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Postoperative coagulation profiles of patients undergoing adult-to-adult living donor liver transplantation—A single-center experience

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ABSTRACT

Objective: To characterize the pre- and postoperative coagulation profiles of patients undergoing adult-to-adult living donor liver transplantation (LDLT), using various coagulation tests and rotational thromboelastometry (ROTEM).

Methods: This single-center observational study evaluated the various coagulation profiles of 22 patients (13 men and 9 women). Blood samples were obtained immediately after the induction of anesthesia (PRE) and on postoperative days (PODs) 1, 3, 5, and 7 after LDLT surgery.

Results: Most procoagulant factors (fibrinogen, platelet, and coagulation factors II, VII, VIII, and IX) improved to levels equal to or greater than the PRE levels on POD 7. The levels of von Willebrand factor significantly increased after surgery, whereas those of disintegrin-like and metalloproteinase with thrombospondin type 1 motif 13 decreased. Although the thrombin-antithrombin III complex increased immediately after surgery, the plasmin-α 2 plasmin inhibitor complex increased only on POD 7. The level of plasminogen activator inhibitor-1 increased on POD 1, returning to PRE levels on POD 3. Almost all ROTEM parameters were decreased or prolonged, compared to the PRE levels, on POD 7.

Conclusions: The values of most coagulation tests showed the improvement or acceleration of coagulability on POD 7 than at PRE, with almost all the ROTEM parameters decreased or prolonged. Therefore, it cannot be concluded whether ROTEM reflects the net effect of hemostatic balance after liver transplantation.

1. Introduction

Liver transplantation for patients with end-stage liver disease is considered as the standard treatment, although the mortality rate at 1 year remains at 10%−20%, due to persisting complications, including bleeding and thrombosis [1]. Hemostatic rebalancing, an important contributor to bleeding and thrombotic complications, is assumed to occur in patients with end-stage liver disease [2]. However, this is difficult to verify because standard laboratory tests do not reflect the in vivo coagulation status, as these tests mainly reflect deficiencies in procoagulant factors without anticoagulant factors [3]. Nevertheless, measurement of hemostatic rebalancing would be important because of hemostatic fragility with risks of bleeding or thrombosis in patients with end-stage liver disease [4].

Perioperative coagulation profiles that may not be comprehensively evaluated by standard laboratory tests are very important, because complex hemostatic alterations can occur during liver transplantation [5]. Thrombotic events resulting from hypercoagulability after liver

Abbreviation: DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; ROTEM, rotational thromboelastometry; FFP, fresh frozen plasma; PT-INR, prothrombin time-international normalized ratio; PC, platelet concentrate; POD, postoperative day; PRE, pre-operation; APTT, activated partial thromboplastin time; CT, clotting time; CFT, clot formation time; MCF, maximum clot firmness; TAT, thrombin-antithrombin III complex; PIC, plasmin-α2 plasmin inhibitor complex; PAI-1, plasminogen activator inhibitor-1; vWF, von Willebrand factor; ADAMTS13, a disintegrin-like metalloproteinase with thrombospondin type 1 motif 13

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transplantation can lead to the need for re-transplantation [6]. Two studies have previously detailed the postoperative coagulation profiles of patients undergoing deceased donor liver transplantation (DDLT) [7,8], but not those of patients undergoing living donor liver transplantation (LDLT).

Viscoelastic tests, including thromboelastography and thromboelastometry, can be used to evaluate hemostatic functions that cannot be measured using isolated laboratory tests [9], although the clinical utility of these tests is currently undetermined [10,11].

Recent clinical reports in patients with cirrhosis suggested that rotational thromboelastometry (ROTEM; TEM International GmbH, Munich, Germany) may be an appropriate diagnostic tool for predicting bleeding or portal vein thrombosis [12,13]. Another report showed that ROTEM analysis enhanced assessment of postoperative hemostatic balance and hypercoagulation status in cirrhotic patients after a major liver surgery [14]. However, the ability of viscoelastic tests to identify variations in coagulation after liver transplantation has not been reported. Therefore, the aim of our study was to characterize the pre- and postoperative coagulation profiles of patients undergoing adult-to-adult LDLT, using various coagulation tests and ROTEM.

