Thromboelastography maximum amplitude predicts short-term mortality in patients with hepatitis B virus-related acute-on-chronic liver failure

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Received July 27, 2019; Accepted May 29, 2020

DOI: 10.3892/etm.2020.8990

Abstract. Patients with hepatitis B virus (HBV)-related acute-on-chronic liver failure (ACLF) exhibit complex hemostatic defects. Thromboelastography (TEG) can be used to reveal global hemostasis in patients with liver disease; however, little is known about the association between TEG and the outcome of patients with HBV-related ACLF. The present study aimed to investigate the value of TEG for predicting 90 day mortality in patients with HBV-related ACLF. A total of 51 patients with HBV-related ACLF, 26 patients with chronic hepatitis B (CHB) and 26 healthy controls (HC) were enrolled in the present study. TEG, standard coagulation tests, routine blood tests, biochemical markers and demographic variables were recorded and assessed for prognostic value. The results indicated that a prolonged reaction and kinetics (K) time, a shortened α angle and a decreased maximum amplitude (MA) and coagulation index (CI) were observed in patients with HBV-related ACLF, compared with CHB and HC subjects. Patients with HBV-related ACLF in the mortality group exhibited a decrease in α angle, MA, lysis at 30 min, CI, fibrinogen and platelet count, and an increase in K time, international normalized ratio (INR) and the model for end-stage liver disease (MELD) score in comparison with the survival group. MA and INR were two independent predictors of 90 day mortality in patients with HBV-related ACLF, with hazard ratios of 0.918 (95% CI, 0.867-0.971; P=0.003) and 3.141 (95% CI, 1.843-5.354; P<0.001) respectively. When predicting 90 day mortality, MA + INR exhibited the highest area under the receiver operating characteristic curve, followed by INR, MELD score and MA. Patients with ACLF and MA ≤51.5 mm exhibited a poorer outcome than those with MA >51.5 mm, as revealed via the Kaplan-Meier analysis. In summary, the findings of the present study suggested that TEG MA was associated with 90 day mortality in patients with HBV-related ACLF, and a combination of MA and INR was superior to MA, INR and MELD score in terms of prognostic value.

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Key words: thromboelastography, maximum amplitude, acute-on-chronic liver failure, hepatitis B, platelet

Introduction

Acute-on-chronic liver failure (ACLF) is an acute deterioration of liver function in patients with chronic liver disease (CLD), which is characterized by high short-term mortality (1,2). Patients with ACLF exhibit abnormal standard coagulation tests (SCTs), such as prolonged international normalized ratio (INR) (3). INR ≥1.5 is one of the major indicators in diagnosing ACLF according to Asian Pacific Association for the Study of the Liver (APASL) criteria (4), and a higher INR is associated with a worsened outcome (3).

Patients with CLD exhibit a risk of variceal bleeding, and INR is a poor predictor of bleeding, although it is prolonged (5,6), and may be associated with the fact that INR is performed with platelet-poor plasma, which only reflects the function of procoagulant factors. Therefore, INR has been suggested to be unsuitable to evaluate blood coagulation in patients with liver disease (5,7). However, unlike INR, thromboelastography (TEG) is a viscoelastic test that may be used to evaluate the hemostatic function of whole blood, from clot formation to thrombolysis, which is useful for investigating global hemostasis in patients with liver failure (8). TEG, which was first described by H. Hartert in 1948, has been widely used to monitor blood coagulation during liver transplantation (LT) (8,9). Previous studies have indicated that TEG was beneficial in reducing blood transfusion during invasive procedures in patients with liver disease (8-10), and

predicting re-bleeding in patients with cirrhosis and variceal bleeding (5).

