Received: 5 February 2024 | Accepted: 21 February 2024

https://doi.org/10.1016/j.rpth.2024.102362

ORIGINAL ARTICLE

Fibrinogen contribution to clot strength in patients with sepsis and hematologic malignancies and thrombocytopenia—a prospective, single-center, analytical, cross-sectional study

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Handling Editor: Sanfilippo.

Abstract

Background: Patients with hematological malignancies (HM) frequently present thrombocytopenia and higher risk of bleeding. Although transfusion is associated with higher risk of adverse events and poor outcomes, prophylactic transfusion of platelets is a common practice to prevent hemorrhagic complications. Thromboelastometry has been considered a better predictor for bleeding than isolated platelet counts in different settings. In early stages of sepsis, hypercoagulability may occur due to higher fibrinogen levels.

Objectives: To evaluate the behavior of coagulation in patients with HM who develop sepsis and to verify whether a higher concentration of fibrinogen is associated with a proportional increase in maximum clot firmness (MCF) even in the presence of severe thrombocytopenia.

Methods: We performed a unicentric analytical cross-sectional study with 60 adult patients with HM and severe thrombocytopenia, of whom 30 had sepsis (sepsis group) and 30 had no infections (control group). Coagulation conventional tests and specific coagulation tests, including thromboelastometry, were performed. The main outcome evaluated was MCF.

Results: Higher levels of fibrinogen and MCF were found in sepsis group. Both fibrinogen and platelets contributed to MCF. The relative contribution of fibrin was significantly higher (60.5 ± 12.8% vs 43.6 ± 9.7%; $P < .001$) and that of platelets was significantly lower (39.5 ± 12.8% vs 56.4 ± 9.7%; $P < .001$) in the sepsis group compared with the control group.

Conclusion: Patients with sepsis and HM presented higher concentrations of fibrinogen than uninfected patients, resulting in greater MCF amplitudes even in the presence of thrombocytopenia.

KEYWORDS
hematological malignancies, platelet transfusion, sepsis, thrombocytopenia, thromboelastometry

Essentials

- Thromboelastometry can support the decision on platelet transfusion in hematological patients.
- Hematological patients with low platelet count with and without sepsis were studied.
- Both fibrinogen and platelets contributed to clot strength.
- Higher fibrinogen concentration was associated with increased clot strength in patients with sepsis.

1 | INTRODUCTION

Thrombocytopenia is a common complication in patients with hematological malignancies (HM), whether as a result of the malignancy or caused by chemotherapy treatment, and is associated with an increased risk of bleeding [1]. Traditionally, prophylactic platelet transfusion has been indicated based on the platelet count to reduce the risk of spontaneous bleeding or bleeding associated with invasive or surgical procedures [2]. However, transfusion is also associated with an increased risk of adverse events, and the indication levels for prophylactic platelet transfusions also vary between different groups. Among allogeneic blood components, platelet concentrates carry a high risk of infection and acute lung injury, so it is advisable to avoid them in patients with compromised immunity [3–5]. Thus, a reduction in prophylactic platelet transfusion could be safer and cost effective for these patients, considering the increased costs and reduced availability of platelet concentrates [6–9]. Furthermore, patients with HM have an increased risk of developing sepsis and septic shock, often leading to multiple organ dysfunction syndrome and death [10]. In early stages of sepsis, there is an activation of the coagulation cascade, leading to a hypercoagulable state. Acute phase proteins such as fibrinogen, factor VIII, and von Willebrand factor are usually increased at this stage [11,12].

Fibrinogen is rapidly produced in large amounts by the liver after the onset of infection and inflammation. Fibrinogen concentration increases up to 20-fold following tissue injury, infection, and inflammation, triggered by interleukin-6 release [13]. Fibrinogen also serves as a protective barrier, acting through the fibrin network to trap and contain bacteria, contributing to immunothrombosis. The rapid increase in fibrinogen concentration in sepsis enhances the hypercoagulability response [14].

Fibrin and platelets are determinants of clot strength (or clot firmness) in healthy individuals, and a decrease in one might be compensated by the other [15–17]. In the face of an acute systemic inflammatory disease, fibrinogen appears to play the main role in blood coagulability. Studies on dilutional coagulopathy in trauma and cardiac surgery with thrombocytopenia have shown the role of fibrinogen concentrate as capable of compensating for the deleterious effect of thrombocytopenia, improving the clot strength, and, consequently, reducing bleeding [18–21]. Hemostatic therapy using a strategy based on clot strength improvement might prevent spontaneous bleeding and decrease bleeding complications associated with invasive procedures [22]. Viscoelastic testing reduces the need for allogeneic blood transfusion and improves outcomes in cardiac surgery, trauma, and liver transplantation [23–28].

We hypothesized that in patients with HM and thrombocytopenia, the presence of sepsis would trigger an increase in the fibrinogen concentration due to the activation of the systemic inflammatory response, leading to a compensatory increment in clot strength and, consequently, a greater tendency to hypercoagulability. Accordingly, we investigated the behavior of the coagulation cascade in patients with HM and thrombocytopenia in the presence and absence of sepsis by analyzing whether the higher concentration of fibrinogen as an acute phase protein could compensate for the impairment of maximum clot firmness (MCF) caused by thrombocytopenia.

2 | METHODS

2.1 | Study design

In this single-center, analytical, cross-sectional study, we evaluated consecutive adult patients with a diagnosis of HM admitted with severe thrombocytopenia to a tertiary hospital between December 17, 2019, and March 29, 2021. We assessed coagulation using conventional and specific tests, including thromboelastometry (TEM) and thrombin generation assay (TGA), as described below, and compared the results between a group with sepsis (sepsis group [SG]) and another group with no infection (control group [CG]).