2. Materials and methods

2.1. Patients

This single-center, prospective, observational study was approved by the university's ethics committee (Approval No. 10050718), and each participant provided informed consent. Consecutive patients who underwent LDLT between July 2011 and December 2012 and who were 18 years and older were included.

2.2. Preoperative and intraoperative management

Patients who underwent ABO incompatible LDLT had plasma apheresis before surgery, if their antibody titer was >64.

Patients received propofol and remifentanil for anesthesia, with rocuronium for muscle relaxation. Plasma albumin and serum Ca2+ levels were maintained at >2.5 g/dl and >1.2 mmol/l, respectively. During surgery, all patients received the anticoagulant nafamostat mesylate through continuous infusion (0.2 mg/kg/h) and tranexamic acid at a loading dose of 1 mg/kg, followed by a continuous infusion of 1 mg/kg/h. All patients received 1500 U of antithrombin III before skin closure.

Standard laboratory tests, including plasma fibrinogen, were performed every 2 h during the surgery. Blood products were transfused according to our intra-operative management protocol, including red blood cells for a hematocrit level <20%; fresh frozen plasma (FFP) with a prothrombin time-international normalized ratio (PT-INR) <30%; or a plasma fibrinogen level <100 mg/dl; and platelet concentrate (PC) for a platelet count of $<5.0 \times 10^4$/μl.

Splenectomy was performed during LDLT in patients with hepatitis C or a preoperative platelet count $<5.0 \times 10^4$/μl.

2.3. Postoperative management

After surgery, all patients were transferred to the intensive care unit with continued nafamostat mesylate, at a dose of 0.2 mg/kg/h, until postoperative day (POD) 3. Antithrombin III was administered until POD 7 to maintain the level of antithrombin activity at >70%. FFP and PC were administered to patients with an increased tendency toward bleeding in the same manner as done intra-operatively. Blood products were not administered postoperatively to patients who did not have an increased bleeding tendency, even if their platelet counts and standard coagulation values were low. Other anticoagulation medications (such as heparin and warfarin) and anti-platelet therapies were not administered during the study period.

Postoperative small-for-size syndrome was defined as a serum total bilirubin level >10 mg/dl after POD 7, coagulopathy with an international normalized ratio >1.5, and ascites with drain output >2 L/day in the absence of an obvious technical problem [15].

2.4. Study protocol

Blood samples were obtained immediately after the induction of anesthesia: pre-operation (PRE), and on PODs 1, 3, 5, and 7, using standard laboratory tests and ROTEM parameters obtained at each time point. Standard laboratory tests included the platelet count, PT-INR, activated partial thromboplastin time (APTT), and fibrinogen. INTEM (an assay that evaluates the intrinsic pathway) clotting time (CT), EXTEM (an assay that evaluates the extrinsic pathway), CT, clot formation time (CFT), maximum clot firmness (MCF) and α angle, and FIBTEM (an assay that evaluates the fibrin polymerization) MCF were the parameters measured using the ROTEM instrument. The level of coagulation factors II, VII, VIII, and IX (FII, FVII, FVIII, and FIX), thrombin-antithrombin III complex (TAT), plasmin-a2 plasmin inhibitor complex (PIC), plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (vWF), and a disintegrin-like metalloproteinase with thrombospondin type 1 motif 13 (ADAMTS13) were measured at PRE and on PODs 1, 3, and 7. All tests, excluding the ROTEM parameters, were performed in an independent institution (SRL Inc., Tokyo, Japan).

2.5. Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of the distribution of continuous variables. Within-group comparisons from PRE to PODs 1, 3, 5, and 7 were evaluated using an analysis of variance for repeated measures or Friedman's test, depending on the underlying distribution, followed by Dunn's post hoc test with Bonferroni's corrections. Statistical significance was defined as $p < 0.05$. All values are expressed as a median (interquartile range) or number (%). Statistical analyses were performed using IBM SPSS Statistics (version 24.0) software for Windows (IBM Japan, Tokyo, Japan). The statistical methods of this study were reviewed by Sato S from the clinical research center of Nagasaki University Hospital.