Recently, TEG has been used as a tool to assess the prognosis of patients with liver disease (11-13). A retrospective study at the Mayo Clinic revealed that although post-LT TEG was not associated with mortality in patients who received LT, some parameters of TEG were predictive of the increased length of hospitalization and early allograft dysfunction (EAD) (11). Recently, Premkumar *et al* (12) indicated that the TEG parameter coagulation index (CI) and lysis at 30 min (LY30) were two independent predictors of mortality in patients with ACLF. Blasi *et al* (13) revealed that the hypocoagulable thromboelastometry (TE) profile was associated with a higher 28 and 90 day mortality in patients with ACLF. However, it was indicated that patients with ACLF represent a heterogeneous population, which is based on various etiologies and diagnostic criteria (14). The leading etiology of ACLF in China is hepatitis B virus infection (15). In contrast to patients with non-HBV ACLF, which is characterized by kidney and cerebral failure, patients with HBV-related ACLF exhibit liver and coagulation failure (3). The association between TEG and the outcome of patients with HBV-related ACLF remains poorly elucidated. Therefore, a prospective study was performed to investigate the value of TEG for predicting the 90 day mortality in patients with HBV-related ACLF.

Materials and methods

Patient selection. A total of 51 patients with HBV-related ACLF, who were admitted to Hwa Mei Hospital, University of Chinese Academy of Science (Ningbo, China) from October 2017 to September 2018, were enrolled in the present study. A total of 26 age- and gender-matched patients with chronic hepatitis B (CHB) and 26 healthy controls were also recruited from out-patient department and physical center of Hwa Mei Hospital, University of Chinese Academy of Science from April 2018 to September 2018. ACLF was diagnosed according to the recommendations of the APASL (4). Patients with alcohol-related liver disease, autoimmune hepatitis, drug-induced hepatitis, infection with human immunodeficiency virus, hepatitis A, C, D and E virus, who were pregnant, suffered from malignancies, were transfused with frozen plasma or platelet products and received anticoagulant or antiplatelet therapy within 7 days, were excluded from ACLF and CHB groups in the present study, whilst individuals with a history of liver disease were excluded from the healthy control group. Patients with HBV-related ACLF were followed up from the date of their diagnosis to the date of their decease or the end of the 90 day follow-up period. Data regarding clinical characteristics and laboratory parameters were collected from the electronic medical record (EMR). The model for end-stage liver disease (MELD) and Child-Pugh scores were calculated using the data from EMR (16). The present study was approved by the Ethics Committee of Hwa Mei Hospital, University of Chinese Academy of Sciences, and all enrolled patients signed a written informed consent.

Laboratory analysis. SCTs, including INR, activated prothrombin time (aPTT), thrombin time (TT), fibrinogen (FIB) and D-dimer, were analyzed using the ACL TOP® 750 automatic coagulation analyzer (Instrumentation Laboratory). Routine blood tests, including white blood cell (WBC) count, platelet count and hemoglobin (Hb), were measured using the COULTER® LH 750 hematology analyzer (Beckman Coulter, Inc.). Biochemical parameters, including total bilirubin (TBil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), were determined using the ADVIA® 2400 Chemistry System (Siemens AG).

TEG was performed on the TEG® 5000 Thrombelastograph Hemostasis Analyzer System (Haemoscope Corporation). In brief, 1 ml citrated whole blood was activated by kaolin, and 340 μl activated blood and 20 μl 0.2 M $CaCl_2$ were added into a plastic cup. Subsequently, the cup was loaded onto a holder and the test commenced immediately. Finally, reaction (R) and kinetics (K) time, α angle, maximum amplitude (MA), LY30 and CI were recorded.

R time (normal range, 5-10 min) represents the time from the start of the test to initial clot formation, reflecting the function of clotting factors. K time (normal range, 1-3 min) represents the period between the end of R time and the curve reaching 20 mm. α angle (normal range, 53-72˚) is the angle between the tangent of the curve and the baseline. K time and α angle represent the function of FIB for blood clotting. MA (normal range, 50-70 mm) represents the maximal clot strength, which is primarily influenced by the platelet function and count. LY30 represents the percentage decrease in amplitude at 30 min after MA was reached, and reflects fibrinolysis. Prolonged R time suggest clotting factor deficiency, whilst prolonged K time and shortened α angle indicate inadequate fibrinogen. Reduced MA suggests thrombopenia or platelet dysfunction. CI was calculated using the R time, K time, α angle and MA, with a normal range from -3 to +3 (17,18). Therefore, prolonged R and K time, shortened α angle and decreased MA and CI indicate a hypocoagulable state.

