Association between Clot Waveform Analysis Parameters and the Severity of Liver Cirrhosis

Kessarin Thanapirom[1,2,3] Sirinporn Suksawatamnuay[1,2,3] Panarat Thaimai[1,2,3] Prooksa Ananchuensook[1,2,3] Pitiphong Kijrattanakul[4] Pantep Angchaisuksiri[5] Pisit Tangkijvanich[6] Sombat Treeprasertsuk[1] Piyawat Komolmit[1,2,3]

[1] Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand
[2] Center of Excellence in Liver Fibrosis and Cirrhosis, Chulalongkorn University, Bangkok, Thailand
[3] Excellence Center in Liver Diseases, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand.
[4] Division of Hospital and Ambulatory Medicine, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand
[5] Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[6] Department of Biochemistry, Center of Excellence in Hepatitis and Liver Cancer, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Address for correspondence Kessarin Thanapirom, MD, PhD, Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand (e-mail: kessarin.t@chula.ac.th).

Thromb Haemost 2025;125:1141–1149.

Abstract

Background Clot waveform analysis (CWA) provides a global assessment of hemostasis and may be useful for patients with cirrhosis with complex hemostatic abnormalities. This study aimed to assess the association between prothrombin time (PT-) and activated partial thromboplastin time (aPTT-) based CWA parameters and cirrhosis severity and prospectively evaluate the role of CWA in predicting mortality and acute decompensation (AD) over 1 year.

Methods This prospective study included adult patients with cirrhosis between June 2021 and December 2023 at Chulalongkorn University Hospital. The PT- and aPTT-based CWA parameters were obtained using an automated coagulation analyzer.

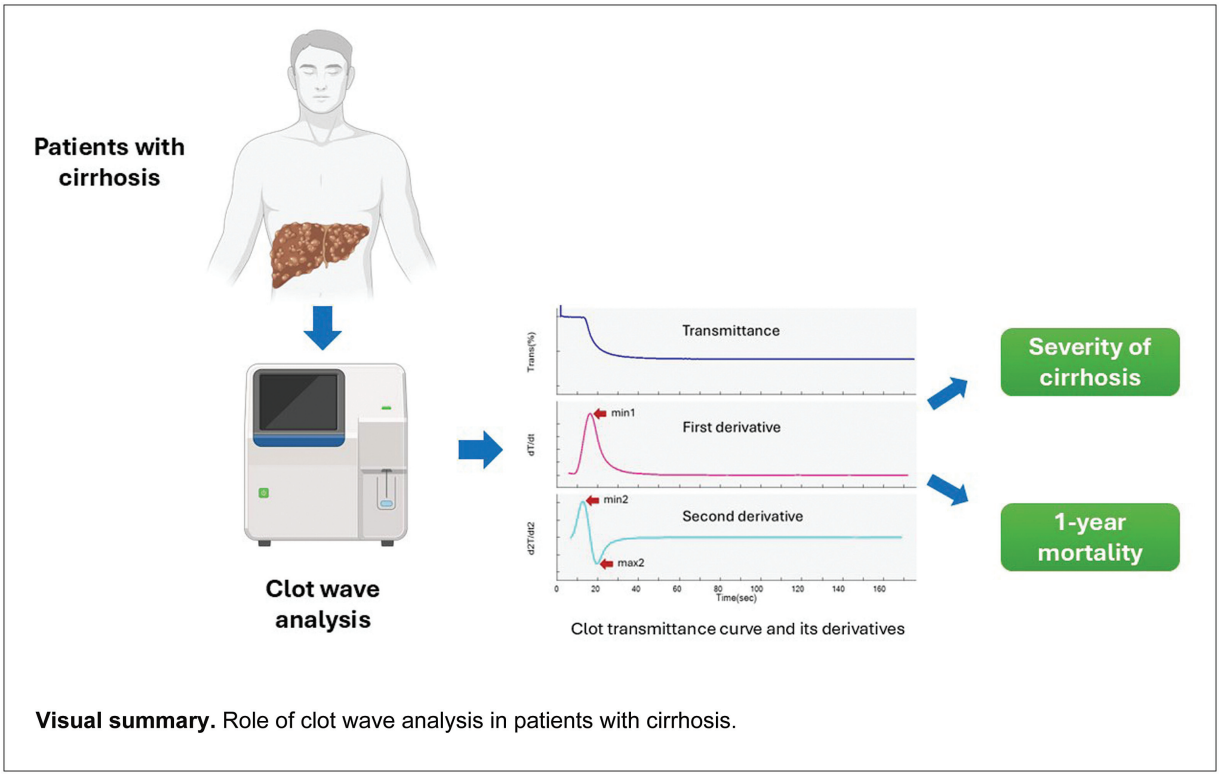
Results A total of 560 patients with cirrhosis were included; 165 (29.5%) and 47 (11.5%) had Child–Turcotte–Pugh (CTP) B and C cirrhosis, respectively. The PT- and aPTT-based CWA parameters, including maximum velocity (min1), maximum acceleration (min2), and maximum deceleration (max2), were significantly lower ($p \leq 0.05$) in patients with decompensated cirrhosis than in those with compensated cirrhosis. Additionally, CWA values were significantly higher in patients with higher CTP and Model for End-Stage Liver Disease (MELD) scores. Multivariable analysis revealed that liver stiffness (LS) and max2 of PT-based CWA assay were independently associated with CTP B/C. In addition, min2 and max2 of PT-based CWA assay were independently

Keywords
- clot wave analysis
- cirrhosis
- severity of liver cirrhosis
- portal vein thrombosis
- clinical outcomes

received
August 13, 2024
accepted after revision
December 16, 2024
article published online
January 9, 2025

DOI https://doi.org/10.1055/a-2505-8616.
ISSN 0340-6245.

Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany



Visual summary. Role of clot wave analysis in patients with cirrhosis.

associated with 1-year mortality. No significant differences in CWA parameters were observed between patients with and without portal vein thrombosis. CWA parameters were not related to AD during the 1-year follow-up.

Conclusion A hypocoagulable profile based on CWA parameters is associated with advanced-stage cirrhosis. CWA may be a useful objective marker for assessing cirrhosis severity and predicting 1-year mortality.

Introduction

The liver plays an important role in hemostasis because it produces several proteins involved in hemostasis. Patients with cirrhosis develop complex changes in primary hemostasis, including hypocoagulable and hypercoagulable features.[1] A range of pro- and anti-hemostatic pathways change simultaneously, resulting in a relatively neutral effect known as rebalanced hemostasis.[2,3] However, this new hemostatic balance is likely more fragile than the balance in individuals with normal liver function. Consequently, patients with cirrhosis are at increased risk of hemostasis-related bleeding and thrombotic events.[4,5] Portal vein thrombosis (PVT) is the most common thrombotic event in patients with cirrhosis, affecting 4.6% of patients with compensated cirrhosis and 16.6% of those with decompensated cirrhosis.[6,7]

Conventional coagulation tests, such as platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT), are unreliable for identifying the risk of bleeding or thrombosis or assessing the efficacy of blood transfusion or hemostatic agent infusion in patients with cirrhosis.[8–10] Viscoelastic tests, including thromboelastography and rotational thromboelastometry, are increasingly being used to evaluate hemostasis in patients with liver diseases. Unlike conventional coagulation tests, viscoelastic tests provide better global hemostatic capacity. However, these tests have some limitations. They are insensitive to von Willebrand factor and protein C and unable to detect platelet dysfunction and factor XIII deficiency.[11,12] Moreover, whether viscoelastic tests can predict clinical outcomes, such as bleeding and thrombosis, in patients with liver disease remains unclear. Therefore, viscoelastic tests cannot be recommended for guiding clinical decision-making until more evidence is available.

Clot waveform analysis (CWA) is a new global coagulation assay that reflects the overall effects of all hemostatic factors. This assay is based on the continuous observation of changes in light transmittance or absorbance caused by fibrin formation in plasma during the performance of routine clotting tests, including PT and aPTT. This assay can be performed easily using special software for coagulation analyzers.[13] Previous studies have evaluated the role of CWA in the diagnosis and treatment of hemophilia[14,15] and disseminated intravascular coagulation.[16] However, evidence of an

association between CWA parameters and the severity or complication of liver cirrhosis is limited. Therefore, this study aimed to evaluate the association between PT- and aPTT-based CWA parameters and the severity of cirrhosis and PVT and to prospectively evaluate the role of CWA parameters in predicting acute decompensation (AD) in patients with compensated cirrhosis.

Methods

Study Participants

This prospective study included consecutive patients aged 18 to 80 years who were diagnosed with cirrhosis, with or without complications, at the Liver Clinic at Chulalongkorn University Hospital, Bangkok, Thailand, between January 2021 and December 2023. The diagnosis of cirrhosis was based on clinical or laboratory data and confirmed by radiological imaging. The exclusion criteria were recent bleeding within the preceding month, recent plasma or coagulation factor transfusion within the preceding day, bleeding disorders such as hemophilia, use of antiplatelet or anticoagulant medications, renal replacement therapy, hepatocellular carcinoma, and extrahepatic malignancy. Data were recorded at enrollment, including patient characteristics, laboratory data, CWA parameters, imaging findings, and liver stiffness (LS) evaluated using FibroScan® (Echosens, Paris, France). The patients were followed up for 12 months, and cirrhosis-related complications and death were recorded.

The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB no. 350/63), and conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent for study participation. The study protocol was registered with the Thai Clinical Trial Registry (TCTR20200730001, July 30, 2020).

Cirrhosis Severity

Cirrhosis severity was determined using the Child–Turcotte–Pugh (CTP) classification[17] and the Model for End-Stage Liver Disease (MELD) score.[18] Patients with at least one of the following cirrhosis-related complications were diagnosed with decompensated cirrhosis: overt hepatic encephalopathy, ascites, or variceal bleeding.

Clot Waveform Analysis Data

PT- and aPTT-based CWA parameters were obtained from a CS-2500™ automated coagulation analyzer (Sysmex Corporation, Kobe, Japan) using poor-platelet plasma. The transmittance curve was generated during fibrin formation and measured at 660 nm using a turbidity-based principle with a built-in algorithm tool on the analyzer. The first derivative curve represents the velocity of the clotting process, whereas the second derivative represents the acceleration and deceleration of the clotting process. The PT- and aPTT-based CWA parameters obtained were maximum velocity (min1; expressed as %/sec), maximum acceleration (min2; expressed as %/sec^2), and maximum deceleration (max2; expressed as %/sec^2). Lower values of min1, min2, and max2 indicate a more hypercoagulable profile.

Statistical Analysis

Categorical variables were expressed as numbers and percentages. Between-group comparisons were performed using Pearson's chi-square or Fisher's exact test. The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data were expressed as mean and standard deviation, whereas non-normally distributed data were expressed as median and interquartile range (IQR). The CWA parameters were compared between the groups using the independent *t*-test or Mann–Whitney U test. Spearman's correlation analysis was performed to assess the correlations between CWA parameters, LS values, CTP score, and MELD score. Univariable and multivariable analyses were performed to identify independent factors associated with the severity of cirrhosis and outcomes during the 1-year follow-up period. Kaplan–Meier curves were performed to estimate survival probability based on CWA parameters. All statistical analyses were performed using SPSS version 22 (IBM®, Armonk, NY). A two-sided *p*-value <0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 784 outpatients with cirrhosis were screened. Among them, 224 were excluded for meeting at least one of the exclusion criteria. Finally, 560 patients were included in this study. ►**Figure 1** shows a flowchart of patient enrollment. The median age of the patients was 61 (IQR: 53–67) years, with 64.1% being males ($n=359$). The most common causes of cirrhosis were chronic hepatitis B virus infection (28.2%, $n=158$), chronic hepatitis C virus infection (20.0%, $n=112$), and metabolic dysfunction-associated steatotic liver disease (16.8%, $n=94$). The median CTP and MELD scores were 6 (IQR: 5–8) and 11 (IQR: 8–14), respectively. The median LS value was 21.1 (IQR: 9.3–41.9) kPa.