3. Results

3.1. Patients

The clinical characteristics of the patient group are reported in Table 1. Twenty-five patients (14 men and 11 women) were included, with three patients excluded. Two patients underwent plasma exchange because of suspicion for thrombotic microangiopathy during the study period, and the other patient underwent hemostatic surgery three times and massive blood transfusions on PODs 1, 2, and 4. All investigated parameters during the study period were completely obtained from all 22 patients.

Preoperative plasma apheresis was performed in 6/22 (27%) patients. Twelve patients had liver cancer, 11 patients had hepatocellular carcinoma, and 1 patent had intrahepatic cholangiocarcinoma. Intraoperatively, 16/22 (73%) patients underwent splenectomy, and 14 of them had hepatitis C. Graft types were 16 left lobes (73%), 5 right lobes (23%), and 1 right posterior sector (0.5%). The number of grafts that included the middle hepatic vein was 15/22 (68%). Postoperatively, the incidence of small-for-size syndrome was 7/22 (32%) patients.

3.2. Postoperative operation and transfusion

Only two patients (9%) included in our analysis required re-operation on POD 1 because of postoperative bleeding. Postoperative transfusions were generally administered over the first 24 to 48 h after

Table 1
Clinical characteristics of the patient group.

Age (years)	58 (52, 62)
Sex (M/F)	13/9
Height (cm)	163 (154, 167)
Weight (kg)	67 (54, 73)
MELD score	15 (11, 22)
ABO mismatch	12 (55)
Graft volume to standard liver volume (%)	35.8 (30.5, 41.5)
Operative time (min)	792 (711, 907)
Anhepatic period (min)	178 (109, 233)
Intra-operative bleeding (ml)	6540 (3288, 9520)
Intra-operative transfusion	
Red cell concentrates (ml)	1680 (560, 4200)
Fresh frozen plasma (ml)	960 (480, 1920)
Platelets concentrates (ml)	200 (0, 400)
Etiology of liver disease	
Hepatitis C	14 (64)
Hepatitis B	2 (9)
Fulminant hepatic failure	1 (0.5)
Alcoholic liver disease	1 (0.5)
Alcoholic liver disease plus hepatitis C	1 (0.5)
Caroli disease	1 (0.5)
Primary sclerosing cholangitis	1 (0.5)
Nonalcoholic steatohepatitis	1 (0.5)
Liver cancer	12 (55)

Values are expressed as medians (interquartile ranges) and numbers (percent).
MELD: model for end-stage liver disease; M: male; F: female.

surgery, with small volumes of FFP and PC administered: FFP, 0 (0, 900) ml on PODs 1 and 2; and PC, 0 (0, 200) ml on PODs 1 and 2.

3.3. Coagulation profiles

The standard laboratory tests and coagulation factor activities are shown in Figs. 1 and 2. On POD 1, the standard laboratory values, excluding the platelet count, and the coagulation factor activities were low or prolonged compared to the PRE values. These parameters improved on POD 3 and returned to levels equal to or greater than those at PRE on POD 7. The results of the other coagulation tests are shown in Fig. 3. TAT had the highest value on POD 1, compared to the other time points, and the higher values were maintained throughout the postoperative period compared to the PRE values ($p < 0.01$). PAI-1 levels were increased on POD 1, compared to PRE levels ($p < 0.01$), with a subsequent decrease equal to that at PRE on PODs 3 and 7. Meanwhile, PIC was higher on POD 7 than on PODs 1 ($p = 0.01$) and 3 ($p = 0.01$). vWF was higher than normal during the study period, specifically on POD 7, than at all the other time points (versus PRE and POD 1, $p < 0.01$ and POD 3, $p = 0.03$). ADAMTS13 was lower during the postoperative period than at PRE ($p < 0.01$). Regarding the ROTEM parameters, EXTEM CT (reflecting coagulation activity); CFT, MCF and α angle (reflecting the function and quantity of platelets, fibrinogen and FXIII, respectively); and FIBTEM MCF (reflecting fibrin polymerization) were all decreased or prolonged on PODs 5 and 7 compared to at PRE (Fig. 4).