Ethical approval was obtained from the Research Ethics Committee of Hospital Israelita Albert Einstein, protocol number 81865517.4.0000.0071. Informed consent was obtained before participants were included in the study.

2.2 | Study population and setting

This study was carried out in both the intensive care unit (ICU) and the hematology department (ward) of Hospital Israelita Albert Einstein, a referral center for oncology, hematology, and transplantation

in São Paulo, Brazil. Patients aged 18 years or over, admitted within the first 24 hours to the ward with a diagnosis of HM (including post–bone marrow transplant patients) and presenting severe thrombocytopenia (platelet count below 50.000 per mm^3), were included. For analysis, they were allocated to the CG if they had no infection, defined as absence of fever, no antibiotic use, and negative blood cultures, and to the SG if they had sepsis within the first 24 hours of diagnosis, defined according to the Sepsis-3 criteria, and were admitted to the ICU [29] (Figure 1).

We excluded patients with chronic kidney failure, pregnancy, von Willebrand's disease, or any other known inherited coagulation abnormalities. We also excluded patients who were undergoing antiplatelet therapy within 7 days before blood sampling.

2.3 | Sample size calculation

Based on our primary hypothesis of sepsis triggering an increase in the fibrinogen concentration due to the activation of the systemic inflammatory response, ultimately leading to hypercoagulability, we calculated the sample size necessary to detect an increase of at least 10 mm in extrinsic coagulation pathway (EXTEM) MCF [30]. This threshold was based on previous studies determining the main cutoff values for bleeding risk [31]. Considering a baseline value of this parameter in patients with HM and thrombocytopenia of 35 ± 11 mm (mean ± SD) and using a power of 90% and a CI of 95%, the sample size required to perform the study was 26 patients in each group. However, we decided for a total sample size of 60 patients (30 patients in each group), considering possible dropouts.

2.4 | Data collection and study outcomes

Part of the data used in this study are routinely collected in the hospital and were extracted from medical records. Additional blood samples were required for specific coagulation tests. Blood tests were collected only on day 0, while on the 21st day after inclusion of patients in the study, data related to clinical outcomes were recorded in a specific Case Report Form .

Demographic and baseline data assessed were date of admission to ward and ICU; date of birth; sex; smoking history; alcohol history; comorbidities, including hypertension, chronic obstructive pulmonary disease, diabetes mellitus, and malignancies; and drug use history. Clinical outcomes we evaluated were transfusion, bleeding, and death. Bleeding events were defined according to the criteria of International Society on Thrombosis and Haemostasis (ISTH) as clinically overt bleeding, followed by a drop in the hemoglobin level by 20 g/L and/or leading to the transfusion of 2 or more units of red blood cells in the first 21 days after inclusion of the patient in the study [32].

Once the patient was admitted to hospital and included in the study, we collected information on day 0 about coagulation conventional tests (CCT), levels of coagulation factors, inhibitors, fibrinolysis markers, TGAs (Technothrombin, DPM Diagnostica), and rotational

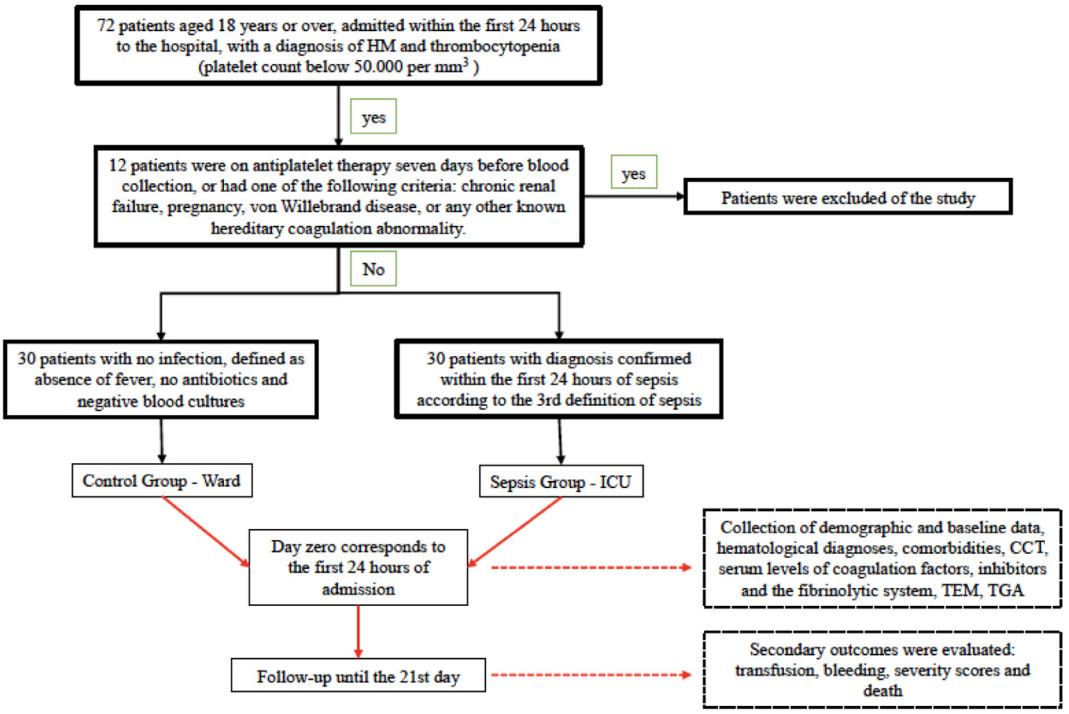

FIGURE 1 Study flowchart. HM, hematological malignancies; ICU, intensive care unit; CCT, conventional coagulation tests; TEM, thromboelastometry; TGA, thrombin generation assay.

TEM (ROTEM *delta*, TEM Innovations). The laboratory tests performed are listed in Supplementary Table S1.