Regarding liver disease severity, 179 (32.0%) patients had decompensated cirrhosis. In total, 348 (62.1%) patients had CTP class A, 165 (29.5%) had CTP class B, and 47 (8.4%) had CTP class C. ►**Table 1** shows the baseline characteristics and laboratory findings categorized by CTP classification. The higher the CTP score, the higher the proportion of decompensated cirrhosis, and the higher the MELD score and LS value.

Clot Waveform Analysis Parameters and Cirrhosis Severity

►**Table 2** shows the CWA parameters according to the CTP class. The PT- and aPTT-based CWA parameters, including min1, min2, and max2, were associated with cirrhosis severity. A higher CTP class was associated with a more hypocoagulable profile and lower min1, min2, and max2. In the PT-based CWA, the median (IQR) values of min1 were 3.2 (2.6–4)%/s, 2.6 (1.8–3.4), and 1.8 (1.3–2.6)%/s^2 for CTP classes A, B, and C, respectively. The median (IQR) values of min2 were

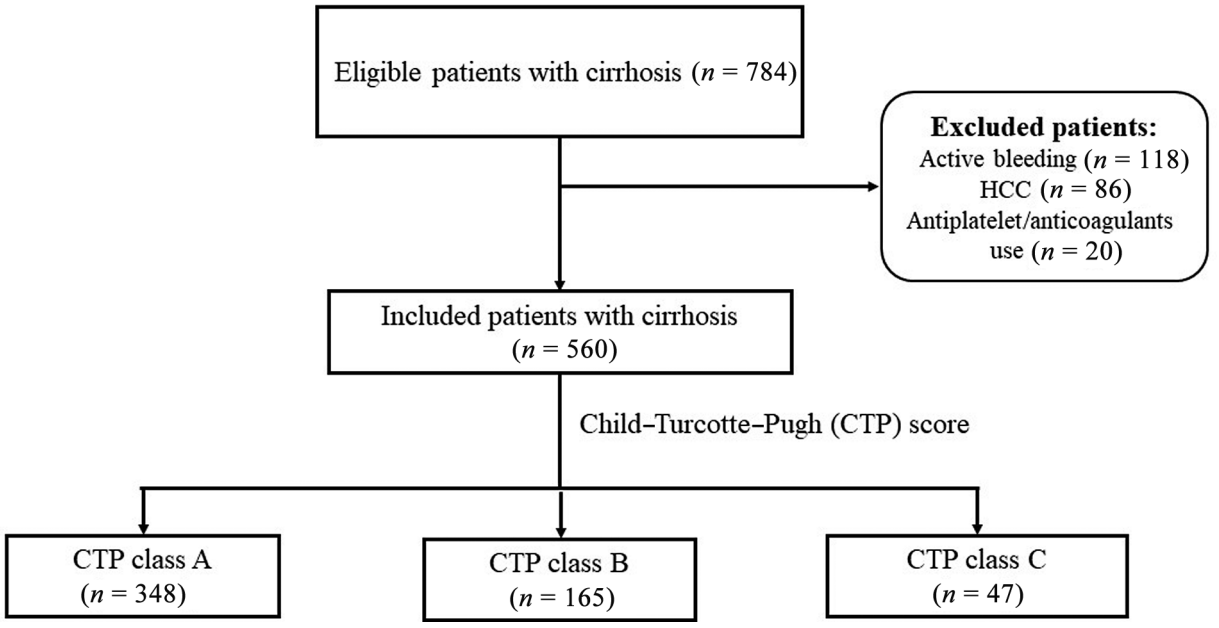


Fig. 1 Flow chart of patient enrollment.

Table 1 Baseline patient characteristics classified according to the severity of liver cirrhosis

	CTP-A ($n = 348$)	CTP-B ($n = 165$)	CTP-C ($n = 47$)	*p*-value
Age, years	61 (53–67)	62 (55–65.5)	58 (46–63)	0.07
Male, *n* (%)	229 (65.8%)	97 (58.8%)	33 (70.2%)	0.37
Cause of cirrhosis, *n* (%)				
HBV	114 (36.9%)	36 (36.5%)	8 (21.1%)	0.03
HCV	76 (24.6%)	29 (21.3%)	7 (18.4%)	0.58
MASLD	76 (24.6%)	16 (11.8%)	2 (5.3%)	<0.001
ARLD	51 (16.5%)	33 (24.3%)	7 (18.4%)	0.16
Decompensation, *n* (%)	28 (8.0%)	109 (66.1%)	42 (89.4%)	<0.001
Hemoglobin, g/dL	12.6 (10.8–14.0)	10.3 (8.8–12.0)	9.4 (8.3–11.0)	<0.001
White cell counts (cells/μL)	5,290 (3,920–6,910)	4,580 (3,360–6,810)	6,080 (4,980–8,140)	0.002
Platelet, ($\times 10^9$/l)	134 (88–207)	96 (62–157)	101 (67–140)	<0.001
PT, seconds	13.2 (12.3–14.1)	15.3 (14.0–16.6)	20.7 (16.3–24.1)	<0.001
INR	1.2 (1.1–1.3)	1.4 (1.2–1.5)	1.9 (1.5–2.2)	<0.001
aPTT, seconds	26.8 (25.1–28.3)	29.3 (26.9–31.9)	33.9 (29.0–42.7)	<0.001
TB, mg/dL	0.9 (0.7–1.3)	2.2 (1.3–3.1)	5.6 (3.3–10.4)	<0.001
AST, U/L	33.0 (25.0–51.0)	55.0 (37.3–74.3)	85.0 (58.0–152.0)	<0.001
ALT, U/L	28.0 (20.0–43.0)	32.0 (18.8–49.0)	51.0 (30.0–75.0)	<0.001
Albumin, g/dL	3.9 (3.5–4.2)	3.0 (2.7–3.4)	2.5 (2.0–2.7)	<0.001
Creatinine, mg/dL	0.8 (0.7–1.01)	0.8 (0.7–1.2)	0.9 (0.7–1.1)	0.43
Sodium, mEq/L	138.0 (136.0–140.0)	137.0 (134.0–139.0)	133.0 (130.7–137.3)	<0.001
MELD score	9 (8–10)	14 (12–17)	21 (18–24.5)	<0.001
Liver stiffness, kPa	14.7 (8.1–27.5)	40.5 (21.7–74.7)	69.5 (46.0–75.0)	<0.001