Statistical analysis. Normally distributed continuous data are presented as the means ± standard deviation. ANOVA was used to compare differences among multiple groups, followed by post hoc comparisons using Fisher's Least Significant Difference test. Unpaired Student's t-test was used for comparisons between two independent groups. Abnormally distributed variables are presented as medians and interquartile ranges, and Kruskal-Wallis test was used to compare multiple groups, followed by post hoc comparisons with the Nemenyi test. Mann-Whitney U test was used for nonparametric comparisons of two independent groups. Categorical variables were expressed as percentages and analyzed using the χ^2 test. Independent predictors of 90 day mortality were identified via multivariate Cox regression analysis, and the mathematical formula of the prognostic model was established as follows: Exp (β_1 x X_1 + β_2 x X_2 +…+ β_m x X_m; β_1, β_2, β_m, regression coefficient; X_1, X_2, X_m, independent predictors). Receiver operating characteristic (ROC) curves were established to assess prognostic values. Additionally, survival curves were estimated via Kaplan-Meier analysis and compared using the log-rank test. Finally, correlations between different variables were examined by Pearson's correlation analysis. All data were analyzed using SPSS v22.0 software (IBM Corp.) and GraphPad PRISM v6.04 software (GraphPad Software, Inc.).

Table I. Thromboelastography parameters, standard coagulation test variables and demographic characteristics in all recruited subjects.

Variables	HC (n=26)	CHB (n=26)	HBV-ACLF (n=51)	P-value
Age (years)[a]	43.77±8.27	44.19±6.57	45.96±10.95	0.557
Male sex, n (%)[c]	18 (69.23)	20 (76.92)	44 (86.27)	0.198
R time (min)[b]	5.45 (4.75-6.30)	5.80 (5.00-6.35)	7.10 (5.50-9.60)[e,g]	<0.001
K time (min)[b]	1.50 (1.28-1.70)	1.90 (1.40-2.33)	2.30 (1.80-3.20)[f,g]	<0.001
α angle (degrees)[b]	68.55 (66.30-70.95)	65.25 (58.70-69.08)	58.80 (51.90-64.60)[f,g]	<0.001
MA (mm)[a]	65.08±3.80	60.66±6.40[d]	49.23±8.46[f,h]	<0.001
LY30 (%)[b]	0.35 (0.00-1.25)	0.40 (0.00-0.0.73)	0.90 (0.00-2.50)	0.153
CI[a]	1.17±1.19	-0.01±1.88	-3.51±3.40[f,h]	<0.001
INR[a]	1.03±0.04	1.01±0.13	2.32±0.75[f,h]	<0.001
aPTT (s)[b]	33.10 (31.38-34.65)	32.20 (29.80-35.95)	51.70 (42.50-62.10)[f,h]	<0.001
TT (s)[b]	19.85 (19.08-20.78)	12.70 (11.00-21.85)	28.90 (25.70-38.10)[f,h]	<0.001
FIB (mg/dl)[a]	377.08±60.64	312.82±87.95[e]	216.10±74.73[f,h]	<0.001

[a]Normally distributed continuous data, which are presented as the mean ± standard deviation. One-way ANOVA was used to compare differences among multiple groups, followed by post hoc comparisons using Fisher's Least Significant Difference test; [b]Abnormally distributed variables, which are expressed as medians and interquartile ranges. The Kruskal-Wallis test was performed for multiple comparisons, followed by post hoc comparisons using the Nemenyi test; [c]Categorical variables, which are expressed as percentages. The significances were analyzed via the χ^2 test; [d]P<0.05, [e]P<0.01 and [f]P<0.001 vs. HC; [g]P<0.05 and [h]P<0.001 vs. CHB. HC, healthy controls; CHB, chronic hepatitis B; HBV, hepatitis B virus; ACLF, acute-on-chronic liver failure; R, reaction; K, kinetics; MA, maximum amplitude; LY30, lysis at 30 min; CI, coagulation index; INR, international normalized ratio; aPTT, activated prothrombin time; TT, thrombin time; FIB, fibrinogen.

P<0.05 was considered to indicate a statistically significant difference.

