Five-minute parameter of thromboelastometry is sufficient to detect thrombocytopenia and hypofibrinogenaemia in patients undergoing liver transplantation

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Editor’s key points

- Rapid diagnosis of coagulopathy is critical to appropriate treatment of perioperative bleeding.
- Early parameters of clot formation measured by rotational thromboelastometry were studied in liver transplant patients.
- The clot amplitude at 5 min correlated with low platelet counts and low fibrinogen concentration, which might serve as a rapid guide to transfusion in these patients.

Background. Early detection of coagulopathy is important to prevent bleeding during liver transplantation (LT). Rotation thromboelastometry (ROTEM®) provides the earliest parameter of clot amplitudes at 5 min (A5). We evaluated whether A5 correlates with platelet count (PLT) and fibrinogen concentration (Fib) and can predict thrombocytopenia and hypofibrinogenaemia in hypocoagulable patients undergoing living-donor LT (LDLT).

Methods. A total of 3446 retrospective ROTEM® measurements, including 1139 EXTEM, 1182 INTEM, and 1125 FIBTEM, with simultaneously measured PLT and Fib, were analysed during LDLT in 239 patients. The correlations between A5 and maximum clot firmness (MCF) index, PLT, and Fib were calculated. Receiver operating characteristic analysis with area under the curve (AUC) was used to assess A5 thresholds predictive of PLT and Fib.

Results. The median PLT was 47 000 mm⁻³ and the median Fib was 100 mg dl⁻¹ during LDLT. The A5 parameters of EXTEM (A5EXTEM) and INTEM (A5INTEM) were highly correlated with MCF (r=0.96 and r=0.95, respectively), PLT (r=0.76 and r=0.77, respectively), and Fib (r=0.63 and r=0.64, respectively). A5 of FIBTEM (A5FIBTEM) was also correlated with MCF (r=0.91) and Fib (r=0.75). A5EXTEM thresholds of 15 and 19 mm predicted PLT <30 000 mm⁻³ (AUC=0.90) and <50 000 mm⁻³ (AUC=0.87), respectively, whereas A5FIBTEM 4 mm predicted Fib <100 mg dl⁻¹ (AUC=0.86). Biases from A5EXTEM and A5FIBTEM to their MCFs were 16.4 and 1.3 mm, respectively.

Conclusions. A5 as an early variable of clot firmness is effective in detecting critically low PLT and Fib. A5 can therefore be a reliable fast index guiding transfusion therapy in hypocoagulable patients undergoing LDLT.

Keywords: blood coagulation; liver transplantation; thromboelastometry

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Patients who undergo liver transplantation (LT) often experience massive bleeding requiring transfusion. The transfusion of many allogeneic blood products, however, without a fast and reliable monitoring system, can further aggravate the haemostatic disorders of these patients, resulting in poor overall outcomes.1–4 Early detection and timely correction of coagulopathy are crucial in preventing further exacerbation of bleeding diathesis and in breaking the vicious cycle of coagulopathy during LT, in addition to improving overall patient outcomes.

Rotation thromboelastometry (ROTEM® delta, TEM International GmbH, Munich, Germany) is a point-of-care coagulation monitoring system that evaluates the viscoelasticity of whole blood, allowing the entire clotting process, from clot initiation and formation to clot stability, to be assessed.5 6 In contrast to conventional laboratory tests (e.g. measurements of platelet count (PLT), prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen concentration (Fib)], ROTEM® can measure early variables, such as clot amplitude at 5 min (A5) and 10 min (A10) after clotting time (CT) in EXTEM, INTEM, and FIBTEM. Owing to its rapid assessment of PLT and Fib, ROTEM® is frequently used to guide transfusion therapy.7–10 Moreover, a recent study with a large database demonstrated that early measures of clot firmness, including A5, A10, and clot amplitude at 15 min (A15), are linearly correlated with ROTEM® determined maximum clot firmness (MCF), allowing the fast and reliable prediction of MCF in non-cardiac patients, including those with subnormal, normal, and supranormal MCF values.11

