Bleeding Following Pediatric Liver Transplantation: A Brief Overview

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ABSTRACT

End-stage liver disease (ESLD) occasionally needs liver transplantation (LT) as a life-saving treatment. In pediatric population, LT procedure is more complicated than adults, since they are mainly caused by extrahepatic cholestasis, has a variety of age groups, and has various infection susceptibilities. Furthermore, there is a complication related to LT, such as bleeding, which cannot be disregarded because it may aggravate patients' conditions and necessitate reoperation. Moreover, in the case of hepatic artery thrombosis and portal vein thrombosis, which is caused by severe bleeding, patients and grafts' survival may be significantly reduced. In this review, we are discussing bleeding following LT phenomena from the basic introduction, pathophysiology, prevention, monitoring, and treatment.

Keywords: Hemorrhage; liver transplantation; pediatric; rotational thromboelastometry; thromboelastogram

Perdarahan Pasca Transplantasi Hepar pada Anak: Suatu Gambaran Singkat

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ABSTRAK

Penyakit hati stadium akhir (end-stage liver disease/ESLD) seringkali membutuhkan transplantasi hati (liver transplantation/LT) sebagai terapi untuk menyelamatkan nyawa penderita. Pada populasi anak-anak, prosedur LT lebih rumit dibandingkan orang dewasa, karena sebagian besar kasusnya disebabkan oleh kolestasis ekstrahepatik, memiliki kelompok umur yang bervariasi, serta kerentanan infeksi yang beragam. Selain itu, terdapat komplikasi terkait LT, seperti perdarahan, yang tidak dapat diabaikan karena dapat memperburuk kondisi pasien serta memerlukan operasi ulang. Selain itu, dalam kasus trombosis arteri hepatik dan trombosis vena portal, yang disebabkan oleh perdarahan hebat, kelangsungan hidup pasien dan penerima transplantasi dapat berkurang secara signifikan. Dalam ulasan ini, kami membahas fenomena perdarahan pasca LT mulai dari pengenalan dasar, patofisiologi, pencegahan, pemantauan, dan pengobatan.

Kata Kunci: *Pediatri; perdarahan; transplantasi hati; rotational thromboelastometry; tromboelastogram*

INTRODUCTION

End-stage liver disease (ESLD) is a term used to describe a late-stage of liver disease in which the liver has sustained significant damage and is no longer capable of performing its normal functions. Liver transplantation (LT) is a life-saving treatment that has transformed ESLD care.[1] This procedure is performed both in pediatric and adult populations.[2]

The pediatric population is not like adults and the same holds for LT. They have a broad range of illnesses that can cause either acute or chronic ESLD. Data in United States presented pediatric LT cases comprised 7.3% of the total LT cases, which shows a great discrepancy from adult patients.[3] Extrahepatic cholestasis, specifically biliary atresia, accounts for 50% of ESLDs requiring LT, while the remaining cases are a combination of metabolic diseases (including Wilson's disease, non-syndromic paucity of intrahepatic bile ducts, α1-antitrypsin deficiency, Crigler-Najjar syndrome, urea cycle disorders, acid lipase defect, tyrosinemia, oxaluria type I, and disorders of carbohydrate metabolism), intrahepatic cholestasis (sclerosing cholangitis, non-syndromic paucity of intrahepatic bile ducts, Budd-Chiari syndrome, Alagille's syndrome, and progressive familial intrahepatic cholestasis syndrome), acute liver failure, and other causes (liver tumor, choledochal cyst, Caroli disease, and cystic fibrosis). Synthetic failure (extended prothrombin time, low albumin), encephalopathy, and failure to thrive are ESLD consequences that require LT in the pediatric population. Another indicator of the needs of LT is intractable itching that lowers the quality of life. Additionally, the pediatric population includes a variety of age groups (neonate, infant, toddler, preschool, school, and adolescents) with various infection susceptibilities, therefore management may vary and provide particular difficulties.[4,5] According to the most recent data from the Scientific Registry of Transplant Recipients (SRTR), 599 liver transplants were done in children in United States in 2017. There have been considerable developments in the pediatric area of liver transplantation in recent decades. Nowadays, liver transplants from deceased donors have one, five, and ten-year survival rates of 90%, 80%, and 70%, respectively. Improvements in surgical methods, immunosuppression, and critical care can be ascribed to these successful results.[6,7] The majority of donors in developing nations, like Indonesia, came from living subjects, which is less desired than LT from deceased donors. In addition, Indonesia had a 22% rate of chronic rejections during the first year of transplantation in 2018, which was much higher than the rates in other nations including the United States and India (8% and 2.5%, respectively).[8]