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; ARLD, alcohol-related liver disease; AST, aspartate aminotransferase; CTP, Child–Turcotte–Pugh class; HBV, hepatitis B virus; HCV, hepatitis C virus; kPa, kilo pascal; INR, international normalized ratio; MASLD, metabolic-associated steatotic liver disease; MELD, model for End-Stage Liver Disease; PT, prothrombin time; TB, total bilirubin.
Categorical variables were expressed as number and frequency, while continuous variables were expressed as mean ± standard deviation or median (interquartile range), as appropriate.

Table 2 Clot wave analysis values categorized by Child–Turcotte–Pugh classification

	CTP A ($n = 348$)	CTP B ($n = 165$)	CTP C ($n = 47$)	*p*-value
PT, seconds	13.2 (12.3–14.1)	15.3 (14.0–16.6)[a]	20.7 (16.3–24.1)[a,c]	<0.001
aPTT, seconds	26.8 (25.1–28.3)	29.3 (26.9–31.9)[a]	33.9 (29.0–42.7)[a,c]	<0.001
CWA values of PT assay				
Min1 (%/s)	3.2 (2.6–4.0)	2.6 (1.8–3.4)[a]	1.8 (1.3–2.6)[a,c]	<0.001
Min2 (%/s^2)	0.6 (0.5–0.7)	0.5 (0.3–0.6)[a]	0.3 (0.2–0.5)[a,c]	<0.001
Max2 (%/s^2)	0.5 (0.4–0.6)	0.3 (0.3–0.5)[a]	0.2 (0.1–0.3)[a,c]	<0.001
CWA values of aPTT assay				
Min1 (%/s)	4.0 (0–5.2)	3.1 (1.5–4.6)[b]	1.8 (1.0–2.8)[a,c]	<0.001
Min2 (%/s^2)	0.7 (0–0.8)	0.5 (0.2–0.7)[b]	0.3 (0.1–0.4)[a,c]	<0.001
Max2 (%/s^2)	0.6 (0–0.7)	0.4 (0.2–0.6)[a]	0.2 (0.1–0.3)[a,c]	<0.001

Abbreviations: aPTT, activated partial thromboplastin time; CTP, Child–Turcotte–Pugh; CWA, clot wave analysis; max2, maximum deceleration; min1, maximum velocity; min2, maximum acceleration; PT, prothrombin time; s, seconds.
[a]$p < 0.001$ compared with CTP-A.
[b]$p < 0.05$ compared with CTP-A.
[c]$p < 0.001$ compared with CTP B and C.

0.6 (0.5–0.7)%/s, 0.5 (0.3–0.6), and 0.3 (0.2–0.5)%/s^2 for CTP classes A, B, and C, respectively. Additionally, the median (IQR) values of max2 were 0.5 (0.4–0.6)%/s, 0.3 (0.3–0.5, and 0.2 (0.1–0.3)%/s^2 for CTP classes A, B, and C, respectively. The PT- and aPTT-based CWA waveforms in patients with CTP A, B, and C are shown in ►**Fig. 2**. Moreover, patients with decompensated cirrhosis exhibited significantly higher PT- and aPTT-based CWA parameters than those with compensated cirrhosis (►**Supplementary Table S1** [available in the online version only]).

Cirrhosis severity was classified into three groups based on MELD scores (MELD <10, 10–20, and >20). The median values of min1, min2, and max2 in the PT- and aPTT-based CWA were significantly higher in patients with higher MELD scores. This supports the scores, indicating an association between CWA values and cirrhosis severity (►**Supplementary Table S2** [available in the online version only]).

Logistic regression analysis was conducted to identify factors related to the severity of cirrhosis. Patients were divided into two groups: CTP A and CTP B/C. The univariable analysis found that LS and all CWA values were related to CTP B/C. However, multivariable analysis showed that LS (adjusted odds ratio [aOR] = 1.047, 95% CI: 1.032–1.062, $p < 0.001$) and max2 of PT-based CWA assay (aOR = 0.002, 95% CI: 0.001–0.018, $p < 0.001$) were independently related to CTP B/C (►**Table 3**).

