Rotational Thromboelastometry (ROTEM) reduces the need for pre-emptive transfusion in cirrhosis: A randomized controlled Trial (NCT:05698134).

Rahul Kumar

rahul.kumar@singhealth.com.sg

Changi General Hospital https://orcid.org/0000-0002-5092-4821

Xiang Long Louis Ng

Changi General Hospital

Yu Jun Wong

Changi General Hospital

Chin Kimg Tan

Changi General Hospital

Louis Zizhao Wang

Changi General Hospital

Tian Yu Qiu

Changi General Hospital

Benny Wong

Changi General Hospital

Kenneth Weicong Lin

Changi General Hospital

James Weiquan Li

Changi General Hospital

Andrew Boon Eu Kwek

Changi General Hospital

Tiing Leong Ang

Changi General Hospital

Roshni Sadashiv Gokhle

Changi General Hospital

Tirukonda Prasanna Sivanath

Changi General Hospital

Research Article

Keywords: Cirrhosis, Elective-procedure, ROTEM, pre-emptive transfusion

Posted Date: May 7th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4329141/v1

Abstract

Backgrounds and Aim:

Viscoelastic tests (VET) like Rotational Thromboelastometry (ROTEM) assess global hemostasis in cirrhosis. We aimed to assess whether ROTEM-guided blood product transfusion results in lower blood product requirement in patients with cirrhosis undergoing elective invasive procedures as compared to standard of care (SOC) based on conventional coagulation test (CCT).

Methods

In this open label randomized controlled trial, patients with cirrhosis and abnormal CCT who were undergoing an invasive procedure were randomized to receive blood products either by ROTEM-guidance or SOC. The primary outcome was the difference in blood products (fresh frozen plasma (FFP) or platelets) transfused between the group. The secondary outcome was procedure-related bleeding or complications within 7 days of the procedure. The trial protocol is registered at clinicaltrails.gov; NCT05698134.

Results

From August 2021 to January 2023, a total of 40 patients were recruited (ROTEM: (n = 20) and SOC (n = 20)). The trial was terminated earlier during interim analyses due to compelling benefit in the ROTEM group after a scheduled interim analysis. The ROTEM group required substantially less blood transfusion than the SOC group (40% [8/20] vs 100% [20/20], p < 0.001). The benefit was consistent across all types of blood product including fresh frozen plasma (< 0.001) and pooled platelet (p = 0.046). No patients experienced clinically significant bleeding events. Transfusion associated adverse events occurred in one patient (5%) in the SOC group (allergic reaction) and none in ROTEM group (p = NS). The mortality in both groups at 30 and 90 days were similar.

Conclusions

Viscoelastic tests like ROTEM provides global assessment of hemostasis in patients with cirrhosis. Institution of ROTEM based transfusion strategy significantly reduces the need for blood product transfusion in patients with cirrhosis undergoing elective procedure without any increased risk of bleeding events.

Introduction

The assessment of hemostasis is an arduous process in patients with cirrhosis [1]. Although the traditional concept of cirrhosis being a coagulopathic state has been challenged, it remains a common practice to empirically transfuse patients with fresh frozen plasma, platelet concentrate, or pro-haemostatic agents based on the derangements in conventional tests to reduce peri-procedure bleeding risk [1–2]. Recent literature has suggested that the concomitant decrease in procoagulant and

anticoagulant factors in cirrhosis results in a complex but a finely balanced hemostatic state and pre-emptive transfusions for patients undergoing elective procedure may not be necessary [1–2].

Conventional coagulation tests (CCT) like platelet count, activated partial prothrombin time (aPTT) and pro-thrombin time (PT) do not assess the loss of anticoagulation factors and fibrinolytic mechanisms so are not reflective of the in vivo hemostatic profile [3]. Although there is increasing awareness of these hemostatic changes and shortcomings of the CCT's in assessing hemostatic potential in patients with cirrhosis, the perceived risk of bleeding associated with an invasive procedure usually results in pre-emptive transfusions of blood product [1, 4]. In stable cirrhosis patients either compensated or decompensated, procedure-related bleeding rates appear to be low and prophylactic transfusion based on arbitrary thresholds lack evidence of clinical benefit. Moreover, blood transfusion increases portal pressure in a linear fashion. Even though the scientific literature to support pre-emptive transfusions is scant; many relevant scientific society guidance statements recommend correction of international normalized ratio (INR) > 1.5 and platelet count < 50,000/mm3 before invasive procedures to prevent bleeding-related complications [5, 6, 7].

Notwithstanding the fact that blood product transfusions can be lifesaving in certain clinical situations, the risks associated with transfusions in patients with cirrhosis can range from exacerbation of the portal hypertension from volume expansion, bacterial and viral contamination, immunogenic complications, anaphylactic reactions, and increased cost of care. Although the immunogenic risks are fewer than risks posed by increased portal pressure [8], transfusion related acute lung injury (TRALI), and the development of HLA antibodies can impair the ability of a patient to receive further blood transfusions and liver transplantation when these could be lifesaving. The risks of TRALI increases particularly when plasma and plasma containing blood products are utilized [9].

In view of the lack of standardized tests that reliably predict bleeding risks in cirrhosis, invasive procedures in these patients are often met with a degree of unease. A potential proposed solution is the use of commercially available whole blood viscoelastic tests (VET), which is increasingly being recommended for use in patients with cirrhosis. The commercially available VET including Rotational Thermoelectrometry (ROTEM™ Sigma, TEM international GmbH, Munich, Germany) and Thromboelastography (TEG™, Haemonetics Corporation, Braintree, MA, United States) are point-of-care, dynamic tests that measures the viscoelastic changes occurring during the hemostatic process. VETs provide real-time, comprehensive reflection of the interaction between plasma, blood cells and platelet**s**. TEG™ and ROTEM™ is often normal in patients with compensated cirrhosis [10] or can display either hypo or hyper-coagulable features in patients with decompensated cirrhosis [11]. It is widely used in cardiac, obstetric, trauma and liver transplant surgery [12] to assess and correct for coagulation anomalies intraoperatively. Lessons from major liver surgeries, which can be performed without the need for pre-emptive transfusion, suggest that altered hemostatic profile in cirrhosis does not translate to diffuse bleeding risk.