To measure the concentration of fibrinogen, the Clauss method was used, carried out using a sample of citrated plasma poor in platelets, at a temperature of 37 °C (ACL TOP 750 LAS, Instrumentation Laboratory Company).

For TEM analysis, the following tests were performed: evaluation of the EXTEM, evaluation of the intrinsic coagulation pathway (INTEM), and evaluation of the extrinsic coagulation pathway with platelet inhibition by cytochalasin D (FIBTEM). The parameters of TEM evaluated were as follows: 1) clotting time (CT, seconds): time from the beginning of the tests until reaching the amplitude of 2 mm; 2) clot formation time (CFT, seconds): time between amplitudes of 2 to 20 mm; 3) parameters that assess clot firmness at different times: amplitude at 5 (A5) and 10 (A10) minutes (mm) after CT and MCF (mm); and 4) lysis index (%) and maximum lysis (%). The additional test platelet contribution to clot firmness (PLTEM) was calculated by subtracting the amplitudes at A5, A10, and the MCF obtained in FIBTEM from those obtained in EXTEM (Figure 2) [33,34]. The percentage of fibrin contribution is obtained by dividing the parameters that assess clot firmness (A5, A10, and MCF) in FIBTEM by the respective parameters in EXTEM. And for the contribution of platelets, the same parameters (A5, A10, and MCF) of PLTEM are divided by those found in EXTEM [15,35].

ROTEM was performed with a 300 µL citrated whole blood sample (ROTEM delta, TEM Innovations) collected by venipuncture in a citrate tube (3.2%; Sarstedt). The blood sample was placed in a fixed cup along with the reagent tests in 1 of the 4 available channels, and then the immersed pin rotated 4° 75′. As fibrin beams form, pin rotation is restricted in proportion to the clot strength; pin movement is detected by an optical sensor, providing a graphical representation of the clot formation process. All tests were performed by laboratory technicians within a maximum period of 2 hours after blood collection, as recommended by the manufacturer. There was no change in the methodology for the performance of the tests and its controls (Rotrol N and Rotrol P).

The collected data were used to evaluate the course of the coagulation system in patients with HM and thrombocytopenia in the presence or absence of sepsis by analyzing whether the increase in the concentration of fibrinogen as an acute phase protein could compensate for the impairment of MCF caused by thrombocytopenia as the primary outcome.

As secondary outcomes, we assessed the following:

- The relative contribution of fibrinogen and platelets to clot strength in patients with HM and severe thrombocytopenia with and without sepsis.
- The behavior of the coagulation system in patients with HM with and without sepsis, according to CCT, TEM, and the TGA.
- The dependence of clot strength on fibrinogen and platelet levels, identifying the lowest critical point in fibrinogen concentration and platelet count when a significant decrease in clot firmness occurs [36].
- The severity of the disease using the Sequential Organ Failure Assessment score to assess organ dysfunction and disseminated intravascular coagulation (DIC) scoring systems, including ISTH, Japanese Ministry of Health and Welfare (JMWH), and Association Japanese Medicine of Acute Diseases (JAAM), to predict the risk of mortality in patients with critically illness.

2.5 | Statistical analysis

We described quantitative variables as means (SDs), minimum and maximum levels for normally distributed data, and medians and IQRs for not normally distributed data; we used absolute and relative frequencies for qualitative variables, as appropriate. We compared patient characteristics and laboratory test measurements as well as scores between groups using chi-squared or Fisher exact tests and Student's *t*-tests or Mann–Whitney tests, depending on the data distribution, which we verified using Shapiro–Wilk tests, boxplots, histograms, and graphs of quantile comparisons.

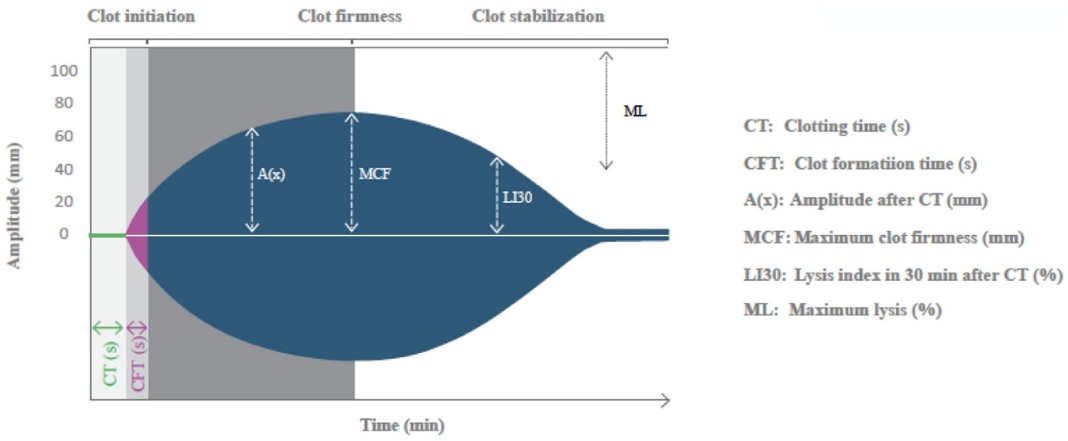

FIGURE 2 Representation of rotational thromboelastometry (ROTEM) tracing (TEMogram). A(x), amplitude in the variable time (x); CFT, clotting formation time; CT, clotting time; LI30, maximum lysis in 30 minutes; MCF, maximum clot firmness; ML, maximum lysis.

The relationship between fibrinogen and MCF was verified using generalized linear models with gamma distribution and identity link function, considering MCF in EXTEM as outcome and fibrinogen and platelet count as response variables. The results were presented based on the ratio of means of 95% CIs and *P* values. To assess the contribution of fibrinogen and platelets to clot firmness (A5, A10, and MCF), we calculated the mean (SD) of FIBTEM MCF/EXTEM MCF x 100 (in percentage) and the mean (SD) of PLTEM MCF/EXTEM MCF x 100 (in percentage) and compared the results between the 2 groups.

