*

†To avoid bias, we excluded 22 cases with both hypercoagulation and hypercoagulation based on ROTEM. *$p < 0.05$. *p* (AB): Wilcoxon-Mann-Whitney test for comparing the values of INR, aPTTr, platelet counts, and fibrinogen levels between the normal coagulation and the pure hypocoagulation groups. *p* (AC): Wilcoxon-Mann-Whitney test for comparing the values of INR, aPTTr, platelet counts, and fibrinogen levels between the normal coagulation and the pure hypercoagulation groups. *p* (BC): Wilcoxon-Mann-Whitney test for comparing the values of INR, aPTTr, platelet counts, and fibrinogen levels between the pure hypocoagulation and the pure hypercoagulation groups. ROTEM, rotational thromboelastometry; INR, international normalized ratio; aPTTr, activated partial thromboplastin time ratio; PLT, platelet count.

Table IV. Comparison of the change in ROTEM parameters between the ROTEM-based hypercoagulation and ROTEM-based hypocoagulation groups in our study.

ROTEM parameters	Main components affect ROTEM parameters	ROTEM-based hypercoagulation		ROTEM-based hypocoagulation	
		Criteria	Our study	Criteria	Our study
CT	Coagulation factors Anticoagulation Tissue factor	Shortened	Rarely	Prolonged	**Common**
CFT	Platelet and fibrinogen	Shortened	Rarely	Prolonged	Less common
MCF	Platelet and fibrinogen	Increased	**Common**	Decreased	Less common

CT, clotting time; CFT, clot formation time; MCF, maximum clot firmness; ROTEM, rotational thromboelastometry.

is critical to note that hemostasis involves the interaction of numerous components. ROTEM estimates the viscoelastic properties of whole blood. In contrast, INR and aPTTr solely evaluate the procoagulant factors of the plasma component; platelets and other cellular components are removed during the preanalytical step[27]. Thus, previous studies[9,18,19,27,28] have reported inconsistent results for ROTEM and CCTs. They suggested that ROTEM more accurately reflected the actual coagulation status in patients with cirrhosis[18,27], surgery[9], polytrauma[19], burns[27], and COVID-19[28]. ROTEM-guided blood product transfusion guidelines, such as the European guideline[29], have been implemented in clinical practice.

Based on ROTEM, hypercoagulability is determined by decreased CT, CFT or increased MCF in INTEM/EXTEM[6]. Our research revealed that the most popular criterion for ROTEM-based hypercoagulability was an increased MCF (95.1%, Table II), whereas a shortened CT or CFT had an extremely low rate. MCF depends on fibrinogen and platelets, whereas CT relies on the level of coagulation factors[25] (Figure 1, Table II, and

Table IV). Typically, an increased MCF is due to elevated fibrinogen levels, platelet counts, or both. Of note, our study revealed that hyperfibrinogenemia was common in patients with sepsis, in approximately 80% of cases (126/158), similar to other studies[20,30-32]. Moreover, the ROTEM-based hypercoagulation group had higher fibrinogen levels than the other groups. This finding has also been reported by Kim et al[16]. In addition to its function in clot formation, fibrinogen is involved in the host defense against bacterial invasion[33]. In sepsis, hyperfibrinogenemia predominantly results from increased fibrinogen synthesis as an acute response to infection[31]. Furthermore, elevated C-reactive protein levels are strongly associated with hyperfibrinogenemia, providing evidence of an inflammatory etiology[30]. In contrast, our study revealed that thrombocytosis was uncommon in patients with sepsis, with 5.7% (9/158) of patients having PLT >450 (10^3/mm^3). Other studies[34,35] have demonstrated that thrombocytosis prevalence is much lower than that of thrombocytopenia in patients with sepsis. Therefore, increased MCF levels were due to hyperfibrinogenemia and elevated fibrinogen levels induce hypercoagulation in patients with sepsis.