However, LT is not without its drawbacks, both for patients and for civilization as an entirety. The impact of LT on patients' quality of life is multifaceted, and it can be altered by factors like complications and long-term management of the disorder. Furthermore, there is a substantial risk of complication due to many LT-related outcomes, such as hypotension, hypoxia, ischemia, and hepatotoxic medications. Moreover, there are several donor-related aspects (hepatic steatosis, use of vasoactive drugs, hemodynamic alteration), surgical-related factors (intra- or postoperative hemorrhage, vascular or biliary complications), or immune responses (rejection) that could worsen the outcome.[9] A study in a hospital in the United States found that 15% of recipients had massive intraoperative blood loss, which lead to a significantly higher length of stay than pediatric patients without massive blood loss (31.5 vs. 11 days, $p<0.001$). A similar situation applies to those who need massive blood transfusion (length of stay: 34 vs. 11 days, $p<0.001$), which happened in 15% of the pediatric liver transplant recipients.[10]

Bleeding after LT should not be disregarded because it may aggravate patients' conditions and necessitate reoperation (around 10.8% of LT patients).[11,12] Bleeding can occur in a variety of body systems, including in vascular anastomosis, gastrointestinal (due to ulcers, enteritis, portal hypertensive injuries, Roux-en-Y (RY) anastomosis bleeds, and other causes) and intracranial (spontaneous intraparenchymal hemorrhage/IPH and extra-axial hemorrhage/EAH).[13–15] Furthermore, hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT) are the most common postoperative vascular complication and decrease patient and

graft survival which could be associated with massive hemorrhage.[16] Reoperation for bleeding cases is related to the Model For End-Stage Liver Disease score, the number of platelets transfused, and the use of aminocaproic acid. Patients who have reoperation will require more intensive care unit (ICU) time and hospitalization. Furthermore, they had a higher risk of death (HR = 1.89; 95% CI = 1.26-2.85).[11] Despite these challenges, LT remains an essential treatment option for patients with end-stage liver disease, highlighting the need for continued research and innovation in the field of LT. In this review, we are discussing bleeding following liver transplantation phenomena from the basic information, pathophysiology, prevention, and treatment.

HOMEOSTASIS ALTERATION IN LIVER DISEASE: MECHANISM OF BLEEDING PRE, DURING, AND POST LIVER TRANSPLANTATION

Bleeding in LT has a complex and multiple etiology. The liver is an essential organ in controlling the coagulation pathway because it produces and synthesizes coagulation factors. However, the liver's capacity to produce and control coagulation factors is impaired in people with ESLD.[17] As a result, coagulopathy, or reduced clotting capacity, may develop and may increase the risk of bleeding during and after LT.[18,19] The surgical procedure, the patient's coagulation state, the presence of portal hypertension, and the degree of liver dysfunction are some factors that affect the bleeding development. The development of bleeding may be impacted by the surgical approach employed during LT. For instance, by shortening the time between ischemia and reperfusion, venovenous bypass or piggyback procedures can reduce the risk of bleeding. Contrarily, the prolonged ischemia, and reperfusion associated with the use of conventional methods can raise the risk of bleeding.[20–22]

It is important to remember that, prior to LT, patients with ESLD (especially those with cirrhosis) had developed platelet dysfunction, both in terms of quantity (thrombocytopenia from splenic sequestration) and in vitro platelet function. The process is primarily countered by a rise in von Willebrand factor (vWF) levels, which creates an additional surface area for thrombin production.[23] This is made possible by a greater discharge of vWF from endothelial cells and decreased levels of ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 repeats) in ESLD patients.[24] This situation has an effect on the preservation of primary hemostasis.[25] In severe liver illness, the decline of factor V and vitamin K-dependent factors (II, VII, IX, and X) that affect secondary hemostasis (which depends on coagulation factors) is compensated by the decline of proteins S and C (vitamin K-dependent anticoagulants). The compensatory process impacts both concentration and anticoagulation factor activity, such as proteins S, protein C, and antithrombin III (ATIII).[26]