A number of studies have evaluated the use of TEG to guide the pre-emptive blood product transfusion in cirrhosis patients undergoing invasive procedures and most have shown a significant decrease in transfusion requirements [13, 14]. However, there is paucity of data as far as ROTEM guided transfusion strategies are concerned. Two recent studies [15, 16] have described the use of ROTEM in similar setting, While the study by Rocha et al [15] compared 3 transfusion protocols including one which was based on ROTEM guidance, the study involved patients in intensive care unit (ICU) undergoing central venous catheterization, Maria et al [16] compared ROTEM based transfusion versus SOC in cirrhotic children undergoing invasive procedures. Both the studies have limited applicability in non-ICU adult patients. This study was thus designed to evaluate whether ROTEM™ guided transfusion strategy results in significant reduction of pre-emptive transfusion in patients undergoing elective procedure compared to that based on CCT's. We hypothesized that the *ROTEM™ based transfusion strategy will reduce transfusion volume by at-least 20%.*

Methods

Patients: Adult patients (>21 years of age) with cirrhosis who were scheduled to undergo an elective invasive procedure were screened for the eligibility of the study. Patients with coagulopathy based on CCT (platelet count < 50,000/mm3 and /or INR >1.5) and able to give informed consent were randomized. The major exclusions **(Table 1)** were emergency or life-saving procedures, on-going active bleeding, known coagulation disorders other than those relating to liver disease, use of anticoagulant medications (e.g. warfarin, enoxaparin, rivaroxaban, dabigatran, apixaban, heparin, clexane etc.), anti-platelet aggregation agents other than aspirin (e.g. clopidogrel, ticagrelor), active malignancy except hepatocellular carcinoma, patients who have received FFP, platelet transfusion, cryoprecipitate within last 7 days, with stage 4 or 5 chronic kidney disease or on renal replacement therapy, in active sepsis as defined by the third international consensus definition of sepsis and septic shock criteria **[17]** or pregnancy. The inclusion and exclusion criteria for the study were well defined and are summarized in **Table 1.** Briefly, we included adult cirrhotic patients with coagulopathy and undergoing an elective procedure. The diagnosis of cirrhosis was based on established clinical, biochemical, imaging, as determined by hepatologists.

During the study period one major and 4 minor amendments were made to the study protocol. The major amendment in the protocol was to allow for an embedded observational study where patients with acute on chronic liver failure (ACLF) were recruited, these patients were not part of the randomized trial. The minor amendments were carried out to primarily to add or remove study team members.

Study Design: In this open label, randomized, controlled, intention to treat trial, patients meeting inclusion and exclusion criteria were randomized into ROTEM or standard or care (SOC) group. The patients randomized to SOC group received pre-emptive blood products according to current institutional practice and patients in the ROTEM™ group received pre-emptive transfusion based on ROTEM™ value guided transfusion triggers. In case a patient requires pre-emptive transfusion, CCT and ROTEM™ were

repeated within 2 hours after completion of transfusion. The transfusion triggers in both groups were as follows

SOC Group: Patients in this group received FFP at the dose of 10 ml/kg of ideal body weight if INR > 1.5 and 1 unit of pooled platelets when the platelet count was below 50,000/mm^3.

ROTEM Group: ROTEM™ cut offs for transfusion were based on pre-existing institutional guidelines, which is based on trauma guidelines. One unit of pooled platelets (CSP) was transfused if EXTEM MCF was less than 45mm and FIBTEM MCF greater than or equal to 10mm irrespective of platelet count. Patients received FFP at a dose of 10 mL/kg of ideal body weight if EXTEM CT > 80 seconds or INTEM CT >240 seconds irrespective of INR/PT/APTT. To avoid interference of ascites and/or pleural effusion, the amount of blood products administered both in SOC and ROTEM group was based on ideal body weight, which was calculated using the Devine formula. FFP transfusion was completed before starting the procedure.

Outcomes measures: Efficacy Assessment

The primary outcome measure was the volume of fresh frozen plasma (in ml) pre-emptively transfused. We also compare the volume of cryoprecipitate (in units) and platelet transfusion (ml and units) between ROTEM and SOC group.

The secondary outcomes were: 1) peri-procedural bleeding complications defined as an overt bleeding or hemoglobin drop (>2 gm) requiring packed red cell transfusion, 2) transfusion related side effects defined as any side effect occurring within 6 hours of blood product transfusion 3) procedure related complications other than bleeding, 4) length of stay in hospital, 5) thrombotic complications and survival at 30 and 90 days.

The study was conducted according to the protocol, the ethical principles originating from the Declaration of Helsinki, and consistent with ICH Guidelines. All aspects of this study were conducted in accordance with all national laws of the regulatory authorities. The study was monitored and supervised through regular review by an independent safety monitoring board. Data management, study monitoring and analysis of samples were performed by independent individuals not directly involved in patient recruitment. All patients provided written informed consent. The study protocol was approved by the institutional review board of SingHealth (2020/3087; Clinical Trial ID: NCT 05698134).

Standard Management

All patients underwent baseline assessment with review of clinical history, clinical paraments and lab works including full blood count (FBC), renal panel (RP), liver function tests (LFT's), blood typing and cross matching (GXM), conventional tests of coagulation (PT/INR, aPTT), fibrinogen levels and ROTEM test before the procedure on the on the same day. Patients were observed after the procedure for any kind of immediate complications. If patients developed symptoms based on physician's discretion an imaging study was performed (either a computed tomography or an ultrasound scan). All patients had

their post procedure blood tests repeated 48 hours after the procedure. The patients were followed up via phone calls on 30 and 90 days from procedure.

Method of ROTEM™ determination

ROTEM™ test was done according to manufacturer's instructions. It was performed after taking venous blood sample from the anti-cubital vein. ROTEM™ was performed before the elective procedure on native blood sample by a fully automated ROTEM™ sigma machine (ROTEM™, TEM, Munich, Germany). Sample was processed for 30 min and various parameters determined by the ROTEM™ was automatically recorded by machine.