4. Discussion

We investigated the pre- and postoperative coagulation profiles of patients undergoing adult-to-adult LDLT. On POD 7, most procoagulant factors returned to values equal to or greater than the PRE levels. In contrast, almost all ROTEM parameters on POD 7 were decreased or prolonged compared to the PRE levels. Therefore, it cannot be concluded whether ROTEM reflects the net effect of hemostatic balance after liver transplantation.

Coagulation factor activities recovered at a much slower rate after LDLT in our study than in two previously reported studies investigating coagulation factor activities after DDLT. Stahl et al. reported that the values of FII, FIX, FX, FXI, and FXII returned to normal on POD 1, with

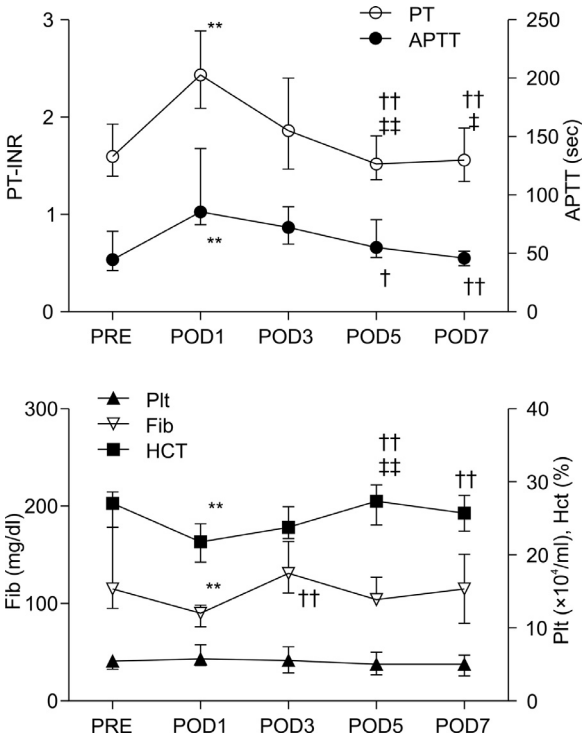

Fig. 1. Standard laboratory tests. The results of standard laboratory tests are shown.
PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Plt: platelet; Fib: fibrinogen; Hct: hematocrit; POD: postoperative day; PRE: pre-operation. $^{**}p < 0.01$ compared to PRE, $\dagger p < 0.05$, $\dagger\dagger p < 0.01$ compared to POD 1, $\ddagger p < 0.05$, $\ddagger\ddagger p < 0.01$ compared to POD 3. Symbols and error bars express medians and interquartile ranges.

FV and FVII returning to normal values on POD 3, whereas FVIII was higher than normal on POD 3 [7]. Meanwhile, the level of antithrombin III and proteins C and S were still subnormal on POD 5 [7]. Velasco et al. reported that the FII, FV, FXI, and FXII values returned to normal values on POD 1, whereas FIX, FVII, and FX values on POD 2 [8]. However, antithrombin III and protein C values took 7–14 days to return to normal values [8]. Generally, functional recovery of the liver after grafting and reperfusion is dependent on the graft size and the cold ischemic time. Previous reports have shown that functional recovery after LDLT, reflected by the PT and lactate levels, is slower than after DDLT [16]. Additionally, these reports indicate that a ratio of the graft volume to the standard liver volume exceeding 40% may be necessary to avoid small-for-size syndrome [17], and that the graft size correlates with early graft function [18]. The coagulation factor activities took longer to recover in this study, which used a small-sized graft (with a median ratio of graft volume to standard liver volume of 35.8%), than in previous studies.