The pre-anhepatic phase is marked by the occurrence of pre-existing coagulopathy superimposed with other causes, such as coagulopathy brought on by the surgical procedure, intraoperative bleeding associated with surgical trouble, bleeding brought on by the formation of collateral circulation and portal hypertension, increased capillary fragility, and dilution coagulopathy brought on by fluid replacement.[27] In the meantime, the anhepatic phase, coagulation factor generation, and hepatic clearance are decreased (from the blockage of hepatic vasculature to revascularization of the donated liver). Due to a lack of tissue plasminogen activator (tPA) clearance and relatively stable levels of Plasminogen activator inhibitor-1 (PAI-1), hyperfibrinolysis may be the predominant issue throughout this period.[27,28] The reperfusion phase is the most vulnerable of the three stages because it may be affected by both procoagulant and anticoagulant systems as a result of many imbalances that are part of a further ischemia/reperfusion injury (IRI) syndrome. Reperfusion harm the endothelial cells lining the blood vessels, releasing pro-inflammatory cytokines and activating the coagulation cascade. Hypercoagulability or disseminated intravascular coagulation (DIC), a dangerous condition marked by extensive bleeding and clotting, may happen.[18,19] Thrombocytopenia is immediately noticeable, primarily because platelets are trapped in the liver sinusoids, but platelet activation is also taking place.

The so-called heparin-like effect (HLE), which results in the expulsion of heparinoids from the donor tissue's endothelium and an accelerated discharge of tPA that causes hyperfibrinolysis, also causes further issues.[27,29,30] Furthermore, immunosuppressive drugs, including calcineurin inhibitors (tacrolimus) can impair platelet function and increase the risk of bleeding.[31]

MONITORING OF BLEEDING AND COAGULATION STATUS FOR LIVER TRANSPLANTATION

As a result of the significant alterations in blood coagulation state that liver transplant patients encounter, preoperative hemostasis monitoring is essential for identifying the likelihood of bleeding during surgery.[32] To avoid and treat bleeding during LT, it is generally accepted that coagulation factor monitoring is necessary. However, because of the time-consuming characteristics of the test, conventional coagulation tests (CCT) monitoring such as activated partial thromboplastin time (aPTT) and prothrombin time (PT) are inadequate to forecast bleeding or transfusion probability.[33] Moreover, conventional hemostatic assays such as PT, INR, and aPTT merely assess the action of procoagulants and fail to reflect the influence of in vivo inhibitors, platelet, or other cellular components. These assays, which quantify clotting, are plasma-based and rely on the fact that fibrin clot forms quickly even when just 5% of the total thrombin is produced. These investigations do not offer details about the remaining 95% of thrombin created, fibrin formation, or clot lysis because the conclusion of these assays occurs at the start of the propagation phase.[34]

These drawbacks are overcome by viscoelastic coagulation tests like rotational thromboelastometry (ROTEM) and thromboelastogram (TEG), which offer a more thorough and precise picture of the patient's coagulation function. These tests can evaluate several different elements of whole-blood coagulation simultaneously, including plasmatic coagulation, fibrinolytic factors, and inhibitors that represent the majority of hemostasis-related processes.[35] Pre-operative conventional coagulation tests, such as the clotting time (CT), only have limited capacity due to the multifaceted nature of coagulopathy disorders and bleeding issues during liver transplantation, which can be explained by deficiencies in liver functions, decreased platelet count, and bone marrow repression.[36] These tests only represent the plasma's pro-coagulant features and fail to offer precise details about the quantity of bleeding, transfusion, and other factors.[37] The explanation of ROTEM and TEG (Fig. 1 and Tab.1).