The A10 of EXTEM (A10EXTEM) was shown to be rapid and valuable in predicting coagulation status, and also being useful in assessing the need for perioperative transfusion of platelets and fibrinogenic.8 The correlations of the more rapid A5 with PLT count and Fib concentration have not been determined, and it remains unclear whether A5 could determine quantitative PLT and Fib level in hypocoagulable patients undergoing living-donor LT (LDLT) surgery. We therefore assessed whether A5 on ROTEM®

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analysis is an early and reliable index for the transfusion of PLT and Fib during LDLT. We also assessed A5 cut-off values predicting thrombocytopenia and hypofibrinogenaeemia in patients undergoing LDLT.

**Methods**

**Patients**

A total of 401 patients who underwent LT at Asan Medical Center, Seoul, Republic of Korea, between June 2010 and May 2011 were enrolled. Of these, 162 patients were excluded from this analysis, including 73 who received orthotopic LT, 53 who had incomplete ROTEM® and laboratory test data, and 36 patients aged <18 yr. The remaining 239 LDLT recipients were included in this retrospective analysis. Records about anaesthesia, available on computerized databases, were analysed retrospectively. This study protocol was approved by the Institutional Review Board of the Asan Medical Center.

**Anaesthetic technique**

General anaesthesia for LDLT surgery was performed according to our institutional standard protocol. Briefly, anaesthesia was induced with i.v. thiopental, fentanyl, and vecuronium, and maintained with 1% sevoflurane, a 50% O2/air mixture, and continuous infusion with fentanyl and vecuronium. Twenty-gauge femoral and radial arterial catheters were inserted to monitor arterial pressure and to sample blood. A 7.5 French pulmonary artery catheter (Swan–Ganz CCOmbo V CCO/SvO 2/CEDV, Edwards Lifesciences LLC, CA, USA) was inserted to monitor haemodynamic variables. Body temperature was measured using a thermistor in a pulmonary artery catheter. Transfusions of packed red blood cells, fresh-frozen plasma, and cryoprecipitate were based on clinical decisions or guided by standard laboratory tests or the transfusion algorithm based on ROTEM parameters. According to institutional standards, transfusions were administered to maintain PT < 2.0 INR, Fib > 100 mg dl⁻¹, and PLT > 30,000 mm⁻³. Synthetic colloidal solution was not used, but solutions of 5% albumin with balanced crystalloid were administered during LDLT.

**Blood sampling and thromboelastometry**

During LDLT, standard coagulation assays and ROTEM® tests were routinely performed, using blood samples at pre-established time points, including 1 h after induction of general anaesthesia, 1 h after surgical incision, 30 min after hepatectomy, and 30 min after graft reperfusion and after hepatic artery anastomosis. ROTEM® tests were performed according to the manufacturer’s instructions, using equipment and test reagents provided by Tem International GmbH. The ROTEM® device was placed in the operating theatre and all tests were performed by transplantation anaesthesiologists or anaesthesia nurses trained to perform ROTEM® tests. Of the ROTEM® tests performed, inadequate runtime, patients who received thrombin inhibitor or signs of hyperfibrinolysis were excluded. Finally, 1139 EXTEM, 1182 INTEM, and 1125 FIBTEM tests were included in the study. ROTEM® variables recorded included: (i) clotting time (CT), defined as the time (s) from the start of measurement to the initiation of clotting, defined as a clot firmness of 2 mm; (ii) clot formation time (CFT), defined as the time (s) from initiation of clotting until a clot firmness of 20 mm; (iii) MCF, defined as the maximal amplitude (mm) of the graphical trace of clot firmness; (iv) α-angle (α), defined as the tangent to the graphic trace at an amplitude of 2 mm; and A5 and A10 (mm), which reflect the amplitudes 5 and 10 min, respectively, after CT. At each time point, blood samples were withdrawn from the radial artery, and haemoglobin, PT, PLT, and Fib were measured.