Results

Characteristics of study subjects. The TEG parameters, SCTs and demographic characteristics of all recruited subjects are presented in Table I. A total of 51 patients with HBV-related ACLF were included in the current study. The majority of the patients were males (86.27%), and the mean age was 45.96±10.95 years. Additional, 26 healthy cases and 26 patients with CHB were also recruited, with male proportion of 69.23 and 76.92%, and mean age of 43.77±8.27 and 44.19±6.57 years, respectively. No differences were observed in the age or sex distribution among the subjects in the HC, CHB and ACLF groups. MA and FIB in the CHB group were found to be significantly decreased compared with those in the HC group (P<0.05 and P<0.01, respectively; Table I). A prolonged R time and K time, an increased activated partial thromboplastin time, thrombin time and INR, a shortened α angle and a decreased MA, CI and FIB were observed in the ACLF group compared with the HC and CHB groups. However, LY30 exhibited no differences among the three group (Table I).

Analysis of 90 day mortality predictors in patients with HBV-related ACLF. Among 51 patients with HBV-related ACLF, 19 patients succumbed to the disease within 90 days. The patients in the mortality group exhibited a decrease in α angle, MA, LY30, CI, FIB and platelet count, and an increase in K time, INR and MELD score in comparison with the survival group. However, no difference was observed in age, gender, R time, aPTT, TT, TBil, D-dimer, AST, ALT, white blood cell (WBC) count, hemoglobin (Hb) and Child-Pugh score between survival and mortality groups (Table II).

In addition, K time, MA, CI, INR, FIB, platelet count and MELD score were identified as factors that were associated with mortality, as revealed via a univariate Cox regression analysis (P<0.05; Table III). The aforementioned variables together with LY30, age, white blood cell count and Child-Pugh score were subsequently included into a multivariate Cox regression analysis, which revealed that MA and INR were two independent predictors of 90 day mortality, with hazard ratios (HRs) of 0.918 (95% CI, 0.867-0.971; P=0.003) and 3.141 (95% CI, 1.843-5.354; P<0.001), respectively (Table III).

To assess the value of MA alone and in combination with INR in predicting mortality, ROC curves were generated. The area under the ROC curve (AUROC) was 0.771 (95% CI, 0.641-0.900; P=0.001) for MA, 0.865 (95% CI, 0.765-0.966; P<0.001) for INR, 0.898 (95% CI, 0.816-0.980; P<0.001) for MA + INR and 0.811 (95% CI, 0.674-0.948; P<0.001) for MELD score (Fig. 1 and Table IV). The cut-off value of MA was 51.5 mm, as revealed by the ROC curve, and patients with MA ≤51.5 mm exhibited a worsened outcome than those with MA >51.5 mm (Fig 2; P<0.001).

Correlations between MA and INR, MELD score and platelet count, in patients with HBV-related ACLF. To additionally verify the prognostic value of MA, the correlations between MA and INR, MELD score and platelet count were examined in patients with HBV-related ACLF. MA was negatively correlated with MELD score (r=-0.370; P=0.007), and positively correlated with platelet count (r=0.664; P<0.001), whereas it exhibited no correlation with INR (Fig. 3; r=-0.162; P=0.257).

Table II. Comparison of clinical and demographic characteristics between the survival and mortality group in patients with HBV-ACLF.

Variables	Survival group (n=32)	Mortality group (n=19)	P-value
Age (years)[a]	44.06±9.14	49.16±13.12	0.109
Male sex, n (%)[c]	28 (87.50)	16 (84.21)	1.000
R time (min)[b]	6.85 (5.20-8.88)	7.50 (6.20-11.20)	0.149
K time (min)[b]	2.00 (1.63-2.80)	2.60 (2.20-3.70)	0.007
α angle (degrees)[b]	63.00 (53.33-67.75)	57.10 (44.30-60.20)	0.012
MA (mm)[a]	51.66±8.85	45.15±6.00	0.007
LY30 (%)[b]	1.80 (0.04-2.75)	0.3 (0.00-1.00)	0.035
CI[a]	-2.67±3.41	-4.92±3.21	0.024
INR[a]	1.99±0.54	2.89±0.73	<0.001
aPTT (s)[b]	47.25 (42.28-59.80)	53.80 (46.60-68.40)	0.167
TT (s)[b]	27.65 (25.20-39.63)	31.70 (28.10-38.10)	0.144
FIB (s)[a]	238.03±67.28	179.16±73.62	0.005
TBil (mg/dl)[a]	284.14±150.44	335.37±163.17	0.260
D-dimer (ng/ml)[b,d]	468.50 (294.50-843.25)	833.00 (382.00-1322.00)	0.090
AST (U/l)[b]	104.00 (65.00-134.00)	95.00 (65.00-130.00)	0.861
ALT (U/l)[b]	101.00 (60.00-264.00)	83.00 (39.00-227.00)	0.397
WBC count ($x10^9$)[a]	8.08±4.11	10.40±7.61	0.164
Platelet count ($x10^9$)[a]	112.47±57.83	74.05±33.90	0.011
Hb (g/l)[a]	120.22±15.84	115.74±24.94	0.435
MELD score[a]	20.38±4.03	26.60±6.45	<0.001
Child-Pugh score[a]	10.88±0.98	11.47±1.71	0.117