We also investigated a cutoff point in fibrinogen levels when there was a significant reduction in clot strength, considered as EXTEM MCF < 55 mm, EXTEM A10 < 45 mm, EXTEM A5 < 35 mm, FIBTEM MCF < 25 mm, and FIBTEM A5 < 20 mm. The analyses were performed using SPSS v26.0 (IBM, SPSS Inc) and R v 4.3.3 (R Core Team), adopting a significance level of 5%.

3 | RESULTS

3.1 | Baseline laboratory tests

During the study period, 72 patients were initially selected, of whom 12 were excluded because they presented some of the defined exclusion criteria, such as concomitant use of antiplatelet agents and chronic renal failure. Therefore, we evaluated the 60 remaining patients. There were no deaths in the 21 days covered.

Table 1 shows that, except for tobacco use, the groups were similar at baseline. There was no significant difference between the groups regarding the diagnosis of HM (*P* = .68), and the most common diagnoses were leukemia and lymphoma. Other neoplastic diseases were pleomorphic parotid adenoma, idiopathic thrombocytopenic purpura, and granulocytic sarcoma.

We found significant differences between groups for the following comparisons at baseline: fibrinogen, prothrombin time (PT), international normalized ratio, D-dimer, C-reactive protein (CRP), and leukocytes were significantly higher in SG compared with the CG (Table 2).

Following univariable analyses, the variables with unadjusted *P* values less than .05 were used to create a multivariable analysis model after testing for collinearity. Among the variables tested, leucocyte counts, PT, fibrinogen, and D-dimer were selected to be included in the multivariable logistic regression model. The results of multivariable logistic analysis are shown in Supplementary Table S2. The adjusted analysis revealed significant differences between SG and CG for fibrinogen and PT.

Biochemistry laboratory test results were similar between the groups, except for higher levels of albumin in the CG (Supplementary Table S3).

TABLE 1 Baseline characteristics of patients by group.

Characteristics of patients	Control (*n* = 30) *n* (%)	Sepsis (*n* = 30) *n* (%)	*P* value
Male sex	15 (51.7)	20 (64.5)	.32[a]
Age (y), mean ± SD	58 ± 18	51 ± 16	.17[c]
Race/ethnicity			.70[b]
Hispanic and Latino	25 (83.3)	24 (80)	
Indian	3 (10)	2 (6.7)	
Black	0 (0)	1 (100)	
Asian	2 (6,7)	3 (10)	
Smoking history (yes)	13 (43.3)	5 (16.7)	.02[a]
Alcoholism (yes)	1 (3.3)	2 (6.7)	>.999[b]
History of illicit drugs use (yes)	3 (10.3)	1 (3.2)	.61[b]
Hypertension (yes)	12 (40)	8 (26.7)	.27[a]
COPD (yes)	30 (100)	30 (100)	—
Diabetes mellitus (yes)	3 (10)	2 (6.7)	>.999[b]
Hematological diseases			.68[b]
Leukemia	17 (58.6)	14 (45.2)	
Lymphoma	5 (17.2)	9 (29.0)	
Myeloma	4 (13.8)	3 (9.7)	
Myelodysplasia	1 (3.4)	1 (3.2)	
Myelofibrosis	1 (3.4)	2 (6.5)	
Other	1 (3.4)	2 (6.5)	

COPD, chronic obstructive pulmonary disease.
[a]Chi-squared test.
[b]Fisher exact test.
[c]Student's *t*-test.

3.2 | Thromboelastometry parameters

TEM parameters for clot strength were significantly higher in patients with sepsis (Table 3). For EXTEM, CFT was significantly lower, while A5 and A10 were significantly higher in the SG. For FIBTEM, A5, A10, and MCF were significantly higher in the SG. For INTEM, CFT was significantly lower, while A5 was significantly higher in the SG. Considering PLTEM, A5, A10, and MCF were lower in SG, and these differences were significant.

We evaluated whether increased fibrinogen due to the inflammatory response to sepsis would increase MCF in EXTEM and FIBTEM and found that fibrinogen concentration was significantly higher in the SG (Supplementary Figures S1 and S2).

3.3 | Fibrinogen and platelet response model

The increase in plasma fibrinogen concentration contributed significantly to the increase in MCF for both EXTEM and FIBTEM in the gamma regression model (Table 4). In EXTEM, the groups did not differ after adjusting for fibrinogen. In FIBTEM, the increase in fibrinogen concentration also increased MCF. In the FIBTEM test, the

TABLE 2 Laboratory tests results per group (*N* = 60).

Laboratory tests	Control (*n* = 30), median (IQR)[a]	Sepsis (*n* = 30), median (IQR)[a]	*P* value
Fibrinogen (mg/dL), mean ± SD	321.5 ± 76	543.2 ± 186.8	<.001[b]
Platelet count (× 10^3/mm^3), mean ± SD	28.9 ± 9.9	24.8 ± 11.7	.15[b]
Prothrombin time (s)	92 (81-100)	77 (561-92)	.02[c]
INR	1.1 (1.0-1.2)	1.2 (1.1-1.4)	.006[c]
aPTT (s)	29.6 (25.6-31.8)	27.4 (26.0-29.5)	.43[c]
aPTT ratio	1.0 (0.9-1.1)	1.0 (0.9-1.0)	.67[c]
CRP (mg/dL)	9.7 (3.4-50.7)	130.7 (63.1-214.2)	<.001[c]
D-dimer (ng/mL)	847.5 (402-1291)	1514.5 (834-2222)	.005[c]
Leukocytes (mm^3)	205.0 (50.0-580.0)	1590.0 (270-3220)	.002[c]
Hemoglobin (g/dL)	8.9 (8.4-9.8)	8.7 (8.0-9.5)	.37[c]
Hematocrit (%)	25.7 (24.8-28.4)	24.3 (22.2-27.3)	.09[c]

aPTT, activated partial thromboplastin time; CRP, C-reactive protein; INR, international normalized ratio.
[a]Unless otherwise specified.
[b]Student's *t*-test.
[c]Mann–Whitney test.