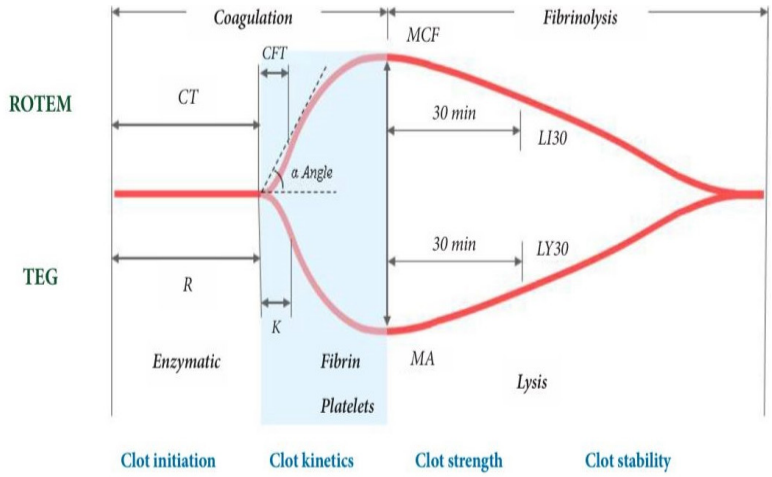

Figure 1. Viscoelastic coagulation examination using whole blood as its sample.
Note: CT = clotting time, R = reaction time, CFT = clot formation time, MCF = maximum clot firmness, MA: maximum amplitude.[35]

Viscoelastic coagulation tests provide point-of-care testing, which lessens the load of collecting blood and transporting it to the lab, making them an effective replacement for CCT. The test allows for real-time monitoring and goal-directed therapy during surgery since it provides results in a shorter period than CCT—within 15 to 25 minutes.[35] According to studies, the viscoelastic coagulation exam is more sensitive to coagulation problems than the CCT and can predict the onset of acute coagulopathy as well as determine whether or not it requires therapy.[38] Additionally, it can lessen bleeding and the ensuing need for blood transfusions. Furthermore, viscoelastic coagulation tests can aid in the prediction of thrombosis and acute myocardial infarction associated with hypercoagulation states that may manifest during the surgical procedure.[39]

Based on the stages of the liver transplantation surgery, different viscoelastic coagulation tests must be performed. The test exhibits low maximum amplitude (MA) and maximum clot firmness (MCF) values during the pre-anhepatic phase, showing thin graphs with extended R and CT.[35] Hyperfibrinolysis occurs during the anhepatic period, necessitating the delivery of anti-fibrinolysis drugs such as tranexamic acid.[40] The influx of heparin-like chemicals into the donated liver may make bleeding worse during the neo-hepatic phase, prompting constant monitoring of coagulopathy diseases using the viscoelastic coagulation test to determine the most immediate course of action.[41]

Although viscoelastic coagulation tests have been investigated as a blood transfusion approach to liver transplantation, there is no established procedure for their usage. Viscoelastic coagulation test parameters can change quickly during liver transplantation, thus treatment choices should take the clinical context and comprehensive coagulation status into account in addition to test results.[35] For the optimization of the overall handling of coagulation and transfusion during liver transplantation, viscoelastic coagulation tests must be used in addition to standard coagulation testing.[42]

Tabel 1. Parameters to be checked during transfusion[41]

TEO	ROTEM	Description	Normal	Abnormality: Cause	Treatment
Reaction Time (R value)	Clotting Time (CT)	Time till commencement of clot formation	5 - 10 min	↑ R value: ↓ factors	FFP prolamine
K value	Clot Formation Time (CFT)	Time to achieve 20 mm clot on assay (representing thrombin-platelet interaction)	1 - 5 min	↑ K/CFT value: ↓ fibrinogen	Cryoprecipitate Fibrinogen
α-angle	α-angle	Rate at which fibrin cross-linking occurs	45 - 75°	↓ α-angle: ↓ fibrinogen	Cryoprecipitate Fibrinogen
Maximum Amplitude (MA)	Maximum Clot Firmness (MCF)	Maximum clot strength	50 - 75 mm	↓ MA/MCF: ↓ platelet count and/or function	Platelets DDAVP
LY-30	Clot Lysis (CL)	Degradation of clot 30 minutes after MA/MCF	0 - 10%	↑ LY-30/CI, ↓ clot breakdown	TXA Amicar

STRATEGIES FOR BLEEDING PREVENTION

There are numerous methods for preventing and controlling bleeding after LT. The physiological balance check, which involves balancing the patient's fluid and electrolyte state, is one of the key tactics. The patient's urine production, serum electrolytes, and the acid-base balance must be constantly monitored to achieve this. Maintaining the balance of these factors is critical in preventing bleeding by decreasing

the danger of hemodilution and maintaining appropriate tissue perfusion.[43,44]