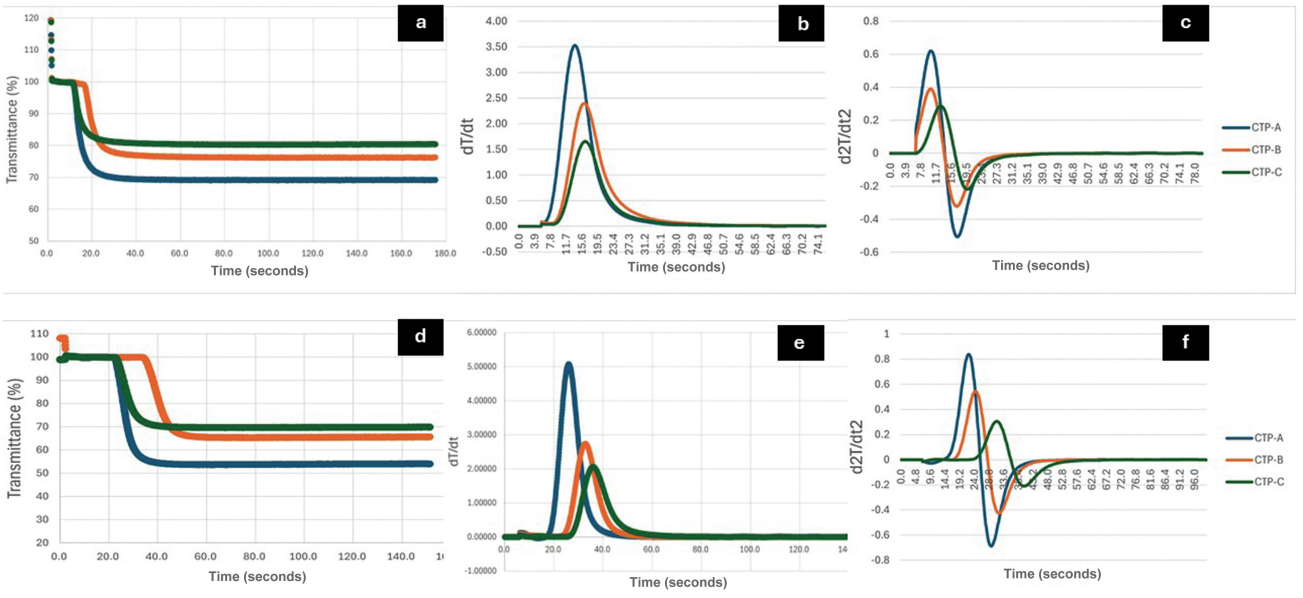


Fig. 2 Clot formation curves, first derivative curve, and second derivative curve of PT (**a–c**) and aPTT assays (**d–f**). aPTT, activated partial thromboplastin time; PT, prothrombin time.

Table 3 Factors related to the severity of cirrhosis

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	0.992 (0.979–1.005)	0.24		
Male	0.824 (0.578–1.174)	0.28		
Platelet count	1.000 (1.000–1.000)	0.42		
Liver stiffness	1.050 (1.037–1.064)	<0.001	1.047 (1.032–1.062)	<0.001
PT-based CWA				
Min1	0.578 (0.486–0.688)	<0.001		
Min2	0.047 (0.019–0.119)	<0.001		
Max2	0.010 (0.003–0.032)	<0.001	0.002 (0.001–0.018)	<0.001
aPTT-based CWA				
Min1	0.877 (0.812–0.947)	<0.001		
Min2	0.440 (0.276–0.702)	<0.001		
Max2	0.278 (0.158–0.488)	<0.001		

Abbreviations: aPTT, activated partial thromboplastin time; CWA, clot wave analysis; max2, maximum deceleration; min1, maximum velocity; min2, maximum acceleration; OR, odds ratio; PT, prothrombin time.

Correlation between Clot Waveform Analysis Parameters, Cirrhosis Severity, Liver Stiffness, and Traditional Measures of Hemostasis

►**Table 4** shows the Spearman correlation coefficients between CWA parameters, cirrhosis severity, LS, and conventional coagulation tests. The PT-based CWA parameters were weakly to moderately negatively correlated with CTP ($r = -0.34$ to -0.43, $p < 0.001$) and MELD scores ($r = -0.36$ to -0.46, $p < 0.001$), whereas the aPTT-based CWA parameters were weakly negatively correlated with CTP ($r = -0.19$ to -0.23, $p < 0.001$) and MELD scores ($r = -0.21$ to -0.25, $p < 0.001$). Furthermore, LS evaluated using transient elastography was weakly negatively correlated with the PT- and aPTT-based CWA parameters ($r = -0.14$ to -0.32, $p < 0.05$).

Spearman correlations between CWA parameters, PT, aPTT, and platelet count were assessed. The PT-based CWA values showed a moderate to strong negative correlation with PT ($r = -0.48$ to -0.61, $p < 0.001$) and platelet count ($r = 0.47$–0.49, $p < 0.001$) but only a weak negative correlation with aPTT ($r = -0.32$ to -0.35, $p < 0.001$) levels. Moreover, the aPTT-based CWA parameters were weakly correlated with PT ($r = -0.31$ to -0.35, $p < 0.001$), aPTT ($r = -0.21$ to -0.29, $p < 0.001$), and platelet count ($r = 0.28$–0.29, $p < 0.001$; ►**Table 4**).