Definition of various parameters in ROTEM™

The ROTEM™ device measures the time dependent development of clot firmness of a whole blood sample. Thus, the involvement of coagulation factors and platelets both can be investigated. There are four important variables obtained from the ROTEM thrombo-elastogram **[18,19].** ***The clotting time*** defined as the time from recalcification and activation of the samples to clot formation is prolonged in patients with coagulation deficiencies, heparin therapy, or on oral anticoagulation. ***Clot formation time*** and **angle alpha** describe the kinetics of clot formation. ***Maximum clot firmness*** is affected by fibrinogen levels and platelet count. Four tests were used in the present study. **EXTEM™** activates coagulation by the addition of tissue factor and has similarities to INR. **INTEM™** is activated by elagic acid, which is an activator of the intrinsic system similar to laboratory aPTT. **FIBTEM™** is an assay activated by tissue factor in the presence of a platelet inhibitor (cytochalasin D) and maximum clot firmness in FIBTEM is therefore a specific measure of fibrinogen concentration. **APTEM™** is a tissue factor activated assay combined with a fibrinolysis inhibitor (aprotinin). Hyperfibrinolysis can be diagnosed by comparison of EXTEM™ and APTEM™ curves.

At the end of the procedure all patients were clinically reassessed and the blood tests including ROTEM and CCT's were repeated if patients received any transfusion. Any bleeding episode and patients' complaints were recorded and evaluated accordingly. Procedures were performed by experienced operators and bleeding events were classified according to the World Health Organization's bleeding score **[20].** Daily patient assessment was carried out till discharge from hospital. Weekly phone calls were made to assess patients' general well-being and survival at 30 and 90 days.

Statistical Analysis

Sample size determination and power calculations: Based on the prevailing institutional practice, patients deemed to be coagulopathic (INR >1.5 and or platelet counts <50,000/uL) are pre-emptively transfused blood products before an invasive procedure. Our institutional preliminary data shows that on average 400-500 ml of FFP is transfused pre-emptively before invasive procedures in these patients. In this study we hypothesized that the use of ROTEM™ guided prophylactic blood product transfusion will result in at least 20% reduction in the volume of blood product transfusion. Assuming a 20% difference in

the transfusion requirement (400 ± 100 mL in the SOC group and 320 ± 80 mL in ROTEM group) with a 5% alpha error and a 10% beta error, 33 patients in each group will be required. With a 10% drop out rate, it was planned to randomize 37 patients in each arm (74 patients in total) in 1:1 fashion. A scheduled interim analysis for primary outcome was planned after enrollment of 40 patients, and the study recruitment may be stopped if primary outcome measure been met at a significance level of 0.001 in accordance with Haybittle-Peto boundaries **[21]**.

Randomization procedures and blinding: All eligible patients who met the predefined inclusion and exclusion criteria and consented for participation in the study were randomized with help of computer-generated random sequence by a statistician in variable blocks of 4 and 6. The random number was delivered in sealed and opaque envelopes. Patients were randomized in either SOC or ROTEM™ group by the study coordinator. The group allocation was concealed from the patient and the proceduralist. The screening and randomization scheme is illustrated in the CONSORT Diagram **(Figure 1).**

Statistical software SPSS (version 28, SPSS Inc. Chicago, IL, USA) and GraphPad were used for analysis. Normally distributed continuous variables are expressed as mean (standard deviation) and the continuous variables with skewed distribution are expressed as median (interquartile range). Student T test and Mann-Whitney U test was used for continuous variables that were normally distributed or non-normally distributed. Chi-square or Fishers test for discrete variables, wherever applicable. A two tailed paired t-test was used to compare paired variables before and after the procedure. Kaplan-Meier's analysis was used to compare the cumulative probability of survival between the ROTEM and SOC group. The P value of <0.05 was of statistical significance.

The centralized institution review approval, patient information sheet, trial protocol with data analysis plan are available as supplementary material.

Results

Baseline characteristics of the study population: A total of 106 patients were screened for eligibility into the study. Sixty-six were excluded and 40 patients were randomized **into** ROTEM (n=20) versus SOC (n=20), between August 2021 to January 2023. The Consort flowchart is displayed in **Figure 1.** Baseline patient characteristics are summarized in **Table 2.** The mean age of the included patients was 57± 9.3-years and 87.5% patients were male. Alcohol-use disorder was the predominant etiology (50%) followed by metabolic associated steatohepatitis (17.5%) and Chronic Hepatitis B (15%). None of the randomized patients had active uncontrolled sepsis or chronic kidney disease stage 4-5. There was no difference in the age, body mass index (BMI), gender predominance, etiology of cirrhosis, clinical features at presentations or clinical parameters between the 2 groups.

There was however lower platelet (66 ± 24 Vs 84 ± 69; p=0.038), lower white cell count (WBC) (5.8 ± 3 Vs 7.4 ± 7; p=0.023), higher total bilirubin (141 ± 143 Vs 72 ± 65; p=0.005) in the ROTEM group. Importantly both groups did not defer significantly with respect to ROTEM parameters and CCT except for platelet count, including fibrinogen levels.

A total of 29 patients had an INR> 1.5 (14 in ROTEM and 15 in the SOC group; p=NS); 22 patients had a platelets count < 50 x 109/L (12 in ROTEM and 10 in the SOC; p=NS). 11 patients had significant abnormalities in both INR and platelet count (6 in ROTEM and 5 in SOC group; p=NS). No protocol violation occurred.

Procedures Performed: A total of 29 patients underwent procedures with periprocedural bleeding risks of less than 3% according to the available literature **[24];** abdominal paracentesis (n=23); hepatic venous pressure measurement and trans-jugular intrahepatic shunt (n=5); central vein cannulation (n=1). Rest (n=11) of the patients underwent procedures with a bleeding risk of more than 3%; microwave ablation of hepatocellular carcinoma and trans-arterial chemo embolization (n=5), percutaneous liver biopsy (n=4) and variceal band ligation (n=1). There was no difference in the type of procedure performed between the groups (p=0.378) **(Table 2).**