SG had higher MCF values than the CG by 5.74 mm (*P* = .02). Higher platelet counts significantly increased PLTEM MCF. An increase in plasma fibrinogen concentration by 100 mg/dL was associated with a mean increase in EXTEM MCF by 4 mm (*P* = .002) and by 6 mm (*P* < .001) for FIBTEM MCF. Increased platelet count was also associated with an increased clot strength. For EXTEM MCF and PLTEM MCF, an average increase of 0.26 mm is expected after an increase in platelet count of 10 × 10^3/mm^3 (*P* = .007 and *P* = .03, respectively).

3.4 | Contribution of fibrin and platelets to clot strength

The relative fibrin contribution to MCF was significantly higher, and relative platelet contribution to MCF was significantly lower in the SG compared with the CG. The same applied for the A5 and A10 parameters (Table 5).

For FIBTEM MCF < 25 mm and FIBTEM A5 < 20 mm, the receiver operating characteristic curve (ROC curve) showed an area under the curve (AUC) of 0.94 (95% CI, 0.88-1.00). According to Youden's criteria, the ideal cutoff point for discrimination between individuals with a significant decrease in clot strength (FIBTEM MCF < 25 mm and FIBTEM A5 < 20 mm) was fibrinogen level equal to 403 mg/dL, with a sensitivity of 0.909 and specificity of 0.842 (Table 6). The critical points in fibrinogen concentration and platelet count corresponding to a significant decrease in clot strength (considered as EXTEM A5 < 35 mm) were 403 mg/dL (ROC AUC, 0.839) and 27,500 platelets/μL (ROC AUC, 0.562), respectively (Table 6).

TABLE 3 Comparison of thromboelastometry parameters between groups (*N* = 60).

Thromboelastometry parameters	Control (*n* = 30), mean ± SD	Sepsis (*n* = 30), mean ± SD	*P* value
FIBTEM A5 (mm)	16.0 ± 4.1	23.6 ± 7	<.001
FIBTEM A10 (mm)	17.6 ± 4.3	25.9 ± 7.5	<.001
FIBTEM MCF (mm)	19.27 ± 4.9	29 ± 8.8	<.001
FIBTEM LI30 (%)	100 ± 0	100 ± 0	>.999
FIBTEM LI45 (%)	100 ± 0	100 ± 0	>.999
FIBTEM LI60 (%)	100 ± 0	100 ± 0	>.999
EXTEM CT (s)	70.33 ± 13.1	70.6 ± 14.7	.09[a]
EXTEM CFT (s)	225.8 ± 163.6	128 ± 77.4	<.001[a]
EXTEM A5 (mm)	25.8 ± 5.6	30.8 ± 6.9	.007
EXTEM A10 (mm)	34.6 ± 6.8	38.9 ± 7.4	.04
EXTEM MCF (mm)	44.3 ± 6.6	47.7 ± 7.4	.096
EXTEM LI30 (%)	100 ± 0	100 ± 0	>.999
EXTEM LI45 (%)	99.1 ± 1.6	100 ± 0	.16
EXTEM LI60 (%)	97.4 ± 3.0	98.75 ± 1.5	.46
INTEM CT (s)	180.4 ± 18.1	197.6 ± 43.1	.07[a]
INTEM CFT (s)	202 ± 156.9	137.8 ± 90.4	.002[a]
INTEM A5 (mm)	26.7 ± 5.7	29.8 ± 6.3	.04
INTEM A10 (mm)	35 ± 6.8	37.1 ± 6.9	.25
INTEM MCF (mm)	43.7 ± 6.5	44.41 ± 7.1	.57
INTEM LI30 (%)	96.9 ± 13.1	100 ± 0	.51
INTEM LI45 (%)	98.8 ± 2.1	98.8 ± 1.5	.67
INTEM LI60 (%)	97.9 ± 2.8	100 ± 0	.14
PLTEM A5 (mm)	9.8 ± 4.1	7.1 ± 4.1	.01
PLTEM A10 (mm)	17 ± 5.6	13 ± 5.6	.005
PLTEM MCF (mm)	25.1 ± 5.8	18.6 ± 6.4	<.001

A5, amplitude at 5 minutes; A10, amplitude at 10 minutes; CT, clotting time; CFT, clot formation time; EXTEM, extrinsic coagulation pathway; FIBTEM, extrinsic coagulation pathway with platelet inhibition by cytochalasin D; INTEM, intrinsic coagulation pathway; LI, lysis index; MCF, maximum clot firmness; ML, maximum lysis; PLTEM, platelet contribution to clot firmness.
[a]Mann–Whitney test.

3.5 | Clotting factors

In Supplementary Table S4, we present the comparison between the plasma levels of coagulation factors, inhibitors, and fibrinolysis markers, as well as TGA parameters. The SG had significantly lower mean FVII activity (*P* = .046) and protein C (PC) activity (*P* = .03). The other clotting factors, markers of the fibrinolytic system, and

TABLE 4 Gamma regression model for clot strength.