Clot Waveform Analysis Parameters and Portal Vein Thrombosis

Further analysis of the CWA characteristics in cirrhotic patients with and without PVT was performed. Of the 560 patients, 78

Table 4 Correlation between clot wave analysis parameters, Child–Turcotte–Pugh, Model for End-Stage Liver Disease score, transient elastography, and conventional coagulation tests

	CTP score	MELD score	Transient elastography	PT	aPTT	Platelet count
CWA values of PT assay						
Min1	−0.34 ($p < 0.001$)	−0.36 ($p < 0.001$)	−0.24 ($p < 0.001$)	−0.48 ($p < 0.001$)	−0.34 ($p < 0.001$)	0.49 ($p < 0.001$)
Min2	−0.35 ($p < 0.001$)	−0.39 ($p < 0.001$)	−0.24 ($p < 0.001$)	−0.51 ($p < 0.001$)	−0.32 ($p < 0.001$)	0.47 ($p < 0.001$)
Max2	−0.43 ($p < 0.001$)	−0.46 ($p < 0.001$)	−0.32 ($p < 0.001$)	−0.61 ($p < 0.001$)	−0.35 ($p < 0.001$)	0.49 ($p < 0.001$)
CWA values of aPTT assay						
Min1	−0.19 ($p < 0.001$)	−0.21 ($p < 0.001$)	−0.15 ($p = 0.01$)	−0.31 ($p < 0.001$)	−0.21 ($p < 0.001$)	0.29 ($p < 0.001$)
Min2	−0.20 ($p < 0.001$)	−0.21 ($p < 0.001$)	−0.14 ($p = 0.02$)	−0.31 ($p < 0.001$)	−0.26 ($p < 0.001$)	0.28 ($p < 0.001$)
Max2	−0.23 ($p < 0.001$)	−0.25 ($p < 0.001$)	−0.19 ($p = 0.002$)	−0.35 ($p < 0.001$)	−0.29 ($p < 0.001$)	0.29 ($p < 0.001$)

Abbreviations: aPTT, activated partial thromboplastin time; CTP, Child–Turcotte–Pugh; CWA, clot wave analysis; max2, maximum deceleration; MELD, Model for End-Stage Liver Disease; min1, maximum velocity; min2, maximum acceleration; PT, prothrombin time.

(13.9%) had PVT at enrollment. The PT- and aPTT-based CWA parameters were not different between patients with cirrhosis with PVT and those without PVT (►**Supplementary Table S3** [available in the online version only]).

Clot Waveform Analysis Parameters as a Predictor of Mortality during the 1-year Follow-up Period

During the 1-year follow-up period, 123 patients (22.0%) died. Patients who died within 1 year were older and more likely to be male and had higher white cell counts, total bilirubin, aspartate aminotransferase, alanine aminotransferase, creatinine levels, CTP and MELD scores, and LS values than those who survived. In contrast, patients who died within 1 year had lower hemoglobin, albumin, and sodium levels than those who survived. One possible explanation for the higher white cell counts and lower Hb and albumin in non-survivors could be that they had more severe liver disease and systemic inflammation, as indicated by the higher CTP score in non-survivors. No significant differences in the PT- and aPTT-based CWA parameters were observed between patients who died and those who survived after 1-year follow-up (►**Supplementary Table S4** [available in the online version only]).

A Cox regression analysis was performed to evaluate the role of CWA values in predicting 1-year mortality (►**Table 5**). The multivariable analysis revealed that min2 (adjusted hazard ratio [aHR] = 0.111, 95% CI: 0.018–0.702, $p = 0.02$) and max2 (aHR = 0.062, 95% CI: 0.007–0.553, $p = 0.01$) of PT-based CWA assays were independent factors associated with the 1-year mortality after adjusting with age, gender, and LS. ►**Supplementary Fig. S1A–F** (available in the online version only) depicts the Kaplan–Meier survival analysis at 1 year, stratified by each CWA value.

Clot Waveform Analysis Parameters as a Predictor of Acute Decompensation during the 1-year Follow-up Period

Of 381 patients with compensated cirrhosis at enrollment, 46 patients (12.1%) developed at least one AD event during the 1-year follow-up period. The baseline PT and aPTT values were significantly higher in patients who developed AD than in those who did not. Additionally, the PT-based CWA parameters were significantly lower in patients with AD than in those without AD ($p < 0.05$). In contrast, no differences in the aPTT-based CWA parameters were observed between patients with and without AD (►**Supplementary Table S5** [available in the online version only]).

Univariable analysis revealed that CTP score and LS were associated with AD development during the 1-year follow-up. However, the multivariable analysis revealed that only LS (aOR = 1.029, 95% CI: 1.004–1.055, $p = 0.03$) was independently associated with AD development (►**Supplementary Table S6** [available in the online version only]).

Discussion

This study investigated the association between CWA parameters, liver disease severity, and clinical outcomes in patients with cirrhosis. Furthermore, the potential role of CWA parameters in predicting mortality and AD during 1-year follow-up was investigated. The main findings of this study were that the PT- and aPTT-based CWA parameters were associated with cirrhosis severity assessed by the cirrhosis stage, CTP classification, and MELD score. Increasing cirrhosis severity was associated with hypocoagulable features in PT- and aPTT-based CWA. LS and max2 of PT-based CWA assay were independently associated with CTP B and C. Furthermore, min2 and max2 of PT-based CWA assays may be the independent factors related to 1-year mortality. In contrast, no differences in CWA parameters were observed between patients with cirrhosis with and without PVT. CWA parameters were not related to AD during the 1-year follow-up.

Patients with cirrhosis may develop bleeding and thrombotic events. Some complications, such as variceal bleeding and PVT, are related to liver dysfunction and portal hypertension rather than hemostatic changes.[19] Conventional coagulation tests fail to reflect hemostasis derangement and inadequately predict bleeding and thrombotic consequences because they partially evaluate the hemostasis

Table 5 Association between clot wave analysis parameters and mortality within 1 year in patients with cirrhosis

	Univariable analysis		Multivariable analysis[a]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
PT-based CWA				
Min1	0.998 (0.850–1.170)	0.98	0.735 (0.508–1.064)	0.10
Min2	0.806 (0.408–1.595)	0.54	0.111 (0.018–0.702)	0.02
Max2	0.481 (0.180–1.286)	0.15	0.062 (0.007–0.553)	0.01
aPTT-based CWA				
Min1	0.979 (0.906–1.058)	0.98	1.073 (0.910–1.264)	0.40
Min2	0.944 (0.587–1.516)	0.81	2.122 (0.761–5.918)	0.15
Max2	0.796 (0.456–1.391)	0.42	1.511 (0.467–4.892)	0.49

Abbreviations: aPTT, activated partial thromboplastin time; CWA, clot wave analysis; HR, hazard ratio; max2, maximum deceleration; min1, maximum velocity; min2, maximum acceleration; PT, prothrombin time.
[a]Adjusted for age, gender, and liver stiffness.

system.[20–22] These tests, particularly the international normalized ratio (INR), are surrogate indicators of liver disease severity. Additionally, global hemostatic tests, such as thrombin generation and whole-blood viscoelastic tests, have several limitations and have not been clinically validated.