Blood product (FFP/Platelets/cryoprecipitate) requirement: While all patients in the SOC group received FFP transfusion, only 8 (40%) patients received FFP in the ROTEM group (p<0.001). Total of 1250 ml FFP was transfused in the ROTEM group vs 6500 ml FFP in the SOC group (p<0.001). The amount of FFP transfused per patient in the ROTEM group was 62.5 + 159.67 ml whereas that in the SOC group was 325+500 ml (p<0.001). **(Table 3).** The overall requirement of platelets was 18 units. A total of 7 patients in the ROTEM group (all 1 unit; 220 ml each) and 9 in the SOC group (7 patients 1 unit each and 2 patients 2 units each) received pooled platelet transfusion **(Figure 2).** The amount of platelet transfused was 70+97.87 ml in RITEM group compared to 110 + 137.26 in the SOC group (p=0.048) **(Table 3).** One patient in the ROTEM group received cryoprecipitate whereas none in the SOC group (p=0.041) **(Table 3).** The overall use of blood products was significantly lower in the ROTEM guided group (p<0.001)

Peri and post procedural events: No periprocedural bleeding were observed in either of the group. The most frequent adverse event observed post procedure was pain at the procedure site (13 patients in ROTEM and 12 in SOC group; p=NS), most being 2-3 in visual analogue pain score which resolved with simple analgesics. All adverse events which occurred were grades 1–2 as per CTCEA grading. There was no immediate or delayed bleeding complications seen in any patient in either group.

The blood tests done post procedure showed no difference between the study groups in hemoglobin levels, platelets, PT, or INR (p=NS). Patients who received transfusions had reduction in the PT levels and increase in platelets.

One patient in the SOC group developed an allergic reaction (p=NS) attributable to transfusion of FFP whereas no transfusion related adverse events were noted in the ROTEM group (p=NS). The patient improved with conservative management. None of the patients transfused either in the SOC or ROTEM group developed transfusion associated lung injury in this study.

There was no immediate or delayed bleeding events in our study noted in patients in either group. No thrombotic events were discovered as well in either of the group.

The length of stay in hospital was similar in both groups, and there were no thrombotic complications noted within a period of 90 days. **(Table 3).** A total of 2 (10%) patient in the ROTEM group died within a span of 30 days while all patients in SOC arm survived (p=NS). At 90 days from the enrollment, 4 (20%) patients from both groups had died (p=NS) (**Figure: 3**). Cause of death was owing to the complications of cirrhosis. While within 90 days, 3 patients died of multi-organ failure secondary to sepsis and acute on chronic liver failure, 1 patient died after developing grade 4 encephalopathy and subsequent aspiration pneumonia.

Discussion

In this open label randomized trial involving 40 patients with cirrhosis undergoing low to intermediate risk elective procedure for periprocedural bleeding, we found that ROTEM based transfusion strategy reduced the need for pre-emptive transfusion significantly. It eliminated the need for transfusion in over 60% patients without exposing them to increased risk of peri-procedure bleeding or other complications. The other important finding of this study is that pre-emptive transfusion was associated with risk of allergic reaction which is potentially avoidable. Furthermore, our study shows that ROTEM based transfusion strategy in these might result in increased use of cryoprecipitate.

Peri-procedure hemostasis and pre-emptive transfusion management for cirrhotic patients undergoing procedures is challenging. Hemostasis in cirrhosis has undergone paradigm shift, it is considered finely balanced with literature suggesting patients maybe at higher risk of thrombotic rather than hemorrhagic complications **(22,23).** Bleeding complications after invasive procedures are concerning in cirrhotic patients, though the incidence varies widely **(24).** Peri-procedure bleeding risk is closely related to alterations in clotting factors as well as the risks inherent to a given procedure, clinical situation **(25)** as well as expertise and confidence in treating these patients. Although increasing number of experts do not recommend the routine correction of perceived coagulopathy before a procedure, many guidance statements still recommend the correction of abnormal INR and platelets, consequently physicians managing these patients almost routinely transfuse these patients with FFP or platelets fearing that impaired CCT's may translate into increased bleeding. A handful of well conducted studies have shown that the use of TEG based transfusion strategies are safe and reduces the need for pre-emptive transfusion in most patients as compared to CCT **(13,14).** The data however is scant and there is knowledge gap for ROTEM based pre-emptive transfusion strategies, which our study fulfills. In one of the published studies **(15)** which used ROTEM as guide for pre-emptive transfusion, only patients undergoing central venous catheterization were included. Other study was conducted in pediatric patients **(16)**. The aim of our study was to find out if by using ROTEM as with TEG, there would be substantial reduction in the need for pre-emptive transfusion. We showed that the blood product requirement was indeed significantly lower in ROTEM arm compared to SOC.

In this study 60% of all patients in ROTEM arm did not need any transfusion whatsoever. In the SOC arm all patients received some form of pre-emptive transfusion, whereas in the ROTEM arm only 8 (40%) patients received either FFP, platelets, cryoprecipitate, or a combination of above. Our results using

ROTEM guidance for pre-emptive transfusion are similar to what has previously been published in similar group of patients but using TEG as the VET **(13,14).** De Petri et al **(13)** reported 16.7% patient receiving transfusion in TEG group and Shalimar et al **(14)** reported 31% patients in the TEG group receiving pre-emptive transfusions while all patients in the SOC groups received transfusion as per protocol. Both studies **(13,14)** randomized patients who were undergoing procedures with low to intermediate risk of peri-procedure bleeding which is similar to our study. Another important finding of our study is that none of the patients undergoing procedures had any clinically significant bleeding events, while all of them were classified as having increased risk of bleeding. While one may argue that the cohort was relatively small, the trial was stopped earlier based on a pre-planned interim analysis demonstrating substantial benefit of ROTEM-guided transfusion strategy over SOC. It would be safe to conclude that patients with cirrhosis with abnormal CCT's are not really at risk of increased periprocedural bleeding.

The results of our study showed that use of ROTEM as VET resulted in increased use of cryoprecipitate which includes fibrinogen, factor VIII, factor XIII and von Willebrand factor. Prior retrospective observational studies in patients undergoing liver transplantation with ROTEM based transfusion triggers have reported increased use of cryoprecipitate and resultant thrombotic events **(25).** Another nonrandomized study comparing ROTEM with CCTs to guide blood products during liver transplantation reported significantly higher numbers of patients receiving cryoprecipitate in ROTEM arm compared to CCTs, however the authors did not report on thrombotic complications **(26).** Previous studies using TEG to guide pre-emptive transfusion **(13,14**) have also shown increased use of cryoprecipitates in TEG group. Although in our study no thrombotic events were observed within 90 days of follow up in either group, more frequent use of cryoprecipitate in VET groups including this study, and its association with thrombotic events **(25)** remains a concern.