**Standard coagulation assays**

PT was assessed using Thromborel S kits (Siemens Healthcare Diagnostics, GMBH, Marburg, Germany), and fibrinogen was assayed using the Dade Thrombin Reagent (Siemens Healthcare Diagnostics). All tests were performed using an automatic coagulometry analyser (Sysmex CA-7000, Siemens Healthcare Diagnostics).

**Statistical analyses**

Continuous variables were expressed as median (inter-quartile range) or mean [standard deviation (SD)]. Between-group comparisons were evaluated using the χ² test, Fisher’s exact tests, t-tests, and Mann–Whitney U-tests, as appropriate. Correlations between standard coagulation test results and those performed on ROTEM® were analysed using Spearman’s rank correlation coefficient (r). The Bland–Altman analyses were performed to estimate the mean difference (bias) (SD) between early measures of clot firmness (A5 and A10) and MCF. Receiver operating characteristic (ROC) curves and the area under the

| Table 1 | Patient characteristics and laboratory data. Values are expressed as median (inter-quartile range) or percentage, as appropriate |
| Variable | |
| Preoperative patient characteristic data | |
| Age (yr) | 53 (48–57) |
| Gender, male (%) | 76.0 |
| Body mass index (kg m⁻²) | 23.8 (21.7–25.9) |
| Model for end-stage liver disease score | 14 (10–21) |
| Child–Pugh score | 8 (6–10) |
| Liver disease (%) | |
| Hepatitis B virus-related cirrhosis | 67.7 |
| Hepatitis C virus-related cirrhosis | 7.0 |
| Alcoholic cirrhosis | 12.7 |
| Autoimmune | 1.4 |
| Others | 11.2 |
| Diabetes (%) | 27.9 |
| Hypertension (%) | 2.2 |
| Intraoperative laboratory data | |
| Haemoglobin (g dl⁻¹) | 9.5 (8.6–10.7) |
| Platelets (× 10³ mm⁻³) | 47 (32–66) |
| Prothrombin time (INR) | 1.8 (1.6–2.2) |
| Fibrinogen (mg dl⁻¹) | 100 (77–137) |
curve (AUC) was used to determine the optimal cut-off values of A5, A10, and MCF on EXTEM, INTEM, and FIBTEM predicting PLT counts <30,000 and <50,000 mm$^{-3}$ and Fib concentrations <100 mg dl$^{-1}$. Sensitivity and specificity were also calculated. All statistical analyses were performed using Medcalc\textsuperscript{®} (Medcalc Software, Mariakerke, Belgium) statistical software. A two-tailed $P$-value of <0.05 was considered statistically significant.

### Results

The patient characteristics, intraoperative laboratory data, and liver transplant results of the 239 included patients are shown in Table 1. During LDLT, the median (inter-quartile range) PLT was 47,000 (32,000–63,000) mm$^{-3}$, the median Fib was 100 mg dl$^{-1}$ (77–137 mg dl$^{-1}$), and the median PT was 1.8 (1.6–2.2) INR, demonstrating that these patients...
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Figure 2. Because the scatterplot seemed to follow a curvilinear fitting (Fig. 3). The curvilinear fits showed better correlations for all comparisons. A5EXTEM, A10EXTEM, and MCFEXTEM showed better correlations with PLT ($r = 0.76$, $r = 0.76$, and $r = 0.75$, respectively, $P < 0.001$ each) than with Fib ($r = 0.63$, $r = 0.65$, and $r = 0.63$, respectively, $P < 0.0001$ each), indicating that MCF parameters are explained better by PLT than by Fib. In addition, A5INTEM, A10INTEM, and MCFINTEM showed good correlations with PLT ($r = 0.77$, $r = 0.77$, and $r = 0.75$, respectively, $P < 0.001$ each) and Fib ($r = 0.64$, $r = 0.66$, and $r = 0.62$, respectively, $P < 0.0001$ each), and A5FIBTEM, A10FIBTEM, and MCFFIBTEM were correlated with Fib ($r = 0.75$, $r = 0.76$, and $r = 0.75$, respectively, $P < 0.0001$ each) (Fig. 3).