Outcome	Factors	Coefficient	SE	95% CI		*P* value
				Lower	Upper	
EXTEM MCF	Intercept[a]	23.18	5.14	13.11	33.26	<.001
	Fibrinogen (g/L)	0.04	0.01	0.02	0.07	.002
	Platelets (× 1000)	0.26	0.10	0.07	0.45	.007
	Group					
	Sepsis	7.10	6.51	−5.66	19.85	.28
	Control	Ref.				
	Interaction group*fibrinogen					
	Sepsis*fibrinogen	−0.022	0.015	−0.05	0.01	.12
	Control*fibrinogen	Ref.				
	Interaction group*platelets					
	Sepsis*platelets	0.007	0.129	−0.25	0.26	.96
	Control*platelets	Ref.				
FIBTEM MCF	Intercept	0.70	1.68	−2.58	3.99	.68
	Fibrinogen (g/L)	0.06	0.01	0.05	0.07	<.001
	Group					
	Sepsis	5.74	2.44	0.96	10.53	.02
	Control	Ref.				
	Interaction group*fibrinogen					
	Sepsis*fibrinogen	−0.02	0.01	−0.03	0.00	.02
	Control*fibrinogen	Ref.				
PLTEM MCF	Intercept[a]	17.64	3.32	11.13	24.16	<.001
	Platelet count (× 1000)	0.26	0.12	0.03	0.48	.03
	Group					
	Sepsis	−5.07	3.70	−12.33	2.19	.17
	Control	Ref.				
	Interaction group*platelets					
	Sepsis*platelets	−0.02	0.13	−0.28	0.25	.91
	Control*platelets	Ref.				

EXTEM, extrinsic coagulation pathway; FIBTEM, extrinsic coagulation pathway with platelet inhibition by cytochalasin D; MCF, maximum clot firmness; PLTEM, platelet contribution to clot firmness; Ref., reference.
[a]Intercept: value at which the adjusted line crosses the y-axis.

parameters of the TGA showed no significant difference between groups. There was no significant correlation between FVII activity and EXTEM parameters (CT, CFT, A5, and MCF) (Supplementary Table S5).

3.6 | Comparison of scores between groups

Clinical scores such as SOFA, DIC ISTH, JMWH, and JAAM were evaluated on the 21st day of group follow-up. We found differences between the groups for the JMWH (P = .006) and JAAM (P = .01) scores, with SG presenting higher scores (Supplementary Table S6).

3.7 | Bleeding, transfusion, transfusion reaction, and mortality

In Supplementary Table S7, we present the comparisons between the coagulation tests and bleeding. We observed bleeding events in 7 patients, equivalent to 11.67% in the first 21 days after inclusion in

TABLE 5 Contribution of fibrinogen and platelets to clot strength.

Thromboelastometry parameters	Control (n = 30), mean ± SD	Sepsis (n = 30), mean ± SD	P value[a]
FIBTEM A5/EXTEM A5 (%)	62.6 ± 12.2	76.7 ± 12.5	<.001
FIBTEM A10/EXTEM A10 (%)	51.6 ± 11.2	66.4 ± 12.6	<.001
FIBTEM MCF/EXTEM MCF (%)	43.6 ± 9.7	60.5 ± 12.8	<.001
PLTEM A5/EXTEM A5 (%)	37.4 ± 12.2	23.3 ± 12.5	<.001
PLTEM A10/EXTEM A10 (%)	56.4 ± 9.7	39.5 ± 12.8	<.001
PLTEM MCF/EXTEM MCF (%)	56.4 ± 9.7	39.5 ± 12.8	<.001

A5, amplitude at 5 minutes; A10, amplitude at 10 minutes; EXTEM, extrinsic coagulation pathway; FIBTEM, extrinsic coagulation pathway with platelet inhibition by cytochalasin D; MCF, maximum clot firmness; PLTEM, platelet contribution to clot firmness.
[a]Student's t-test.

this study. There were more patients in the CG with bleeding events than in the SG, but this difference was not significant. Only FVII was significantly correlated with bleeding. There was no difference between groups for transfusions of platelet concentrates and red blood cells as well as for transfusion reactions (Supplementary Table S8). No deaths were observed until the first 21 days of hospital admission.

4 | DISCUSSION

The main finding of this study in patients with HM and severe thrombocytopenia was that there was an increase in fibrinogen levels and clot strength in patients with sepsis compared with uninfected patients. This points to a tendency toward a hypercoagulable state due to the inflammatory response to sepsis, even in the presence of thrombocytopenia. However, the increase in FIBTEM clot firmness was lower than expected. One reason may be that the contribution of fibrin to clot firmness was already increased in patients with HM, even without infection, due to the inflammatory response to malignancy [37]. Thus, the observed mean increase in EXTEM MCF in the SG (3.4 mm; Table 4) was much smaller than the expected variability we used for the power calculation (10 mm). It is possible that our patients already had fibrinogen at a slightly higher level due to the inflammation caused by the malignant disease. Both fibrinogen and platelets contributed to the clot strength, with fibrinogen being the main determinant of blood coagulability in these patient populations.

4.1 | Variation in fibrinogen concentration in response to sepsis

Confirming our findings, Sharma et al. [38] showed, in a single-center study in children with sepsis, that plasma fibrinogen was significantly higher in patients with sepsis compared with controls, mainly in the early stages of sepsis. Higher fibrinogen levels in sepsis also have been identified in other publications [39,40]. A recent study published by Mori et al. [41] showed that in patients with sepsis-inducing coagulopathy admitted to the ICU, approximately a quarter of the patients showed a tendency toward a progressive decrease in the concentration of fibrinogen over time due to the worsening of the coagulopathy, and these patients had a 28-day mortality rate higher than patients with nondecreasing fibrinogen trends.

4.2 | Contribution of fibrinogen and platelets to clot strength

Maslow et al. [42] reported in a recent publication using thromboelastography (TEG) on the interaction between platelets and fibrinogen in healthy patients, showing strong correlations between platelets and TEG-maximum amplitude (MA) and between fibrinogen and TEG-MA. A linear relationship between fibrinogen and TEG-MA was identified. The authors found that the product of platelet count and fibrinogen concentration was more strongly correlated with TEG-MA than platelet count or fibrinogen concentration alone.