Previous studies have also reported a significant increase in vWF during the perioperative period, with persistent decreases in ADAMTS13 after LDLT [19]. In other reports, TAT values, reflective of ongoing thrombin formation, peaked on POD 1 and then gradually decreased, but were still significantly higher than the normal values [8,20]. These same variations in vWF, ADAMTS13, and TAT were observed in our study, although the changes in PIC, before and after LDLT, differed from those previously reported. Previous studies have also reported an elevation in PIC values during or immediately after surgery, which persisted even on POD 14 [21–23]. In contrast, the PIC values in our study were within the normal range until POD 3 and were slightly elevated on POD 7. Typically, PIC is markedly elevated in hyperfibrinolytic states and slightly elevated in hypercoagulable states. In our study, all patients received nafamostat mesylate for anticoagulation

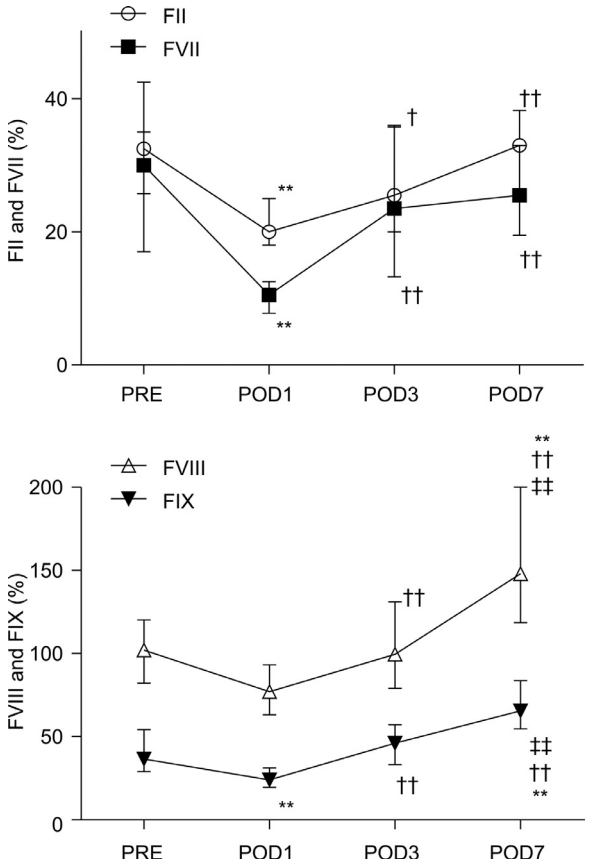

Fig. 2. Coagulation factor activity. The results of the coagulation factor activities are shown. FII: Factor II; FVII: Factor VII; FVIII: Factor VIII; FIX: Factor IX; POD: postoperative day; PRE: pre-operation.
$^{**}p < 0.01$ compared to PRE, $\dagger p < 0.05$, $\dagger\dagger p < 0.01$ compared to POD 1, $\ddagger\ddagger p < 0.01$ compared to POD 3. Symbols and error bars express medians and interquartile ranges.

until POD3, after which anticoagulant therapy was discontinued. Therefore, slight increases in PIC on POD 7 might reflect a hypercoagulable state secondary to the discontinuation of nafamostat mesylate. The variations in vWF, ADAMTS13, TAT, and PIC values altogether showed the acceleration of coagulability after LDLT.

In three previous studies regarding the outcomes after DDLT, the values of PAI-1, an antifibrinolytic factor, were elevated on POD 1 and gradually decreased throughout the postoperative period, and these values were supranormal on PODs 5 and 14 [8,24,25]. Meanwhile, two previous studies on outcomes after LDLT reported an elevation in PAI-1 on POD 1, returning quickly to a normal level on POD 3 [26,27]. The change in PAI-1 after LDLT in our study was similar to that in these reports. PAI-1 is mainly synthesized by vascular endothelial cells and increases in conditions of endothelial cell injury. With respect to liver transplantation, PAI-1 increases secondary to sinusoidal endothelial cell injury after reperfusion [28]. Therefore, continuous elevations of PAI-1 after DDLT may be relevant to endothelial cell damage during grafting, due to longer ischemic times during DDLT than during LDLT.