ROC curve analysis showed that the cut-off values of A5EXTEM and A10EXTEM predicting PLT < 30,000 mm$^{-3}$ were 15 mm (sensitivity: 86%, specificity: 77%) and 22 mm (sensitivity: 85%, specificity: 78%), respectively, and that their cut-off values to predict PLT < 50,000 mm$^{-3}$ were 19 mm (sensitivity: 82%, specificity: 78%) and 27 mm (sensitivity: 82%, specificity: 77%), respectively. AUCs of A5EXTEM and A10EXTEM were 0.90 and 0.989, respectively, for PLT < 30,000 mm$^{-3}$ and were 0.871 and 0.867, respectively, for PLT < 50,000 mm$^{-3}$ (all $P < 0.001$) (Fig. 4).

The cut-off values of A5INTEM and A10INTEM were 16 mm (sensitivity: 82%, specificity: 86%) and 22 mm (sensitivity: 85%, specificity: 83%), respectively, for predicting PLT < 30,000 mm$^{-3}$, and 19 mm (sensitivity: 82%, specificity: 77%) and 27 mm (sensitivity: 79%, specificity: 79%), respectively, for predicting PLT < 50,000 mm$^{-3}$. AUCs of A5INTEM and A10INTEM were 0.914 and 0.915, respectively, for PLT < 30,000 mm$^{-3}$ and were 0.873 and 0.869, respectively, for PLT < 50,000 mm$^{-3}$ (all $P < 0.0001$) (Fig. 4).

ROC curve analysis showed that A5FIBTEM and A10FIBTEM predicting Fib < 100 mg dl$^{-1}$ were 4 mm (sensitivity: 81%, specificity: 77%) and 5 mm (sensitivity: 76%, specificity: 82%), respectively. The AUCs of A5FIBTEM and A10FIBTEM for Fib < 100 mg dl$^{-1}$ were 0.86 and 0.87, respectively (all $P < 0.0001$) (Fig. 4).

**Discussion**

The first major finding of our study was that all correlations and ROC curve analyses, including AUCs, were very similar for A5EXTEM and A10EXTEM and for A5INTEM and A10INTEM, strongly suggesting that A5 is as precise as A10, but can more rapidly predict MCF, thrombocytopenia, and hypofibrinogenaemia in patients undergoing LDLT. Secondly, A5EXTEM and A5INTEM were similar in predicting MCF, with both showing good correlations with PLT and Fib, suggesting that they can be used interchangeably, despite INTEM and EXTEM reflecting different coagulation pathways. Thirdly, FIBTEM analysis showed that the difference (bias) between A5FIBTEM and MCFFIBTEM was small, only 1.3 mm in patients with hypofibrinogenaemia (median Fib = 100 mg dl$^{-1}$). In addition, the ROC curves of A5FIBTEM and A10FIBTEM for Fib < 100 mg dl$^{-1}$ yielded almost identical AUCs, indicating that A5FIBTEM was as useful as A10FIBTEM in consistently predicting hypofibrinogenaemia. Lastly, although replacement guidelines for thrombocytopenia and hypofibrinogenaemia during LT surgery vary widely among institutions, the critical PLT triggering transfusion is generally thought to be around 30,000 to 50,000 mm$^{-3}$.