There were no immediate or delayed bleeding related complications in either of the group. The adverse events related to transfusions are serious concern, especially since it is potentially avoidable. In this study one patient (5%) in the SOC arm developed allergic reaction while none in the ROTEM group, which was mild, and patient recovered with conservative treatment. Overall, the incidence of allergic reaction was 2.5% in this study. No patient developed transfusion associated lung injury in either group likely due to relatively low volume of transfusion. Although the reported rates of transfusion related adverse events are low between 1–2%, it should be avoided by cutting down on unnecessary transfusions **(27,28).**

There was a reduction in the volume of blood products and the proportion of patients receiving any kind of transfusion in the ROTEM arm of this RCT but there was no impact on 30- or 90-day mortality. Within 30-days 2 patients in the ROTEM group (10%) died and within 90- days 4 patients in each group (20% in each group) died due to complications of cirrhosis. None of the deaths were attributable to either the procedure or transfusions that they received. Our results are like previous TEG based studies **(13,14)** in similar patient pool and also broadly in line with in-patients with cirrhosis **(29)** where reported 30-day mortality was around 10%.

The major strength of this study is that to our knowledge this is the first randomized study using ROTEM to guide prophylactic transfusion in adult patients with cirrhosis undergoing various elective procedures reflective of day today clinical practice. Other important strengths of our study are the strict compliance and monitoring, no dropouts and case and procedure mix which reflects the day-today hepatology practice. The results of our study should be interpreted in light of some limitations, however. First, the transfusion triggers in SOC arm based on CCT might may seem rather low, this reflects general hepatology practice in most institutions and is in line with current guidelines. In the same vein, the ROTEM transfusion triggers are based on trauma guidance which may not be applicable to patients with cirrhosis. It should also be kept in mind that currently there are no accepted baseline value of ROTEM parameters in patients with cirrhosis. Furthermore, although in our study different procedures were carried out which has varying degrees of post procedure bleeding risks, there was no difference between the two groups regarding the type of procedure performed. We are aware of the recent consensus statement [30] on the bleeding risk of invasive procedures among cirrhosis patients where most of the procedures would have been classified as low bleeding risk, rendering the study underpowered to detect bleeding-related adverse events. This was not incorporated into the current study since the consensus statement was not available during the conception of this study, therefore future research should focus on high-risk procedures in cirrhosis patients and in patients with overt bleeding to see if use of ROTEM based transfusion strategies can reduce the need for transfusions.

Conclusion

In conclusion, this study for the first time shows that ROTEM guided pre-emptive transfusion strategy significantly reduces the need for transfusion in adult patients with cirrhosis undergoing day-to-day elective procedures without putting patients at additional bleeding risks, which is in line with the previously published data using TEG. Our study also shows that pre-emptive transfusion is associated with risks of transfusion reactions (clinicaltrails.gov; NCT05698134).

Declarations

Acknowledgments: We sincerely acknowledge and thank our clinical research team led by Ms Geraldine, specially to Mr. Benny Wong for his unwavering support and multiple out of office hours calls for patient review and randomization. We would also like to thank the hospital research fund for financing the study.

Conflict of interest statements: All authors do not have any potential conflict of interest related to the study to declare.

Financial support statement: All the authors have no relevant financial disclosures to make. The study was funded by research grant from Changi General Hospital, Singapore.

Authors' contributions: Concept: RK, LN, TPS; Data Collection, entry, and curation: BW: Analysis: LZW, TYQ, RK TCK; Interpretation: All; Manuscript Writing: RK, TYQ, LZW, TCK; Critical Reviewing: All

References

1. Zakeri N, Tsochatzis EA. Bleeding risk with invasive procedures in patients with cirrhosis and coagulopathy. Curr Gastroenterol Rep. 2017; 19:45.
2. Tripodi A, Primignani M, Mannucci PM, Caldwell SH. Changing Concepts of Cirrhotic coagulopathy. Am J Gastroenterol 2017; 112:274–281.
3. Rautou PE, Caldwell SH, Villa E. Bleeding and Thrombotic Complications in Patients With Cirrhosis: A State-of-the-Art Appraisal. Clin Gas Hepatol. 2023; 21(8):2110-2123,
4. Schepis F, Turco L, Bianchini M, Villa E. Prevention and management of bleeding risk related to invasive procedures in cirrhosis. Semin Liver Dis. 2018; 38:215–229.
5. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology. 2006; 105:198–208.
6. Thomas D, Wee M, Clyburn P, et al. Blood transfusion and the anaesthetist: management of massive haemorrhage. Anaesthesia. 2010; 65:1153–1161.
7. Malloy PC, Grassi CJ, Kundu S, et al. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Interv Radiol. 2009;20: S240–S249.
8. Mohanty A, Kapuria D, Canakis A, et al. Fresh frozen plasma transfusion in acute variceal hemorrhage: results from a multicenter cohort study. Liver Int. 2021.
9. Rahimi RS, O'Leary JG. Transfusing common sense instead of blood products into coagulation testing in patients with cirrhosis: overtreatment not equal safety. Hepatology 2016; 63:368-370
10. Tripodi A, Primignani M, Chantarangkul V, Viscardi Y, Dell'Era A, Fabris FM, Mannucci PM. The coagulopathy of cirrhosis assessed by thromboelastometry and its correlation with conventional coagulation parameters. Thromb Res. 2009 May;124(1):132-6.
11. Blasi A, Calvo A, Prado V, Reverter E, Reverter JC, Hernández-Tejero M, Aziz F, Amoros A, Cardenas A, Fernández J. Coagulation Failure in Patients with Acute-on-Chronic Liver Failure and Decompensated Cirrhosis: Beyond the International Normalized Ratio. Hepatology. 2018 Dec;68(6):2325-2337
12. Roullet S, Freyburger G, Cruc M, Quinart A, Stecken L, Audy M, et al. Management of bleeding and transfusion during liver transplantation before and after the introduction of a rotational thromboelastometry-based algorithm. Liver Transpl. 2015 Feb;21(2):169-79.
13. De Pietri L, Bianchini M, Montalti R, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: a randomized, controlled trial. Hepatology 2016; 63:566–573
14. Kumar S, Shalimar, Gamanagatti S, et al. Thromboelastography guided blood product transfusion in patients with chronic liver disease undergoing invasive liver-related procedures: a randomized controlled trial. Hepatology 2018; 68:96A.