Our study confirmed literature data that elevated platelet count is associated with increased clot strength [43,44]. Munk-Andersen et al. [22] showed that fibrinogen concentrate administration increased clot firmness to the same degree as platelet transfusion in patients with nonseptic thrombocytopenia with hematologic malignancies requiring platelet transfusion.

4.3 | Variation of thromboelastometric parameters due to sepsis

Studies in patients with sepsis show that the manifestation of coagulopathy can range from a subclinical state of hypercoagulability with localized venous thrombosis to severe DIC with the formation of diffuse microthrombosis and multiple organ dysfunction to severe hypocoagulability with hemorrhagic complications due to the consumption of fibrinogen, clotting factors, and platelets [45–52]. In our study, there was an increase in parameters that assess the clot strength (A5, A10, or MCF) in TEM assays: EXTEM, INTEM, and FIBTEM, with a concomitant decrease in these parameters in the PLTEM in patients with sepsis. This finding, combined with the reduction in CFT identified in the SG, represents a tendency toward a hypercoagulable state, typical of the initial phase of sepsis. CFT is defined as the time between the onset of coagulation (characterized by a clot firmness amplitude of 2 mm) and the thromboelastometric curve reaching an amplitude of 20 mm. This value provides information on the speed of clot formation and correlates inversely with MCF [53]. MCF represents the MA of clot firmness during the measurement, demonstrating clot strength [34]. It is based on the fibrin polymerization, platelet aggregation, and fibrin-platelet interaction [54].

Levi et al. [55] showed that in the early phase of sepsis, there is a remarkable increase in clot strength and elasticity, indicating a prohemostatic environment. Daudel et al. [56] showed reductions in CT and CFT and an increase in MCF in EXTEM in patients with severe

TABLE 6 Area under the curve and 95% CIs for cutoff points.

Outcome	Variable	AUC	95% CI		Cutoff	Sensitivity (%)	Specificity (%)
			Lower	Upper			
EXTEM A5 < 35 mm	Fibrinogen (mg/dL)	0.839	0.71	0.97	403.0	87.5	64.0
	Platelets (× 10^3/mm^3)	0.562	0.36	0.77	27.5	62.5	52.0
EXTEM A10 < 45 mm	Fibrinogen (mg/dL)	0.853	0.71	0.99	618.5	71.4	90.6
	Platelets (× 10^3/mm^3)	0.496	0.30	0.69	22.5	71.4	43.4
EXTEM MCF < 55 mm	Fibrinogen (mg/dL)	0.856	0.72	0.99	618.5	71.4	90.6
	Platelets (× 10^3/mm^3)	0.558	0.33	0.79	26.0	71.4	47.2
FIBTEM A5 < 20 mm	Fibrinogen (mg/dL)	0.940	0.88	1.00	403.0	90.9	84.2
FIBTEM MCF < 25 mm	Fibrinogen (mg/dL)	0.940	0.88	1.00	403.0	90.9	84.2

A5, amplitude at 5 minutes; A10, amplitude at 10 minutes; AUC, area under the curve; EXTEM, extrinsic coagulation pathway; FIBTEM, extrinsic coagulation pathway with platelet inhibition by cytochalasin D; MCF, maximum clot firmness.

sepsis during the critical phase of the disease compared with admission values, configuring a tendency toward hypercoagulability. In fact, hypercoagulability has been more frequently observed in the acute phase of sepsis. In patients with overt DIC, TEM parameters indicated hypocoagulation, while in patients without DIC, the trend is toward hypercoagulation [50].

In a systematic review published in 2014, the results of TEG/ROTEM measurements in sepsis vary widely between studies and show both hypo- and hypercoagulability. These variations are consistent with the pathophysiology of sepsis. Hypercoagulability with formation of microvascular thrombi is followed by a "consumptive coagulopathy" during DIC, with a later tendency to bleeding due to low levels of platelets, fibrinogen, and other coagulation factors [57]. Ostrowski et al. [58] showed, in patients with sepsis by means of thromboelastography, that in both patients with hypo- and hypercoagulability, only fibrinogen contributed independently to clot strength, whereas platelets and fibrinogen independently contributed to clot strength in patients with normal coagulability.

No difference in thromboelastometric clot lysis indices was observed. In our study, parameters of TEM as well as serum markers of fibrinolysis (plasminogen and alpha-2 antiplasmin) did not show significant differences between the groups. These results differ from the literature, evidencing inhibition of fibrinolysis by increasing the concentration of plasminogen activator inhibitor 1 in response to sepsis [59–62]. Plasminogen activator inhibitor 1 was not evaluated in this study. This can be explained in part because all patients had HM, which influences fibrinolytic activity [63,64], and because the study was not powered to show differences in hypofibrinolysis/fibrinolysis shutdown in patients with sepsis and HM [60–62,65].

4.4 | Variation of CCT and plasma coagulation factors due to sepsis

Patients in the SG had a longer PT as well as significantly higher levels of D-dimer compared with patients in the CG. There was no significant difference for activated partial thromboplastin time. The change found in the PT prolongation probably represents the reduction in FVII levels. We found no statistically significant correlation between FVII activity and EXTEM parameters ($P > .05$). Mesters et al. [66] evaluated the coagulation parameters in patients with severe neutropenia induced by chemotherapy during severe sepsis and septic shock. At the onset of fever, they identified a significant reduction in FVII levels and antithrombin activity in patients who progressed to septic shock compared with those who developed severe sepsis, predicting a lethal outcome. An increase in thrombin generation by increasing fragment 1 + 2 levels in neutropenic patients with septic shock was observed. In our study, PC was significantly lower in the SG. Dellinger et al. [67] showed that in sepsis, the activation of coagulation by toxins occurs directly through upregulation of tissue factor, leading to thrombin formation and generation of fibrin clots. Their study confirmed our findings of a higher amount of PC in the CG once generalized activation of coagulation due sepsis depletes the body's natural antithrombotic factors, including PC.