ROTEM-based hypocoagulation was defined as prolonged CT, CFT, or decreased MCF in INTEM/EXTEM[6]. Our study revealed that 92.1% of the ROTEM-based hypocoagulation group had prolonged CT, whereas prolonged CFT and decreased MCF were less common. As mentioned above, CT depends on coagulation factors, whereas CFT and MCF rely mainly on platelets and fibrinogen (Figure 1, Table II, and Table IV). In sepsis, the levels of coagulation factors (except factor VIII) decrease[30,36], which causes increased INR, increased aPTTr, and prolonged CT, resulting in hypocoagulation. Moreover, thrombocytopenia contributes to a decreased MCF. However, approximately 60% of patients with INR >1.2 and 75% of those with a platelet count <150 (10^3/mm^3) revealed ROTEM-based hypocoagulation in our study. In a retrospective study by Kim et al[16], which investigated 889 patients with septic shock with thrombocytopenia, only 15.4% revealed hypocoagulation, whereas 18% of the patients exhibited hypercoagulation based on TEG. Muzaffar et al[20] reported that up to 80% of patients with sepsis with thrombocytopenia had normal coagulation results on TEG. This phenomenon could be explained by hyperfibrinogenemia, which partly compensates for the low levels of other coagulation factors and thrombocytopenia. Therefore, ROTEM-based hypocoagulation is caused by low levels of coagulation factors and thrombocytopenia, which are partly compensated for by hyperfibrinogenemia.

In clinical practice, ROTEM accurately reflects the need for preprocedural blood product transfusions. According to the case series report of Luckner et al[37], the patients with sepsis who had INR between 2.5-3.1 or aPTT between 61-80 s and concurrently ROTEM-based hypercoagulability underwent successfully invasive procedures without requiring preprocedural transfusion of blood product. In another study, Lukas et al[38] investigated 76 patients with sepsis with a mean INR of 1.59 and concomitantly normal thromboelastometry. Although fresh frozen plasma or other clotting factors were not administered to correct the INR before the procedure, none of these patients experienced severe bleeding events during the invasive procedures, even during high-risk bleeding invasive procedures.

Our study has some utilization in clinical practice. Firstly, in patients with sepsis having INR >1.2 or platelet counts between 50-150 (10^3/mm^3), clinicians should consider performing the ROTEM test before blood product transfusion or invasive intervention for better clinical decisions. Secondly, we revealed that hyperfibrinogenemia causes hypercoagulation, which is common in sepsis; thus, research on antithrombotic agents in populations with sepsis should concentrate on fibrinogen action. Thirdly, to our knowledge, our study is the first to provide a clear and detailed analysis of which coagulation components affect the coagulation status in ROTEM in patients with sepsis. Moreover, our study represents a pioneering effort to use ROTEM to evaluate the coagulation status of adult patients with sepsis in Vietnam.

Limitations

However, this study had several limitations. Firstly, we did not investigate the clinical factors associated with coagulation status classified by CCTs or ROTEM, such as blood transfusion requirement, bleeding in invasive procedures or thrombosis; hence, ROTEM's usefulness in clinical application in patients with sepsis was not comprehensively evaluated. Secondly, coagulation factor levels were not measured. Thirdly, the overall reference values provided by the manufacturer did not account for the age or sex of the healthy Vietnamese population. Therefore, further research is required to determine the utility of ROTEM in predicting hemorrhagic events

or thrombosis in the Vietnamese population with sepsis and to find reference values for ROTEM tests in the Vietnamese population.

Conclusions

In addition to hypocoagulation, ROTEM classified hypercoagulation and normal coagulation in patients with sepsis who had hypocoagulation trends based on CCTs. Hyperfibrinogenemia resulted in ROTEM-based hypercoagulation. Elevated fibrinogen levels compensated for the low platelet counts, which caused ROTEM to identify hypocoagulation at a lower rate than CCTs in patients with sepsis. Therefore, ROTEM tests need to be performed in septic patients with CCTs-based hypocoagulation tendency for evaluating coagulation status more comprehensively. Moreover, studies on treatment modalities that target the role of fibrinogen in hypercoagulable states in patients with sepsis need to be developed.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

The Ethics Committee, University of Medicine and Pharmacy at Ho Chi Minh City approved the study (reference number: IRB-VN01002/IRB00010293/FWA00023448, 349/HĐĐĐ-ĐHYD date May 26th, 2020).

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Authors' Contribution

Bui-Thi Hanh Duyen conceptualized the study and curated the data. Bui Thi Hanh Duyen, Le Minh Khoi, and Nguyen Dang Khoa collected and analyzed the data. To Gia Kien performed the statistical analysis. Le Minh Khoi supervised the study. Bui Thi Hanh Duyen, Nguyen Dang Khoa, Bui The Dung, Tran Hoa, and Nguyen Minh Duc wrote the manuscript. Bui Thi Hanh Duyen, Le Minh Khoi, Nguyen Dang Khoa, Bui The Dung, Tran Hoa, and To Gia Kien revised and edited the manuscript. All authors have reviewed and approved the final version of the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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