15. Rocha LL, Neto AS, Pessoa CMS, et al. Comparison of three transfusion protocols prior to central venous catheterization in patients with cirrhosis: A randomized controlled trial. J Thromb Haemost. 2020;18(3):560-570. doi:10.1111/jth.14672
16. Maria A, Lal BB, Khanna R, et al. Rotational thromboelastometry-guided blood component use in cirrhotic children undergoing invasive procedures: Randomized controlled trial. *Liver Int*. 2022;42(11):2492-2500. doi:10.1111/liv.15398
17. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801–810. doi:10.1001/jama.2016.0287
18. Larsen OH, Fenger-Eriksen C, Christiansen K, Ingerslev J, Sørensen B. Diagnostic performance and therapeutic consequence of thromboelastometry activated by kaolin versus a panel of specific reagents. Anesthesiology. 2011; 115:294–302.
19. Herbstreit F, Winter EM, Peters J, Hartmann M. Monitoring of haemostasis in liver transplantation: comparison of laboratory based and point of care tests. Anaesthesia. 2010; 65:44–9.
20. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207-214.
21. Peto R, Pike MC, Armitage p et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. Introduction and design. Br. J. Cancer 34 (6):585-612.
22. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Eng J Med 2011;365:147-156.
23. Villa E, Camm a C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012;143:1253-1260.e1-4.
24. Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F faculty of the 7th International Coagulation in Liver Disease. Concepts and Controversies in Haemostasis and Thrombosis Associated with Liver Disease: Proceedings of the 7th International Coagulation in Liver Disease Conference. Thromb Haemost. 2018;**118**:1491–1506
25. Nguyen-Buckley C, Gao W, Agopian V, Wray C, Steadman RH, Xia VW. Major Thromboembolic Complications in Liver Transplantation: The Role of Rotational Thromboelastometry and Cryoprecipitate Transfusion. Transplantation. 2021 Aug 1;105(8):1771-1777. doi: 10.1097/TP.0000000000003427. PMID: 32852404.
26. Smart L, Mumtaz K, Scharpf D, Gray NO, Traetow D, Black S, et al. Rotational thromboelastometry or conventional coagula- tion tests in liver transplantation: comparing blood loss, transfusions, and cost. Ann Hepatol 2017;16:916-923.
27. Sapiano MRP, Savinkina AA, Ellingson KD et al. Supplemental findings from the National Blood collection and utilization surveys, 2013 and 2015. Transfusion 2017;57 (suppl 2): 1599-624.
28. Sahu A, Bajpai M. Determining the true incidence of acute transfusion reactions: Active surveillance at a specialized liver center. Hematology, Transfusion and Cell Therapy 2020; 42: 326-332
29. Kanwal, Fasiha MD, MSHS1,2,3; Tansel, Aylin MD1,2; Kramer, Jennifer R PhD1,3; Feng, Hua PhD1,3; Asch, Steven M MD, MPH4,5; El-Serag, Hashem B MD, MPH1,2,3. Trends in 30-Day and 1-Year

Mortality Among Patients Hospitalized With Cirrhosis From 2004 to 2013. American Journal of Gastroenterology 112(8):p 1287-1297, August 2017. | DOI: 10.1038/ajg.2017.175

30. Riescher-Tuczkiewicz A, Caldwell SH, Kamath PS, et al. Expert opinion on bleeding risk from invasive procedures in cirrhosis. *JHEP Rep*. 2023;6(3):100986. Published 2023 Dec 19. doi:10.1016/j.jhepr.2023.100986

Tables

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria:	Exclusion Criteria:
1. Patients undergoing the following elective procedures will be included in the study a. Gastroscopy with endoscopic variceal ligation b. Colonoscopy with polypectomy and endoscopic mucosal resection c. ERCP with sphincterotomy d. Percutaneous liver biopsy e. Biopsy of other sites (excluding liver) f. Hepatic venous pressure gradient with or without liver biopsy g. Elective Transjugular Intrahepatic Portosystemic Shunt h. Portal Vein embolization i. Trans-arterial chemo-embolization (TACE) j. Thermal ablation of hepatocellular carcinoma k. Large volume paracentesis l. Central venous catheter insertion m. Thoracentesis 2. Age: Older than 21 years 3. Coagulopathy based on conventional coagulation tests which is defined as a. INR > 1.5 and/or aPTT > 1.5x ULN for PTT and/or b. Platelets < 50,000/mm^3/uL 4. Able to give informed consent.	1. Emergency procedures. (defined as life-saving procedures) 2. On-going bleeding 3. Under 21 years of age 4. Inability to obtain informed consent from patients 5. Coagulation disorders (other than those relating to liver disease) 6. Patients on anticoagulant medications (e.g. warfarin, enoxaparin, rivaroxaban, dabigatran, apixaban, heparin, clexane etc.) 7. Patients on anti-platelet aggregation agents other than aspirin (e.g. clopidogrel, ticagrelor) 8. Active malignancy except hepatocellular carcinoma 9. Patients who have received FFP, platelet transfusion, cryoprecipitate within last 7 days 10. Patients with stage 4 or 5 chronic kidney disease 11. Patients receiving renal replacement therapy 12. Patients with active sepsis as defined by ACPP-SCCM criteria (21). 13. Pregnant Women