Generation of thrombin also initiates fibrinolysis through the release of tissue plasminogen activator. Once plasmin is activated, it degrades fibrin, producing fibrin degradation/split products, including D-dimer [68]. Thrombin can also inhibit fibrinolysis in combination with thrombomodulin by *thrombin*-activatable fibrinolysis inhibitor activation [69–73]. Our D-dimer, CRP, and leukocyte counts were higher in the SG compared with the CG. Han et al. [74] showed that elevated D-dimer values found in sepsis were independently associated with in-hospital mortality. D-dimer is a marker of activation of coagulation and clot formation as well as of the fibrinolytic system and its degradation [75]. D-dimer has been widely used in clinical practice to rule out the diagnosis of deep vein thrombosis and pulmonary embolism, but it has also been associated with greater severity in patients with cancer [76–78].

4.6 | Secondary outcomes assessed on the 21st day

In our cohort of patients with HM, despite the significant reduction in platelet count, we observed only 7 patients (11.67%) with bleeding

events. Only FVII was significantly correlated with bleeding. Regarding the scales used to predict severity, patients with sepsis showed an increase in the JMWH and JAAM scores.

Our study reinforces the need for a more careful assessment of coagulopathy in patients with HM and thrombocytopenia, especially in those complicated by sepsis, since there are intrinsic compensatory mechanisms not accessed with platelet counts alone. Perhaps prophylactic platelet transfusion in nonbleeding patients should not be based solely on platelet counts but on a more comprehensive assessment of hemostasis.

4.7 | Study limitations

As the objective of this study was to evaluate whether the increase in fibrinogen due to sepsis would be able to compensate for blood coagulability in patients with HM and thrombocytopenia based on TEM parameters, a sample calculation was not performed to assess bleeding. Therefore, as expected, this study does not have enough power to support a recommendation against prophylactic transfusion of platelet concentrates in the context of HM with or without sepsis.

We did not evaluate subgroups by disease if there is evidence that the type of hematological disease affects clot strength. Finally, laboratory data collection was carried out at a single time after patients were included in the study. As per its design, the study did not monitor the evolution of patients with sepsis over time, which could be considered another limitation of this study, considering that the manifestation of coagulopathy can change as the disease progresses.

4.8 | Future perspectives for randomized trials

Despite the fact that transfusions are currently safe, there are risks involved, and alternatives should be considered to avoid unnecessary exposure. Increased awareness of restrictive transfusion thresholds has been set in several scenarios and has prompted international medical societies and multidisciplinary teams to advocate the concept of patient blood management [79–81]. Therefore, the approach to treating bleeding and coagulopathy must focus on optimizing the use of resources such as hemostatic agents and blood products according to the individual needs of each patient and minimizing iatrogenic blood loss.

5 | CONCLUSION

In this study including patients with HM, there was a change in the behavior of the coagulation cascade in those patients who developed sepsis. An increase in fibrinogen concentration was identified due to the activation of the inflammatory response and the coagulation system, characterized by an increase in CRP, leukocytes, and D-dimer, leading to a compensatory increase in clot strength, even in the presence of thrombocytopenia.

The relative fibrin contribution to clot strength was significantly higher, and relative platelet contribution to maximum clot firmness was significantly lower in the SG compared with the CG. TEM, unlike CCT and TGA, allowed identifying a tendency toward hypercoagulability in response to inflammation in malignancy and sepsis.

The ideal cutoff point for discrimination between individuals with a significant decrease in clot strength for FIBTEM MCF < 25 mm and FIBTEM A5 < 20 mm was fibrinogen equal to 403 mg/dL. The same did not occur with platelet levels considering EXTEM. Patients with sepsis had higher JMWH and JAAM scores.

Future studies could be carried out to evaluate whether the supplementation of lyophilized fibrinogen concentrates in patients with HM would be able to improve the clot firmness compromised by severe thrombocytopenia to the point of minimizing the transfusion of platelet concentrates.

ACKNOWLEDGMENTS

The authors thank Patricia Logullo, PhD, Certified Medical Publication Professional (CMPP) (Palavra Impressa), for manuscript editing services and Rogério Ruscitto do Prado, an epidemiologist, for his work in supporting and constructing the tables and statistical interpretation of the data.

FUNDING

Funding to carry out specific coagulation tests, including thromboelastometry, thrombin generation assay, coagulation factors, inhibitors, and fibrinolytic system markers, was provided by CSL Behring Company.

AUTHOR CONTRIBUTIONS

T.C. contributed to the conception and design of the study, acquisition of data, analysis, and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted. E.S. contributed to the conception and design of the study, interpretation of data, and final approval of the version to be submitted. K.G. contributed to the interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted. M.D.P.R. contributed to the acquisition, analysis, and interpretation of data, as well as the final approval of the version to be submitted. J.C.C.G. contributed to the acquisition of data and analysis and final approval of the version to be submitted. D.H.C.C., V.F.A., L.R., G.S.G., R.A.M., F.F.A., and G.R.R.S. contributed to the acquisition of data and final approval of the version to be submitted. M.D.L. and N.H. helped with the conception and design of the study, interpretation of data, and final approval of the version to be submitted.

RELATIONSHIP DISCLOSURE

T.C. has worked as a medical manager at Werfen, Latin America, since 2022. K.G. has worked as the medical director of TEM Innovations since 2012. The other authors have no conflict of interest to disclose.

DATA AVAILABILITY

Data from this research has not been publicly deposited. There is no open material to deposit. The study protocol has been approved by the institutional review board but has not been published.

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SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2024.102362