In the present study, all ROTEM parameters, excluding INTEM CT, were significantly decreased or prolonged on POD 7 than at PRE, even though the values of most coagulation tests showed the improvement or acceleration of coagulability on POD 7 than at PRE. Furthermore, elevated TAT values, which peaked on POD 1, gradually decreased with time, although the value was still higher than normal on POD 7. Two previous studies reported that the recovery of the anticoagulant factors, antithrombin III, protein C, and protein S, was delayed compared to the recovery of the procoagulant factors after DDLT [7,8]. Presumably, it seems that the same trend occurs after LDLT. Additionally, a recent study showed that all ROTEM EXTEM parameters, CT, CFT, alpha angle, and MCF, were decreased or prolonged, depending on the concentration of protein C [29]. These findings may imply that the decreased or prolonged ROTEM parameters on POD 7 were related to the variations in the hemostatic balance caused by delayed anticoagulant recovery. However, there is incomplete information of the coagulant factors to support this speculation. Other procoagulant and anticoagulant parameters (such as FV, FX, FXIII, antithrombin III, and proteins C and S) and thrombomodulin-modified thrombin generation tests need to be evaluated to clarify whether ROTEM reflects variations in hemostatic balance after LDLT.

There was a discrepancy between most coagulation tests and ROTEM parameters in this study. Some clinical reports showed that ROTEM parameters without CT have a good correlation with conventional coagulation tests, especially the platelet count and fibrinogen concentration, in liver transplantation and stable cirrhosis [30–32]. However, the correlation between fibrinogen and ROTEM parameters sometimes decreases, and it may be caused by dysfibrinogenemia [33]. In addition, PT/APTT assess only the initial 5–10% of thrombin generation, and they do not reflect the actual risk of bleeding [34]. Although the platelet count is an important factor of the clot strength as with fibrinogen, this value does not necessarily reflect its functionality [35]. Furthermore, clot formation is attributed to the results of complex interactions and balances by many procoagulant factors, anticoagulant factors, and cellular factors [36]. However, each isolated laboratory test reflects only one component of hemostasis, and the recovery of procoagulant factors and anticoagulant factors after liver transplantation is different from each other as aforementioned. Thereby, viscoelastic tests performed with whole blood can reflect the actual hemostatic condition of patients better than isolated laboratory tests, and viscoelastic tests are recommended for assessing coagulation management in liver disease, although there are insufficient clinical data [37]. In contrast, Lentschener et al. reported that ROTEM might not be appropriate for evaluating hemostasis in patients with cirrhosis, as this test cannot reflect the preserved, or even increased, coagulation profiles that are recognized through thrombin generation tests conducted in the presence of thrombomodulin [38]. Indeed, the ROTEM parameters in our study did not discriminate the ongoing thrombin generation, which was reflected in the elevated TAT values. Although a few clinical reports indicated the utility of the viscoelastic test for assessing the risk of bleeding and thrombotic events in liver cirrhosis and liver transplantation [12,13,39], there is no large number of clinical studies on such topic. Therefore, it is unclear whether ROTEM parameters reflect the net effect of hemostatic balance after liver transplantation, although ROTEM may be better than isolated laboratory tests.

The limitations of our study need to be acknowledged. First, there is no pilot study to support the utility of viscoelastic tests during the postoperative period in liver transplantation, and this study had a small sample size that is insufficient for assessing the relevance between the clinical outcome and the statistically significant findings. Additionally, there were insufficient measurements for evaluating the utility of ROTEM after LDLT. Therefore, the clinical relevance and impact are markedly limited despite the statistical significances in many of these measurements. However, our study is the first organized study that evaluated postoperative coagulation profiles using ROTEM after LDLT. Second, the coagulation status of patients with liver disease varies according to differences in the etiology of the liver dysfunction. Krzanicki et al. reported intra-operative hypercoagulability occurring in patients with primary sclerosing cholangitis, primary biliary cirrhosis, and fulminant hepatic failure, but not in patients with hepatitis B and C, or alcoholic liver disease [40]. Moreover, in our limited study group, the majority of patients presented with viral or alcoholic liver disease (18/22 patients, 82%). Third, we conducted a single-center study, which was representative of the procedures in our hospital only. The intraoperative continuous infusion of tranexamic acid, intra- and post-operative administration of antithrombin III, and the intra- and post-