A previous study showed that the CWA parameters of the aPTT assay were lower in patients with cirrhosis than in healthy controls.[23] Additionally, patients with cirrhosis with high thromboembolic risk had higher CWA parameters than those with low risk. The first derivative of aPTT-based CWA is significantly associated with a high thromboembolic risk score in patients with cirrhosis.[23] Regarding bleeding risk, patients with cirrhosis with high bleeding risk exhibited hypocoagulable features on PT-based CWA compared with those with low bleeding risk. CWA parameters have been reported to be associated with an increased risk of bleeding.[24] However, no previous studies have investigated CWA parameters, liver disease severity, and predictive ability for clinical outcomes. This study showed that the CWA parameters of the PT and aPTT assays were associated with cirrhosis severity. Patients with more severe cirrhosis exhibited more hypocoagulable characteristics based on PT- and aPTT-based CWA parameters. This relationship may be partly explained by the inclusion of INR in the CTP and MELD scores. However, these associations remained significant even after considering the presence of cirrhotic complications. CTP and MELD scores and LS values assessed using vibration-controlled transient elastography showed a weak to moderate negative correlation with CWA parameters. The correlation coefficient of the PT-based CWA assay was slightly higher than the aPTT-based CWA assay. Patients with recent bleeding were excluded from the study to avoid interference with the hemostatic system. The findings of this study contribute to providing the average CWA values associated with each stage of liver cirrhosis.

PVT is a common thrombotic event in patients with cirrhosis, with an annual incidence of 4.6 to 16.6%.[6,7,25] The highest incidence occurs in patients with more advanced liver disease. PVT is associated with increased variceal bleeding and AD.[25] PVT development is associated with liver disease severity, portal hypertension severity, and portal blood flow. A previous study showed no relationship between hemostatic parameters and PVT occurrence.[6] Consistent with these findings, this study showed no significant differences in the CWA parameters between patients with and without PVT. Regarding clinical outcomes, patients with compensated and decompensated cirrhosis have 1-year mortality rates of 1 to 3% and 15 to 57%, respectively.[26,27] Furthermore, the incidence of AD is 11%, 16%, and 25% in 2, 3, and 5 years, respectively.[28] This study showed a 1-year mortality rate of 22.0% in all patients with cirrhosis and a 1-year AD incidence of 12.1% in patients with compensated cirrhosis. Previous studies have demonstrated that INR is an independent factor related to short-term mortality and AD in patients with cirrhosis.[28–30] The current study revealed new findings indicating that min2 and max2 of PT-based CWA assays are independent factors related to 1-year mortality after adjusting with age, gender, and LS. In contrast, CWA parameters were not found to be related to AD during the 1-year follow-up. The discrepancy in findings among the studies might be explained by the variations in the severity and cause of cirrhosis in the enrolled patients, as well as the differences in treatment across the studies. Our findings suggest that CWA values may play a role in determining the severity of liver cirrhosis and predicting mortality within 1 year for patients with cirrhosis.

The study has some limitations. First, patients with a recent history of bleeding, including variceal bleeding, were excluded from this study because they might show a compensatory mechanism, such as increased coagulation, to restore hemostasis. Therefore, only a few patients with CTP class C were included in the study. Second, there are two types of CWA machines. This study used a CWA machine that detects light transmittance during clotting reactions. Therefore, applying the results to a different type of machine requires caution. Third, the results of coagulation factors and fibrinogen levels were not available in the study, which prevented the evaluation of their association with CWA parameters, mortality, and AD. Fourth, we lacked data on CWA values in healthy controls. However, two prior studies showed that CWA values were lower in patients with cirrhosis compared with healthy controls.

In conclusion, PT- and aPTT-based CWA parameters were associated with cirrhosis severity. Furthermore, min2 and max2 of PT-based CWA assays may be the factors related to 1-year mortality. However, CWA parameters were not associated with PVT or AD development during the 1-year follow-up.

What is known about this topic?

- Conventional coagulation tests are unreliable for identifying the risk of bleeding or thrombosis in patients with cirrhosis.
- Clot waveform analysis, a new global coagulation assay, indicates a hypocoagulable profile in patients with cirrhosis compared with healthy controls.

What does this paper add?

- A hypocoagulable profile based on CWA parameters is associated with advanced-stage cirrhosis.
- Min1 and Max2 of PT-based CWA assay may be factors related to 1-year mortality.
- CWA parameters were not associated with PVT.
- CWA parameters were not factors related to AD during a 1-year follow-up in patients with cirrhosis.

Authors' Contribution

K.T. and P.K. designed the study, analyzed the results, and wrote the manuscript. K.T., S.S., Panarat Thaimai, Prooksa Ananchuensook, Pitiphong Kijrattanakul, Pantep Angchaisuksiri, S.T., and Pisit Tangkijvanich were involved in data curation and formal analysis. S.S. performed clot

wave analysis value measurement. All authors had access to the study data and reviewed, and approved the final version of this manuscript.

Funding
The study was supported by the Ratchadapiseksompotch Endowment Fund of the Center of Excellence in Hepatic Fibrosis and Cirrhosis research unit (GCE 3300170037).

Conflict of Interest
None declared.