[a]Normally distributed continuous data, which are presented as the mean ± standard deviation. One-way ANOVA was used to compare differences among multiple groups, followed by post hoc comparisons using Fisher's Least Significant Difference test; [b]Abnormally distributed variables, which are expressed as medians and interquartile ranges. The Kruskal-Wallis test was performed for multiple comparisons, followed by post hoc comparisons using the Nemenyi test; [c]Categorical variables, which are expressed as percentages. The significances were analyzed via the χ^2 test; [d]The number of HBV-ACLF patients who were tested for D-dimer was 14 and 11 in the survival and mortality group, respectively. HBV, hepatitis B virus; ACLF, acute-on-chronic liver failure; R, reaction; K, kinetics; MA, maximum amplitude; LY30, lysis at 30 min; CI, coagulation index; INR, international normalized ratio; aPTT, activated prothrombin time; TT, thrombin time; FIB, fibrinogen; TBil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cell; Hb, hemoglobin; MELD, model for end-stage liver disease.

Discussion

With reductions of both procoagulant and anticoagulant factors, the weakened hemostatic system of patients with end stage CLD renders them susceptible to thrombosis or hemorrhage, in manner that is dependent on major circumstantial risk factors (7). This was also revealed in a recent study by Fisher *et al* (19) using a thrombin generation assay in the presence of thrombomodulin, which indicated that the endogenous thrombin potential in patients with ACLF was equivalent to that of healthy subjects. Conversely, patients with HBV-related ACLF in the present study demonstrated a hypocoagulable profile, which was indicated by the prolonged R and K time, the shortened α angle and the decreased MA and CI, compared with HC and CHB subjects. The contradictory results of the present study in comparison with that of Fisher *et al* (19) may be attributed to the fact that TEG is performed without thrombomodulin, the principal activator of anticoagulant protein C. Moreover, the abnormal TEG and SCTs parameters, including prolonged R time, K time, INR, aPTT and TT, shortened α angle and reduced MA, CI and FIB, in patients with HBV-related ACLF demonstrated the damage of procoagulants, FIB and platelets.

Previous studies have indicated that the hypocoagulability, which was revealed via TEG or rotational TE, was associated with short-term mortality in patients with ACLF (12,13). This was also suggested in the present study. In the present study, patients with HBV-related ACLF in the mortality group exhibited a higher hypocoagulability with a decrease in α angle, MA, CI, FIB and platelet count, and an increase in K time and INR in comparison with the survival group.

It is noteworthy that LY30 was lower in the survival group compared with that in the mortality group, which indicated that a hypofibrinolysis state existed in the mortality group. This finding is in accordance with the studies by Blasi *et al* (13) and Lloyd-Donald *et al* (20), although it is contradictory to the findings of Premkumar *et al*(12) and Goyal *et al* (21). These diverse results may be attributed to the different methods and study subjects that were used in these studies. D-dimer, which is another indicator of fibrinolysis, has been

Table III. Cox regression analysis of variables affecting 90 day mortality in patients with hepatitis B virus-related acute-on-chronic liver failure.