Table 2. Patient characteristics: REDUCE

Variable	All patients (N= 40)	ROTEM Guided (n= 20)	SOC Guided Transfusion (n= 20)
Age (years)	57.4 ± 9.3	56.6 ± 9.9	58.15 ± 8.8
BMI (kg/m2)	26.8 ± 7.3	27.76 ± 9.55	25.78 ± 3.60
Male gender, n (%)	35 (87.5%)	18 (90%)	17 (85%)
Etiology of cirrhosis, n (%)			
Alcohol	20 (50)	10 (50)	10 (50)
HBV	6 (15)	2 (10)	4 (20)
HCV	4 (10)	0 (0)	4 (20)
MASH	7 (17.5)	6 (30)	1 (5)
PBC/PSC/AIH	2 (5)	1 (5)	1 (5)
Wilsons'	1 (2.5)	1 (5)	0 (0)
Clinical features at presentation, n (%)			
Ascites			
None	4 (10)	2 (10)	2 (10)
Mild-Moderate	16 (40)	9 (45)	7 (35)
Severe	20 (50)	9 (45)	11 (55)
Hepatic encephalopathy, n (%)			
None	35 (87.5)	18 (90)	17 (85)
Grade 1 and 2	5 (12.5)	2 (10)	3 (15)
Clinical parameters at presentation			
Temperature (^{o}C)	36.5 ± 0.48	36.6 ± 0.54	36.45 ±0.47
Mean Arterial Pressure (mmHg)	86 ± 12	87 ±13	86 ± 11
Respiratory Rate (/min)	15(12-16)	14 (12-16)	15 (12-16)

Heart Rate (HR) (/min)	78 (64-90)	79 (64-90)	78 (62-93)
Laboratory values			
Haemoglobin (g/dl)	10.3 ± 1.8	10.5 ± 2	10.2 ± 1.7
Platelet Count (x10^9/L)	75 ± 51	66 ±23	84 ± 69
White cell count (WCC) (x10^6/L)	6.6 ± 3.2	5.8 ± 3	7.4 ± 7
Prothrombin Time (sec)	17.01 ± 2.92	17.23 ± 2.61	16.96 ± 3.27
INR (S)	1.65 ± 0.3	1.66 ± 0.3	1.63 ± 0.3
aPTT (Sec)	40 ± 12	41 ± 14	38 ± 10
Total Bilirubin (mmol/L)	103 ± 114	141.07 ± 143.6	74.26± 64.60
Albumin (g/dL)	27.4 ± 6.2	28.25 ± 6.5	26.5 ±5.9
Urea	5.1 ± 3.4	5.5 ± 3.8	4.6 ± 2.9
Creatinine (umol/dL)	82 ± 44	92.05 ± 55.63	72.15 ± 25.13
Sodium (mmol/L)	134 ± 5	134 ± 6	134 ± 5
Potassium	3.8 ± 0.5	3. 9 ± 0. 5	3.7 ± 0.4
Chloride	102 ± 5	102 ± 5	103 ± 5
Bicarbonate	22.7 ± 3	22.6 ± 3	23 ± 3
Prognostic Scores			
Child-Turcotte- Pugh Class			
A (5-6)	4 (10)	2 (10)	2 (10)
B (7-9)	12 (25)	7 (35)	5 (25)
C (10-15)	24 (65)	11 (55)	13 (65)
MELD	17 ± 6	18 ± 7	16 ± 5
MELD-Na	20 ± 7	21.45± 7	19.0 ± 6
ROTEM Parameters			

INTEM CT	221 ± 41	226 ± 41	216 ± 40
INTEM CFT	199 ± 119	204 ± 118	194 ± 122
INTEM MCF	43 ± 9	42 ± 9	44 ± 10
EXTEM CT	76 ± 15	76 ± 11	77 ± 19
EXTEM CFT	188 ± 123	194 ± 162	181 ± 152
EXTEM MCF	44 ± 10	43 ± 9	46 ± 10
FIBTEM CT	106 ± 101		
FIBTEM CFT	659 ± 624		
FIBTEM MCF	9.5 ± 7.5		
APTEM CT	73 ± 16	71 ± 13	75 ± 18
APTEM CFT	221 ± 131	230 ±141	211 ±125
APTEM MCF	43 ± 9	42 ± 9	44 ± 10
Procedures Performed			
OGD with EVL	1 (2.5)	0 (0)	1 (5)
Percutaneous Liver Biopsy	3 (7.5)	3 (15)	0 (0)
Biopsy of Other Sites	1 (2.5)	1 (5)	0 (0)
HVPG	4 (10)	2 (10)	2 (10)
TIPSS	1 (2.5)	0 (0)	1 (5)
TACE	1 (2.5)	1 (5)	0 (0)
MWA	5 (12.5)	2 (10)	3 (15)
LVP	23 (57.5)	10 (50)	13 (65)
CVP	1 (2.5)	1 (5)	0 (0)

West-Haven criteria was used to categorise hepatic encephalopathy.

Abbreviations: AIH: Auto-immune hepatitis; ALD: Alcohol-associated liver disease; CLIF: European Foundation for the study of chronic liver failure; HBV: Hepatitis-B virus; HCV: Hepatitis-C virus; ICU:

MELD-Na: Model for End-Stage Liver Disease-sodium; MASH: Metabolic-associated Steatohepatitis; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis

Categorical variables are displayed in percent and continuous variables as mean ± SD (for Normally distributed data) or median (IQR) (Nonparametric testing for skewed data). Chi-square test was used for categorical variables, paired t-test for normally distributed continuous variable and Mann-Whitney U test was used for Non-parametric testing.

Table 3: Results: Primary and Secondary Outcomes

Variable	All patients (N= 40)	ROTEM Guided (n= 20)	SOC Guided Transfusion (n= 20)	P-value
Blood product requirement				
Fresh Frozen Plasma (mL)	193 ± 268	62.5 ±159.67	325 ± 500	<0.001
Platelets (mL)	90 ± 119	70 ± 97.87	110 ± 137.26	0.048
Cryoprecipitate (UNIT)	1	1	0	0.041
No of patients receiving only FFP	12 (30%)	1 (5%)	11 (55%)	<0.001
No of patients receiving only Platelets	13 (32.5%)	5 (25%)	8 (40%)	<0.001
No of patients receiving both FFP and Platelet transfusions	3 (7.5%)	2 (10%)	1 (5%)	0.312
No of patients receiving Cryoprecipitate	1 (2.5%)	1 (5%)	0	0.423
Bleeding Complications				
Immediate (< 24 hrs of procedure)	0	0	0	NS
Delayed (> 24 hrs of procedure)	0	0	0	NS
Transfusion Related Side Effects				
Allergic Reaction	1	0	1	NS
TRALI	0	0	0	NS
Length of Stay				
Length of Stay in hospital (days)	7.9 ± 8.7	8.45 ± 8.1	7.4 ± 9.4	0.435
Thrombotic Complications within 90 Days	0	0	0	NS
Survival at 30 days	38 (95%)	18 (90%)	20 (100%)	0.152
Survival at 90 days	32 (80%)	16 (80%)	16 (80%)	0.875

Abbreviations: **FFP: Fresh Frozen Plasma, TRALI: Transfusion associated Lung Injury**

Categorical variables are displayed in percent and continuous variables as mean ± SD (for Normally distributed data) or median (IQR) (Nonparametric testing for skewed data). Chi-square test was used for categorical variables, paired t-test for normally distributed continuous variable and Mann-Whitney U test was used for Non-parametric testing.