References

1 Lisman T, Leebeek FW, de Groot PG. Haemostatic abnormalities in patients with liver disease. J Hepatol 2002;37(02):280–287
2 Lisman T, Hernandez-Gea V, Magnusson M, et al. The concept of rebalanced hemostasis in patients with liver disease: communication from the ISTH SSC working group on hemostatic management of patients with liver disease. J Thromb Haemost 2021;19 (04):1116–1122
3 Tripodi A, Primignani M, Chantarangkul V, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology 2009;137(06):2105–2111
4 Intagliata NM, Rahimi RS, Higuera-de-la-Tijera F, et al. Procedural-Related Bleeding in Hospitalized Patients With Liver Disease (PROC-BLeeD): an international, prospective, multicenter observational study. Gastroenterology 2023;165(03):717–732
5 Ambrosino P, Tarantino L, Di Minno G, et al. The risk of venous thromboembolism in patients with cirrhosis. A systematic review and meta-analysis. Thromb Haemost 2017;117(01):139–148
6 Turon F, Driever EG, Baiges A, et al. Predicting portal thrombosis in cirrhosis: a prospective study of clinical, ultrasonographic and hemostatic factors. J Hepatol 2021;75(06):1367–1376
7 Nery F, Chevret S, Condat B, et al; Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology 2015;61(02):660–667
8 Napolitano G, Iacobellis A, Merla A, et al. Bleeding after invasive procedures is rare and unpredicted by platelet counts in cirrhotic patients with thrombocytopenia. Eur J Intern Med 2017;38: 79–82
9 Blasi A, Machlab S, Risco R, et al. A multicenter analysis of the role of prophylactic transfusion of blood products in patients with cirrhosis and esophageal varices undergoing endoscopic band ligation. JHEP Rep Innov Hepatol 2021;3(06):100363
10 European Association for the Study of the Liver. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol 2022;76:1151–1184
11 Speybroeck J, Marsee M, Shariff F, et al. Viscoelastic testing in benign hematologic disorders: clinical perspectives and future implications of point-of-care testing to assess hemostatic competence. Transfusion 2020;60(Suppl 6):S101–S121
12 Lisman T. Interpreting hemostatic profiles assessed with viscoelastic tests in patients with cirrhosis. J Clin Gastroenterol 2020; 54(04):389–391
13 Sevenet PO, Depasse F. Clot waveform analysis: where do we stand in 2017? Int J Lab Hematol 2017;39(06):561–568
14 Matsumoto T, Shima M, Takeyama M, et al. The measurement of low levels of factor VIII or factor IX in hemophilia A and hemophilia B plasma by clot waveform analysis and thrombin generation assay. J Thromb Haemost 2006;4(02):377–384
15 Wada H, Shiraki K, Matsumoto T, et al. A clot waveform analysis of thrombin time using a small amount of thrombin is useful for evaluating the clotting activity of plasma independent of the presence of emicizumab. J Clin Med 2022;11(20): 6142
16 Toh CH, Giles AR. Waveform analysis of clotting test optical profiles in the diagnosis and management of disseminated intravascular coagulation (DIC). Clin Lab Haematol 2002;24(06): 321–327
17 Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60(08):646–649
18 Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33(02):464–470
19 Lisman T, Caldwell SH, Intagliata NM. Haemostatic alterations and management of haemostasis in patients with cirrhosis. J Hepatol 2022;76(06):1291–1305
20 Kovalic AJ, Majeed CN, Samji NS, Thuluvath PJ, Satapathy SK. Systematic review with meta-analysis: abnormalities in the international normalised ratio do not correlate with periprocedural bleeding events among patients with cirrhosis. Aliment Pharmacol Ther 2020;52(08):1298–1310
21 Roberts LN, Lisman T, Stanworth S, et al. Periprocedural management of abnormal coagulation parameters and thrombocytopenia in patients with cirrhosis: guidance from the SSC of the ISTH. J Thromb Haemost 2022;20(01):39–47
22 Northup PG, Garcia-Pagan JC, Garcia-Tsao G, et al. Vascular Liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021; 73(01):366–413
23 Ruberto MF, Sorbello O, Civolani A, Barcellona D, Demelia L, Marongiu F. Clot wave analysis and thromboembolic score in liver cirrhosis: two opposing phenomena. Int J Lab Hematol 2017; 39(04):369–374
24 Ruberto MF, Marongiu F, Sorbello O, Civolani A, Demelia L, Barcellona D. Are prothrombin time and clot waveform analysis useful in detecting a bleeding risk in liver cirrhosis? Int J Lab Hematol 2019;41(01):118–123
25 Zhang Y, Xu BY, Wang XB, et al. Prevalence and clinical significance of portal vein thrombosis in patients with cirrhosis and acute decompensation. Clin Gastroenterol Hepatol 2020;18(11): 2564–2572.e1
26 D'Amico G, Morabito A, D'Amico M, et al. Clinical states of cirrhosis and competing risks. J Hepatol 2018;68(03):563–576
27 de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll CBaveno VII Faculty. Baveno VII - renewing consensus in portal hypertension. J Hepatol 2022;76(04):959–974
28 D'Amico G, Perricone G. Prediction of decompensation in patients with compensated cirrhosis: does etiology matter? Curr Hepatol Rep 2019;18:144–156
29 Musunuri B, Gopal S, Tantry BV, Shenoy S, Shetty AJ. Predictors of short-term mortality in patients of cirrhosis of liver presenting as acute kidney injury: an in-hospital prospective observational study. J Clin Exp Hepatol 2023;13(06):989–996
30 Wang Y, Dong F, Sun S, et al. Increased INR values predict accelerating deterioration and high short-term mortality among patients hospitalized with cirrhosis or advanced fibrosis. Front Med (Lausanne) 2021;8:762291