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)	1.036	0.993-1.081	0.104			
Sex	0.784	0.228-2.696	0.699			
R time (min)	1.087	0.960-1.231	0.188			
K time (min)	1.321	1.003-1.739	0.047			
A angle (degrees)	0.968	0.935-1.002	0.066			
MA (mm)	0.940	0.897-0.984	0.008	0.918	0.867-0.971	0.003
LY30 (%)	0.703	0.475-1.042	0.079			
Coagulation index	0.867	0.771-0.976	0.018			
INR	2.691	1.658-4.369	<0.001	3.141	1.843-5.354	<0.001
aPTT (s)	1.016	0.994-1.039	0.160			
FIB (mg/dl)	0.988	0.981-0.996	0.004			
TBil (μmol/l)	1.001	0.999-1.004	0.363			
WBC count (x10^9)	1.076	0.993-1.165	0.073			
Platelet count (x10^9)	0.987	0.976-0.998	0.019			
MELD score	1.117	1.053-1.184	<0.001			
Child-Pugh score	1.402	0.951-2.066	0.088			

R, reaction; K, kinetics; MA, maximum amplitude; LY30, lysis at 30 min; CI, confidence interval; INR, international normalized ratio; aPTT, activated prothrombin time; FIB, fibrinogen; TBil, total bilirubin; WBC, white blood cell; MELD, model for end-stage liver disease.

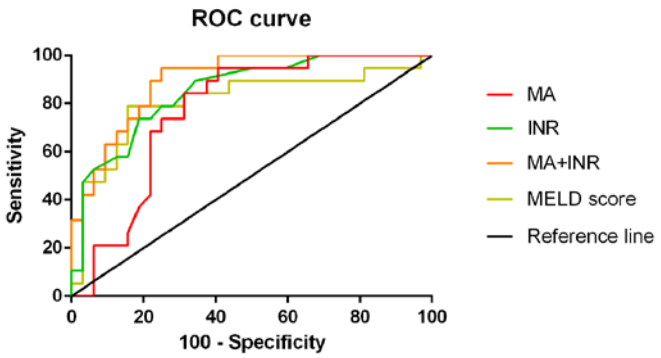

Figure 1. ROC curves of four predictors for 90 day mortality in patients with hepatitis B virus-related acute-on-chronic liver failure. The prognostic values of MA, INR, MA + INR and MELD score were quantified using the ROC curves. ROC, receiver operating characteristic; MA, maximum amplitude; INR, international normalized ratio; MELD, model for end-stage liver disease.

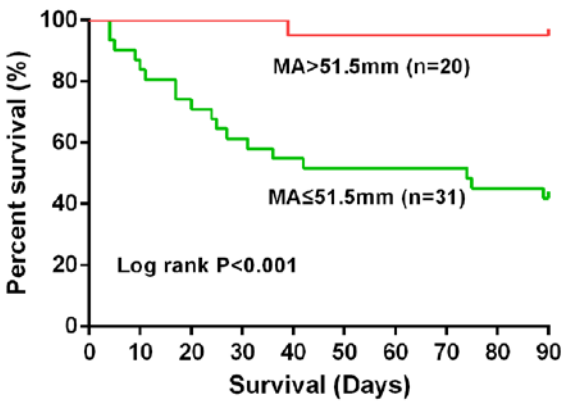

Figure 2. Survival curves of patients with hepatitis B virus-related acute-on-chronic liver failure based on the cut-off value of MA. MA, maximum amplitude

indicated to be at a higher concentration in patients with liver cirrhosis and portal vein thrombosis (22). A previous study by Li *et al* (23) revealed that the prognostic value of D-dimer levels may be moderate for predicting the in-hospital mortality of patients with liver cirrhosis, with an AUROC of 0.729. In the present study, the median value of D-dimer in the survival and mortality group was 468.50 and 833.00, respectively, with no significant difference observed between the groups (P=0.09). However, only 14 and 11 patients with HBV-ACLF in the survival and mortality group were tested for D-dimer. Therefore, it was difficult to explore the prognostic value of D-dimer in the present study. Previous studies have indicated that hypofibrinolysis contributed to thrombotic episodes to aggravate liver failure (13,24), while hyperfibrinolysis was associated with variceal bleeding, another life-threatening complication in patients with ACLF (25). Therefore, additional future studies examining fibrinolysis and the prognosis of patients with ACLF using a larger sample size are required.