Before beginning the LT operation, the patient's preoperative assessment and optimization are crucial. A thorough analysis of the patient's coagulation status, liver function, and any comorbidities that can raise the risk of bleeding should be included as part of the evaluation process.[45] The use of enzymes to stimulate clot formation is an additional strategy that can be employed. By preventing fibrinolysis and encouraging clot formation, enzymes like tranexamic acid, aminocaproic acid, and epsilon-aminocaproic acid are frequently used to stop bleeding. These enzymes are especially helpful for individuals with underlying coagulopathy or who need massive blood transfusions during the procedure.[46]

It is crucial to have effective intraoperative bleeding control. The surgeon must take the necessary precautions to prevent excessive bleeding during the procedure, including clamping the portal vein and employing hemostatic drugs.[47] Cell-based therapeutics are a new approach to managing and preventing bleeding after LT. These treatments encourage tissue repair and regeneration by utilizing stem cells or progenitor cells. Cell-based therapy has demonstrated the potential in boosting liver regeneration and enhancing the patient's coagulation condition after LT.[48] Upon LT procedure, postoperative coagulation status monitoring should be carefully observed, and if bleeding is detected, appropriate action should be performed.[12,49]

TREATMENT OF BLEEDING FOLLOWING LIVER TRANSPLANTATION

Non-pharmacological approaches

It might be difficult for the medical community to control coagulation and transfusion management during liver transplant surgeries, especially for the anesthesiologist.[50] It has been shown that hemodilution with either regular saline or hydroxyethyl starch (HES) corresponds to a considerable reduction in maximum clot firmness (MCF), which is one of the major factors in managing hemostasis after liver procedures.[51] Restrictive fluid transfusion regimens can also lessen the need for transfusions and intraoperative blood loss. Nevertheless, patients with hepatic failure should not use HES.[50]

It has been demonstrated that maintaining a low central venous pressure (CVP) helps to prevent bleeding, but it may also raise the risk of acute renal failure, severe hypoperfusion, and air embolism. Phlebotomy, a method of lowering CVP during the pre-anhepatic period, was linked to a marked decrease in blood loss.[50,52]

Utilizing modest tidal volumes and avoiding having high positive end-expiratory pressure are two other methods to maintain low CVP and prevent portal congestion.[53] Regarding ideal CVP values throughout the post-anhepatic period, there is minimal research. More complicated procedures that target not only preload but also cardiac output or tissue oxygen delivery may prove to be an intriguing tactic to reduce perioperative blood loss in the era of current hemodynamic monitoring equipment.[50] An important surgical technique to decrease perioperative blood product infusions is intraoperative cell salvage (CS). In a prospective study, CS was linked to cost savings and the avoidance of two RBC unit transfusions per patient.[54] However, because of the debris that is released from rescued erythrocytes, CS can raise the risk of acute respiratory distress syndrome, acute renal failure, or disseminated intravascular coagulopathy.[55,56] Last but not least, if bleeding occurs, the patient may require transfusions of red blood cells, platelets, or fresh frozen plasma to replace lost blood components based on the level of hemorrhage.

Pharmacological approaches

Long-term research has been done on antifibrinolytic drugs to reduce perioperative hemorrhage. According to a Cochrane analysis from 2011, aprotinin, an antifibrinolytic drug, significantly decreased the demand for platelets, cryoprecipitate, fresh frozen plasma (FFP), and red blood cell transfusion compared to a placebo.[57] Additional research comparing various aprotinin dosages with different delivery methods (bolus vs. continuous infusion) has not revealed any variations in the quantity of blood lost during surgery and the requirement for transfusions.[58] Although it was later overturned

in 2012 after a new analysis of the trial's final results on the risk of hepatic artery thrombosis, venous thromboembolism, and mortality, the use of aprotinin was initially prohibited from European markets in 2007.[50]