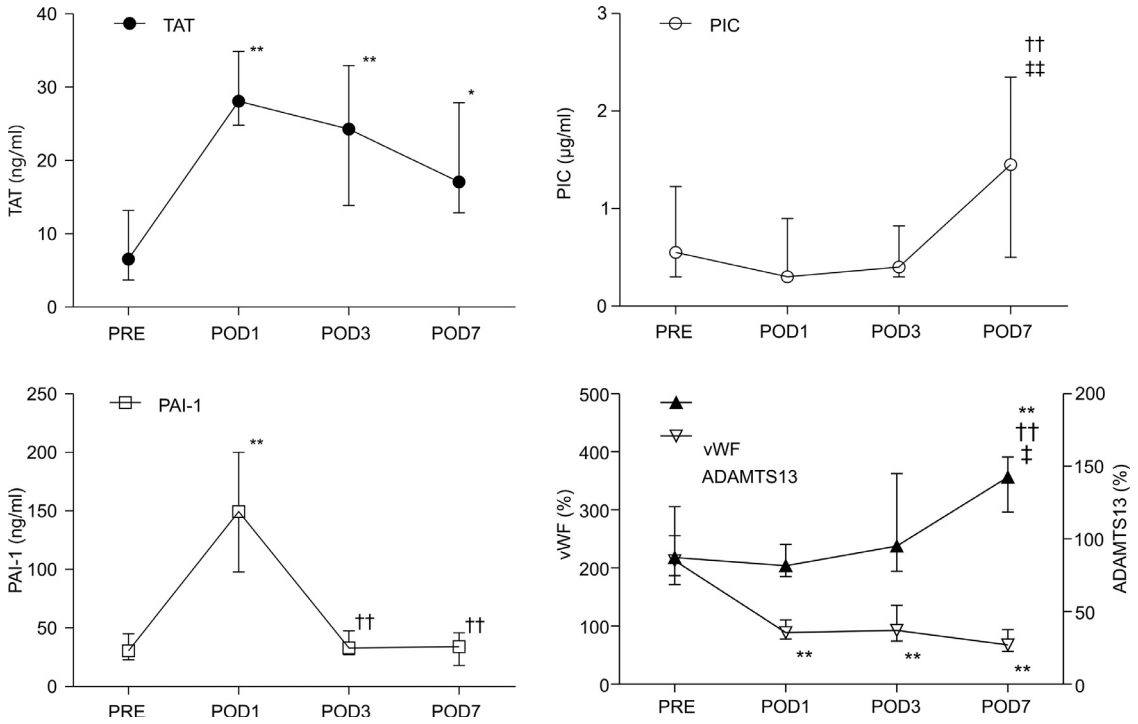

Fig. 3. Other coagulation tests. The results of the other coagulation tests are shown.
TAT: thrombin antithrombin III complex; PIC: plasmin-α2 plasmin inhibitor complex; PAI-1: plasminogen activator inhibitor-1; vWF: von Willebrand factor; ADAMTS13; a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; POD: postoperative day; PRE: pre-operation. $*p < 0.05$, $**p < 0.01$ compared to PRE, $\dagger\dagger p < 0.01$ compared to POD 1, $\ddagger p < 0.05$, $\ddagger\ddagger p < 0.01$ compared to POD 3. Symbols and error bars express medians and interquartile ranges.