In a recent study by Premkumar *et al* (12), CI and LY30 have been indicated to be two predictors of mortality at day 28 in patients with ACLF. However, the results of the present study revealed that MA along with INR were two independent risk factors for 90 day mortality in patients with HBV-related ACLF. Different etiologies of ACLF, sample size and follow-up time may account for the varying results. Furthermore, ROC curve analysis revealed that MA predicted mortality with

Table IV. Comparison of AUROC of four predictors for 90 day mortality in patients with hepatitis B virus-related acute-on-chronic liver failure.

Variables	AUROC (95% CI)	Sensitivity	Specificity	P-value
MA	0.771 (0.641-0.900)	0.947	0.594	0.001
INR	0.865 (0.765-0.966)	0.947	0.656	<0.001
MA + INR	0.898 (0.816-0.980)	0.947	0.750	<0.001
MELD score	0.811 (0.674-0.948)	0.789	0.844	<0.001

MA, maximum amplitude; INR, international normalized ratio; MELD, model for end-stage liver disease; AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

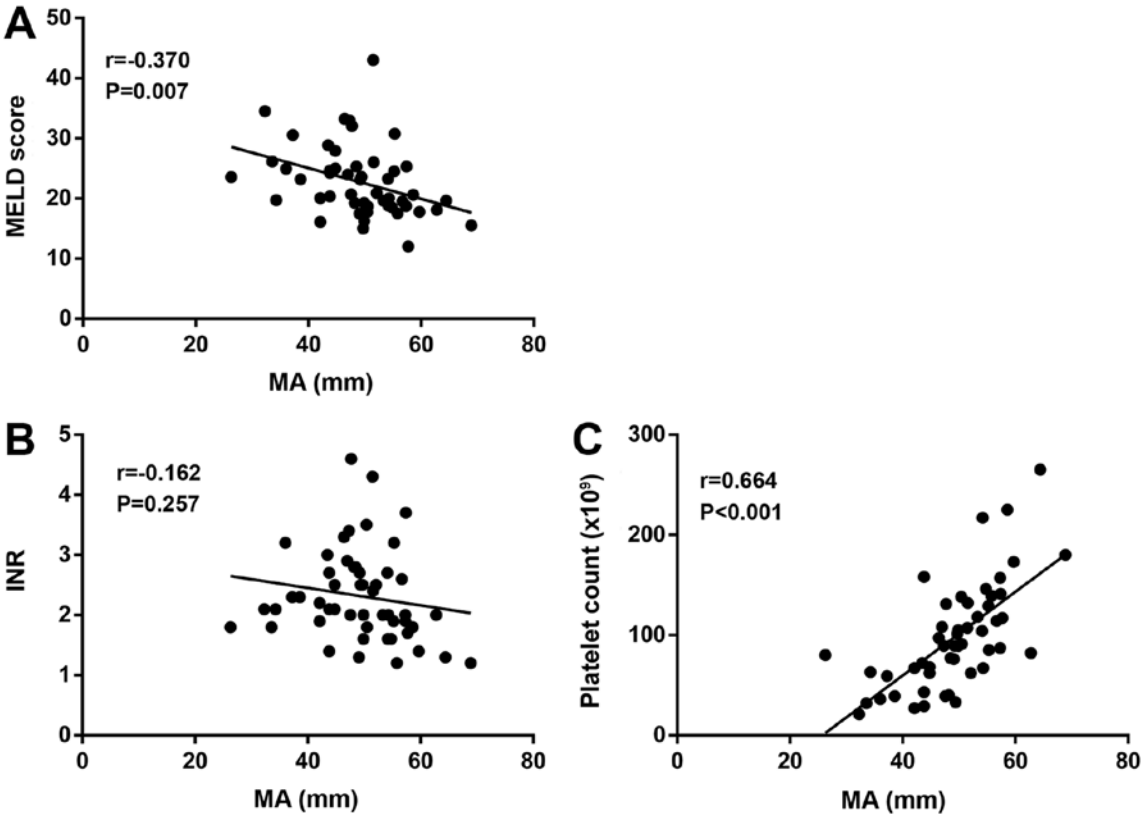

Figure 3. Correlations between MA and (A) MELD score, (B) INR and (C) platelet count in patients with hepatitis B virus-related acute-on-chronic liver failure. MA, maximum amplitude; INR, international normalized ratio; MELD, model for end-stage liver disease.