Figures

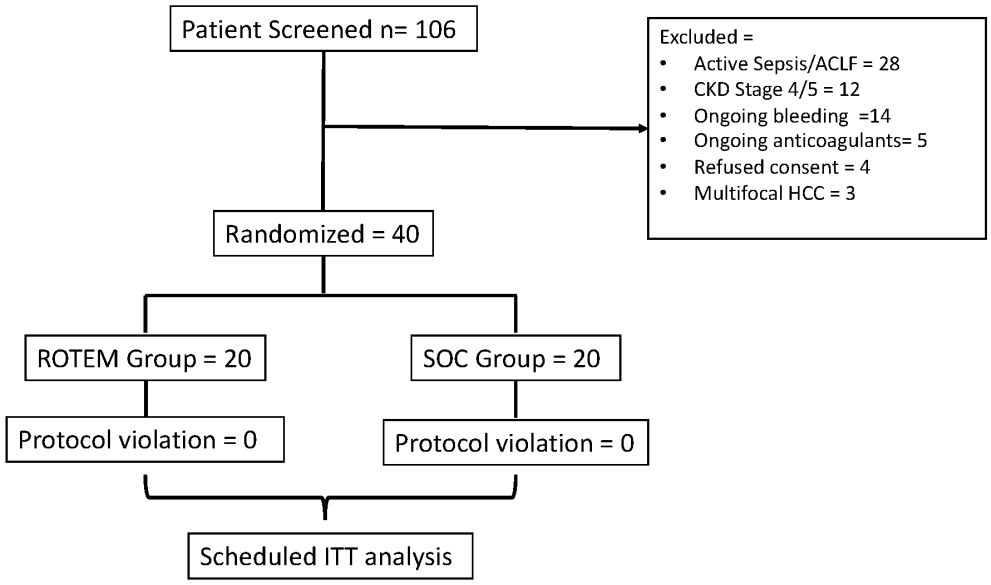


Figure 1: Consort diagram

Abbreviation: CKD: Chronic kidney disease; HCC: Hepatocellular carcinoma, ITT: Intention to treat, ROTEM: Rotational Thromboelastometry, SOC: Standard of care

Figure 1

See image above for figure legend.

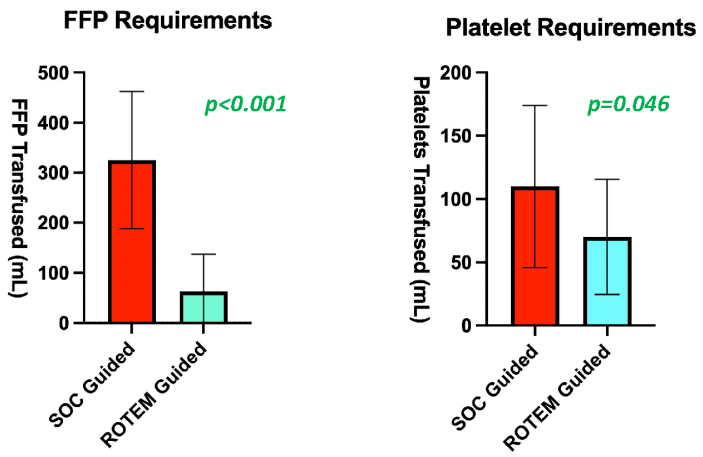
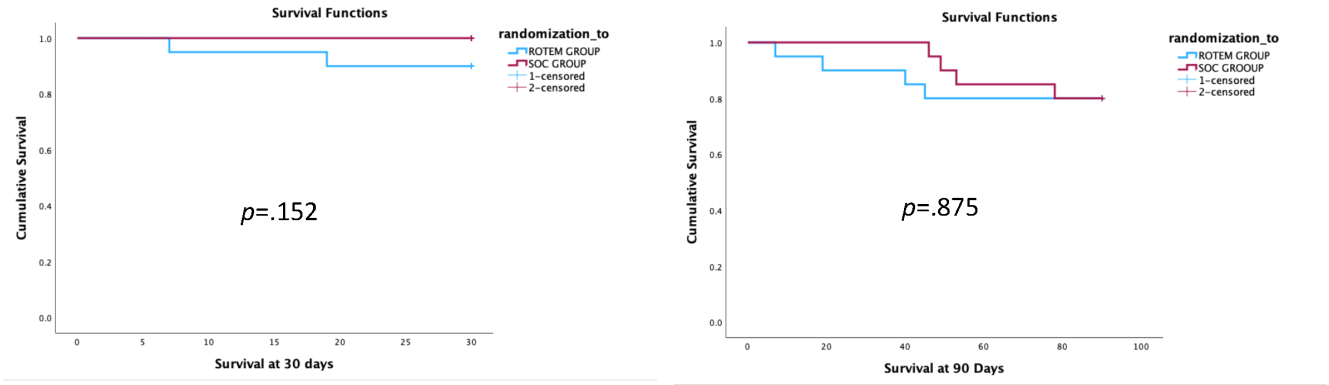


Fig 2: Comparison of Blood product requirements: FFP and Platelets

Abbreviations: FFP: Fresh Frozen Plasma, ROTEM: Rotational Thromboelastometry, SOC: Standard of Care

Figure 2

See image above for figure legend.



Patient at risk	0 Days	10 Days	20 Days	30 Days
SOC	20	20	20	20
ROTEM	20	19	18	18

Patient at risk	0 Days	30 Days	60 Days	90 Days
SOC	20	20	19	18
ROTEM	20	18	18	18

Figure 3: Kaplan Meier survival curve for 30 and 90 days survival

Abbreviations: ROTEM: Rotational Thromboelastometry, SOC: Standard of Care

Figure 3

See image above for figure legend.