Because conventional laboratory tests have long turnaround times in clinical settings, determining when to start a transfusion and the amounts of allogeneic blood products transfused into patients with massive bleeding is difficult. Therefore, early variables assessed by point-of-care ROTEM device, which are available within 10–20 min, have been increasingly used to trigger transfusion of platelets and fibrinogen-rich products. Trigger values were based on evidence that these variables could successfully determine thrombocytopenia and hypofibrinogenaemia in patients undergoing LT and cardiac surgery and those with severe

<table>
<thead>
<tr>
<th>Variables</th>
<th>EXTEM</th>
<th>INTEM</th>
<th>FIBTEM</th>
</tr>
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<tbody>
<tr>
<td>Clot time (s)</td>
<td>71 (52–103)</td>
<td>229 (197–278)</td>
<td>59 (46–95)</td>
</tr>
<tr>
<td>Clot formation time (s)</td>
<td>235 (173–307)</td>
<td>231 (164–309)</td>
<td>NA</td>
</tr>
<tr>
<td>$\alpha$-Angle (°)</td>
<td>49 (39–58)</td>
<td>52 (42–61)</td>
<td>NA</td>
</tr>
<tr>
<td>A5 (mm)</td>
<td>19 (15–25)</td>
<td>20 (15–25)</td>
<td>5 (3–7)</td>
</tr>
<tr>
<td>A10 (mm)</td>
<td>27 (22–34)</td>
<td>27 (22–33)</td>
<td>5 (4–8)</td>
</tr>
<tr>
<td>MCF (mm)</td>
<td>37 (31–43)</td>
<td>37 (31–43)</td>
<td>6 (4–9)</td>
</tr>
<tr>
<td>Bias for A5 (mm)</td>
<td>16.4 (3.7)</td>
<td>16.2 (3.6)</td>
<td>1.3 (1.4)</td>
</tr>
<tr>
<td>Bias for A10 (mm)</td>
<td>8.8 (2.7)</td>
<td>8.8 (2.8)</td>
<td>0.7 (1.0)</td>
</tr>
</tbody>
</table>
In trauma patients, an A10FIBTEM of 5 mm was the threshold that best predicted hypofibrinogenaemia (<100 mg dl⁻¹), whereas an A15INTEM of 46 mm best predicted thrombocytopenia (<50 000 mm⁻³). During LT surgery, our results demonstrated that both A10EXTEM and A10INTEM of 27 mm were the thresholds best predicting thrombocytopenia (<50 000 mm⁻³), whereas an A10FIBTEM of 5 mm best predicted hypofibrinogenaemia (<100 mg dl⁻¹). These findings are in agreement with previous studies showing that an A10FIBTEM of 5 mm was optimal in trauma patients and that an A10EXTEM of 29 mm was the optimal cut-off for thrombocytopenia (<50 000 mm⁻³) during LT.

Notably, this study was the first to show that A5 is a reliable early parameter that can substitute for both A10 and MCF in patients in a hypocoagulable state observed during LDLT (median MCFEXTEM = 37 mm and median MCFFIBTEM = 6 mm). Among the ROTEM parameters, the A5 and A10 indices of both EXTEM and INTEM showed excellent correlations with their MCF values, and A5FIBTEM and A10FIBTEM were highly correlated with MCFFIBTEM. These results are comparable with the excellent correlations observed for A5 and A10 with their MCFs in a heterogeneous study population that included individuals with subnormal, normal, and supranormal MCF values. Our findings also demonstrated that the correlation coefficients of A5EXTEM and A10EXTEM with PLT, A5INTEM and A10INTEM with PLT, and A5FIBTEM and A10FIBTEM with Fib were almost identical. Therefore, these results strongly indicate that A5 is as accurate as A10, allowing earlier parameters to guide PLT transfusion during LT.

We observed biases between early variables (A5 and A10) and MCF of ROTEM analyses. Because the median values of MCFEXTEM, MCFINTEM, and MCFFIBTEM were 37, 37, and 6 mm, respectively, our data characterize patients with subnormal MCF. In EXTEM and INTEM assays, the biases between A5 and A10 and MCF were 16 and 9 mm, respectively. Therefore, to