an AUROC of 0.771, which was < INR and MELD score; however, MA + INR presented the highest predictability of mortality in the current study, with an AUROC of 0.898. Moreover, patients with MA ≤51.5 mm exhibited higher mortality than those with MA >51.5 mm, as revealed via Kaplan-Meier analysis. Subsequent analysis indicated that MA demonstrated a negative correlation with MELD score, however no correlation between MA and INR was observed. As indicated by Stravitz *et al* (26), INR may demonstrate the severity of primary liver injury, while platelets may indicate the extent of systemic inflammation secondary to liver damage. In addition, MA is an indicator reflecting the count and function of platelets (18,27). This may justify why MA + INR was revealed to be the optimal predictor of mortality in the present study.

Patients with CLD suffer from thrombocytopenia and platelet dysfunction (15,28). Systemic inflammatory response syndrome, hypersplenism and a reduced thrombopoietin synthesis have been indicated to be responsible for thrombocytopenia in patients with ACLF (15). On the other hand, platelet function has been demonstrated to decline in patients with cirrhosis independently of platelet count (28). Previous studies have revealed that platelet count is a prognostic factor for patients with ACLF (15,29). MA, however not platelet count, was revealed to be an independent prognostic factor for HBV-ACLF in the present study, and this may be associated with the fact that MA represents both the function and count of platelets. Notably, platelets have been indicated to be a modulator of liver disease (30), which will require additional elucidation in the future.

Recently, several scoring systems, including the Child-Pugh and MELD score, which are combined with certain laboratory variables and clinical symptoms, have emerged to predict the outcome of patients with liver disease (16,31). Therefore, Child-Pugh and MELD scores were included in the present study. The Child-Pugh score employs five clinical variables: Total bilirubin, serum albumin, INR, ascites and hepatic encephalopathy, and each variable is scored with 1-3 points, with the maximum total number of points being 15 (16). However, in the present study no significant difference was observed in Child-Pugh score between the survival and mortality group, therefore Child-Pugh score was not useful as a prognostic factor for patients with HBV-ACLF. This finding is in accordance with that of a previous study, which indicated that Child-Pugh score was a poor predictor of the mortality of patients with cirrhosis and ACLF (16). MELD score is calculated based on the levels of total bilirubin, INR and serum creatinine, and the disease etiology (16). The prognostic value of MELD varies in different studies, with a previous study demonstrating that MELD may be ineffective in predicting the in-hospital mortality of the HBV-related ACLF subgroup according to the APASL criteria, with an AUROC of 0.62 (16). However, another study indicated that the AUROC of the MELD score was 0.838 for predicting short-term mortality in patients with HBV-ACLF (31). The prognostic value of MELD in the present study was amidst that of the aforementioned studies, with an AUROC of 0.811. This discrepancy may be associated with the different severity of the disease of the enrolled patients, the sample size and the follow-up time.

However, there were several limitations to the present study. Firstly, the current study was a single-center study with a small sample size. Secondly, only baseline laboratory variables were assessed, and it was not possible to obtain dynamic data of the TEG parameters for subsequent analysis. Thirdly, patients with HBV-related ACLF were partially tested for D-dimer, which rendered difficult to reveal its effect in the present study. Therefore, prospective multicenter studies with a larger sample size are required.

In conclusion, the present study indicated that the TEG parameter MA was an independent predictor of the mortality of patients with HBV-related ACLF, and the combination of MA and INR was superior to MA, INR and MELD score in terms of prognostic value.

Acknowledgements

Not applicable.

Funding

The present study was funded by the Hwa Mei Research Foundation of Hwa Mei Hospital, University of Chinese Academy of Sciences (grant nos. 2016HMKY07 and 2017HMKY33).

Availability of data and materials

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

Authors' contributions

ZZ and YY performed laboratory analysis and wrote the manuscript. YK, DD, GZ and XH collected and analyzed the data, critical revision of the manuscript for important intellectual content. GG designed the study and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Hwa Mei Hospital, University of Chinese Academy of Sciences (Ningbo, China), and all enrolled patients signed a written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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