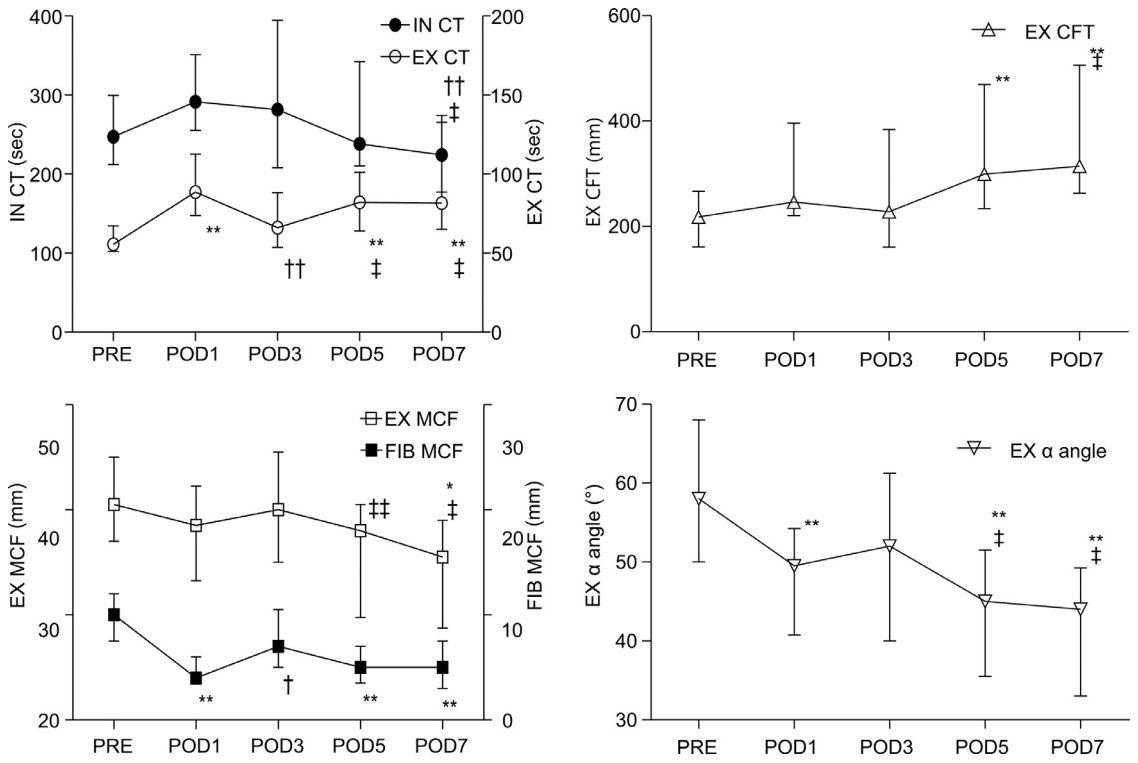

Fig. 4. ROTEM parameters. The results of the ROTEM parameters are shown.
IN: INTEM; EX: EXTEM; FIB: FIBTEM; CT: clotting time; CFT: clot formation time; MCF: maximum clot firmness; POD: postoperative day; PRE: pre-operation. $*p < 0.05$, $**p < 0.01$ compared with PRE, $\dagger p < 0.05$, $\dagger\dagger p < 0.01$ compared with POD 1, $\ddagger p < 0.05$, $\ddagger\ddagger p < 0.01$ compared with POD 3. Symbols and error bars express medians and interquartile ranges.

operative continuous infusion of nafamostat methylate are not standard, but are local practices in our hospital. These interventions may have influenced our results.

4.1. Conclusions

In conclusion, this pilot cohort study was performed to characterize the coagulation profiles of patients undergoing adult-to-adult LDLT. The values of most coagulation tests showed the improvement or acceleration of coagulability on POD 7, compared to the values at PRE, but almost all ROTEM parameters were decreased or prolonged. However, this study has many limitations, including a small cohort, insufficient measurements, and no data about the clinical outcome. Therefore, it cannot be concluded whether ROTEM reflects the net effect of hemostatic balance after liver transplantation. Further examination is necessary to elucidate the clinical utility of ROTEM after liver transplantation.

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Data for reference

: Datasets are available from the corresponding author at taiga@nagasaki-u.ac.jp. Participants gave informed consent for data sharing.

Declaration of Competing Interest

There are no conflicts of interest.

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