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**Fig 2** Intraoperative trends of ROTEM and laboratory parameters. Data are median (SD). T0, 1 h after induction of general anaesthesia; T1, 1 h after surgical incision; T2, 30 min after hepatectomy; T3, 30 min after graft reperfusion; T4, after hepatic artery anastomosis.
Fig 3 Linear ($r$) and curvilinear ($R^2$) relationship between ROTEM parameters and conventional coagulation tests. Note that A5, A10, and MCF on both EXTEM and INTEM showed good correlations with PLTs and moderate correlations with fibrinogen concentration. A5, A10, and MCF of FIBTEM also showed good correlations with fibrinogen concentration.
determine the approximate value of their MCFs, 16 mm should be added to the A5 value and 9 mm to the A10 value in patients undergoing LT. A previous study, however, reported that 19 mm should be added to A5 and 10 mm to A10 (11 mm for patients with MCFEXTEM ≤ 50 mm) to obtain rough estimates of their MCFs. These discrepancies were more pronounced in FIBTEM assays, in that 4.5 mm was added to A5 and 3.4 mm to A10 (1.95 mm in patients with MCF FIBTEM ≤ 9 mm) to obtain rough estimates of MCF FIBTEM. In contrast, we found that only ~1 mm (1.3 and 0.7 mm, respectively) had to be added to the A5 and A10 values of MCF FIBTEM in patients undergoing LT. There are several possible reasons for the differences between our study and previous studies. First, the characteristics of the patient populations in the previous study included all non-cardiac patients, regardless of MCF values. A comparison of study populations showed that 73% and 90% in our study were below the reference ranges on the FIBTEM (MCF FIBTEM ≤ 9 mm) and EXTEM (MCF EXTEM ≤ 50 mm) assays, compared with 14.3% and 49.1%, respectively, in the earlier study. Secondly, preexisting differences in conventional laboratory parameters between studies might have an effect on ROTEM analyses. Tripodi and colleagues...
demonstrated that PLT was the most important determinant in MCF in patients with stable cirrhosis, in which the study population showed low PLT with nearly normal Fib. In contrast, our study population showed both low PLT (47,000 (32,000–64,000) vs 65,000 (24,000–178,000) mm$^{-3}$) and Fib (100 (77–137) vs 199 (108–423) mg dl$^{-1}$), respectively, compared with that study. Thirdly, differences in the use of colloids might have an effect on the observed bias, particularly for FIBTEM. Synthetic colloids such as hydroxyethyl starch solutions are known to have an impact on fibrin polymerization, resulting in decreased MCF. However, as we used only albumin for colloid solution during LDLT, our data would not be affected by synthetic colloids in the bias between early variables of clot firmness (A5 and A10) and MCF. This difference might result in increased bias between A5 (A10) and MCF, in particular in FIBTEM, between our study and the earlier study. Taken together, because of the potentials for selection and observation biases among different studies (e.g. differences in gender, ethnicity, clinical conditions, types of fluid replacement, etc.), care should be taken when interpreting the results of bias between early variables of clot firmness and MCF of ROTEM$^\text{®}$ analyses.

Our study had several limitations. First, it was a retrospective, single-centre study, suggesting caution in interpreting our results as there might have been observation bias and bias in patient selection. Secondly, we did not assess the predictability of transfusion requirements based on ROTEM$^\text{®}$ analysis or standard coagulation tests. Further studies are needed to evaluate whether threshold levels of ROTEM$^\text{®}$ parameters can estimate clinical bleeding and guide transfusion therapy to improve treatment of haemostatic derangements associated with LDLT.

In conclusion, our findings indicate that A5 as an early variable of clot firmness in thromboelastometry is effective to detect thrombocytopenia and hypofibrinogenemia in hypocooagulable patients undergoing LT. A5 on ROTEM$^\text{®}$ analysis might be the earliest, most reliable index in selecting transfusion guidelines based on PLT and Fib during LDLT.

**Authors’ contributions**

J.-G.S.: study design, study data analysis, manuscript preparation, and revision; S.-M.J.: study design and data analysis; I.-G.J.: data collection and analysis; H.-M.L.: data analysis; G.-S.H.: study design, study conduct, data analysis, manuscript preparation, and revision.

**Declaration of interest**

None declared.

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