Before beginning the transfusion operation, there are many factors to consider. There is widespread agreement that packed red cell (PRC) transfusion is not routinely recommended for hemoglobin (Hb) levels greater than 10 g/dL and that RBC transfusion should be contemplated when Hb is 7 to 8 g/dL, according to the needs of the patient. The purpose of red cell unit delivery is to keep hemoglobin (Hb) levels at 8 g%.[59,60] FFP should be given when there are indications of coagulopathy, such as an increased international normalized ratio (INR), prolonged aPTT, or enhanced CT in viscoelastic tests in the presence of clinically substantial bleeding. Despite having a relatively modest fibrinogen level (100-150 mg/dL), FFP is often used for fibrinogen replacement. Cryoprecipitate should also be given when there is clinically substantial bleeding. Fibrinogen concentrate and cryoprecipitate can be administered when fibrinogen is <100 mg/dL, ROTEM EXTEM maximum clot firmness (MCF) <35 mm + ROTEM FIBTEM MCF <8 mm in the absence of diffuse clinical bleeding, or ROTEM EXTEM MCF <45 mm + FIBTEM MCF <8 mm in the presence of diffuse clinical bleeding. As a result of volume overload, prothrombin complex concentrate might be started when ROTEM EXTEM CT > 80 s. When ROTEM EXTEM MCF < 35 mm + ROTEM FIBTEM MCF > 8 mm, platelets may be administered.[61]

The routine use of rFVIIa to reduce perioperative blood loss and the requirement for transfusions during LT have been studied in randomized controlled trials (RCTs). Data from LT recipients did not show that this medication had any impact on the risk of thromboembolic events, graft failure, or other severe adverse effects, despite concerns that employing rFVIIa could increase the risk of arterial thrombosis.[62] The use of rFVIIa as a preventative measure during LT raises the possibility that it could be employed as "rescue therapy" to reduce massive hemorrhage.[53]

Currently, patients receiving long-term therapy with an INR > 1.5 frequently use prothrombin complex concentrated (PCC). Cirrhotic individuals frequently show quantitative and qualitative fibrinogen deficits, according to viscoelastic testing.[63] According to the ROTEM examination, up to 45% of LT patients demanded a fibrinogen concentrate shot to increase clot stiffness. As they include standard doses of fibrinogen and hold a lower risk of pathogen and immune-mediated issues, fibrinogen concentrates are now preferred over cryoprecipitate for managing the quantitative functional deficiencies of fibrinogen in bleeding clients, unless the former is not available. [64]

There are a number of methods in addition to those already mentioned that can be used to assist patients who are bleeding during LT. Endovascular embolization of hepatic artery, which involves injecting a chemical into the blood vessels to block the flow of blood and control bleeding, can also be used. Surgery, such as hepatic artery ligation, may be required to stop the bleeding and repair any damaged blood vessels.[65,66] Additionally, by encouraging the clotting process, hemostatic drugs including topical thrombin, fibrin glue, and oxidized regenerated cellulose can be utilized to stop bleeding.[67,68]

POSTOPERATIVE PROBLEMS: BLEEDING AND THROMBOSIS

Early surgical problems after liver transplantation include graft nonfunction, hemorrhage, hepatic artery thrombosis (HAT), and portal vein thrombosis (PVT). The IRI syndrome is presumably connected to PNF, an uncommon but severe occurrence with an unclear origin. HAT is found in 5%-18% of juvenile transplant recipients, which is between three and four times more prevalent than in adult beneficiaries of transplants. PVT affects 5%–10% of recipients and is more common in children who received biliary atresia transplants. It can result in progressive portal hypertension problems.[27]

A study discovered that there are no coagulation function defects from the monitoring of biochemical markers of coagulation dysfunction (PT, aPTT, fibrinogen, thrombin time, and platelet count) during the first seven days following LT.[69] It was discovered that coagulation activity recovered quickly from day 1 and

reached its optimum level by days 21–28.[70] However, a number of therapeutic modalities, including FFP (15 mL/kg) and intravenous unfractionated heparin (10 IU/kg per hour), can be used in the event of bleeding and coagulation problems to lessen thrombotic and bleeding consequences. Therefore, it is crucial to create clinical recommendations for the treatment of coagulation during surgery for this specific pediatric population.[27]

CONCLUSION

ESLD is an advanced medical condition with the only definitive treatment for ESLD is liver transplantation. However, there are risks connected to this operation, such as the chance of bleeding due to coagulation issues and hypercoagulability. Monitoring coagulation status and making required medication adjustments are crucial for controlling bleeding following LT. The usage of blood components like fresh frozen plasma or platelets, as well as the injection of procoagulant medications, can help to treat hemorrhage. In life-threatening cases, endovascular embolization or surgical intervention may be required to stop the bleeding. All of these steps are necessary to avoid future problems and enhance patient outcomes.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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