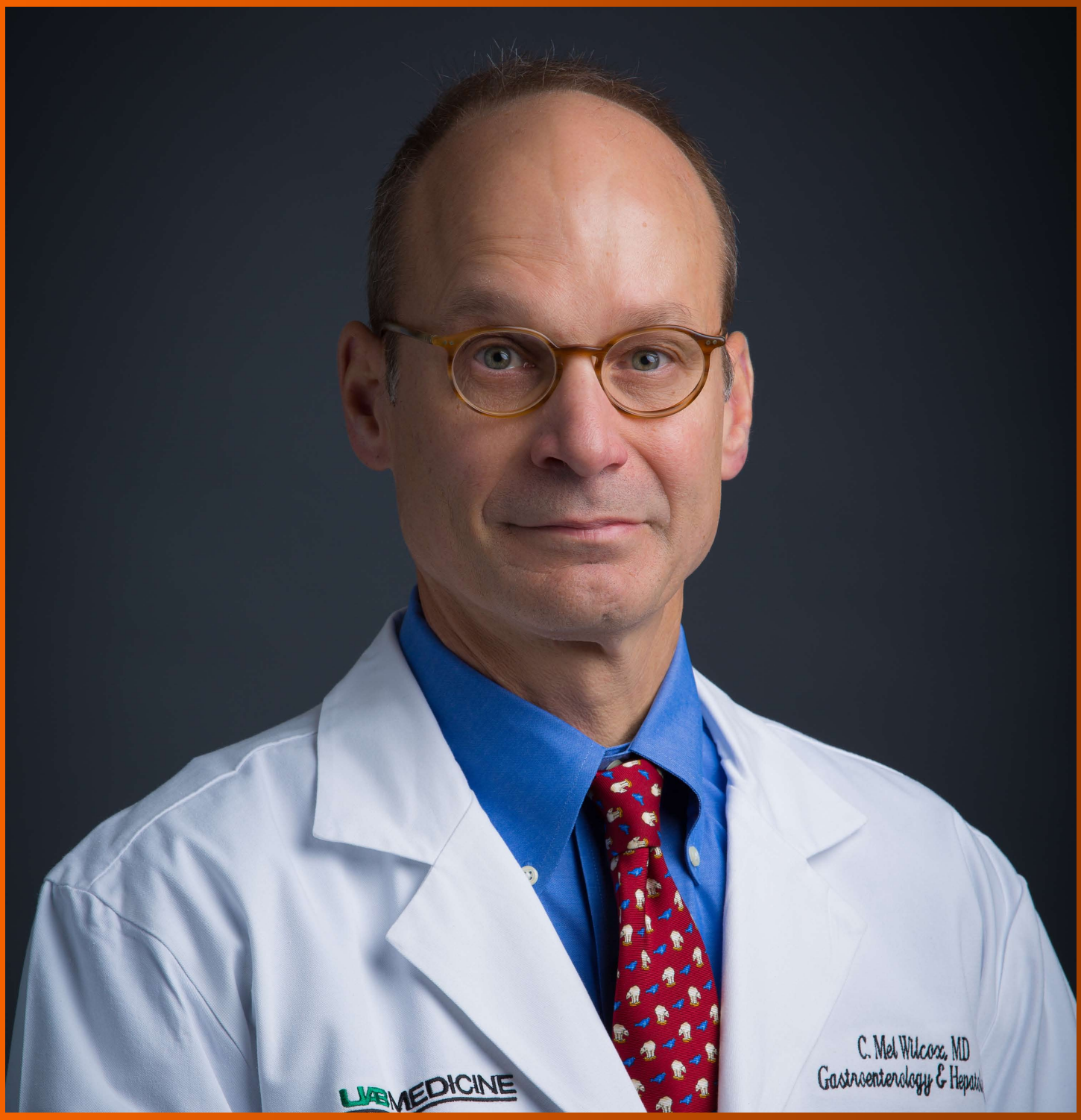
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2018 July 21; 24(27): 2921-3054



Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 24 Number 27 July 21, 2018

EDITORIAL

2921 Indocyanine green-based fluorescence imaging in visceral and hepatobiliary and pancreatic surgery: State of the art and future directions
Baiocchi GL, Diana M, Boni L

REVIEW

2931 Perioperative thromboprophylaxis in liver transplant patients
De Pietri L, Montalti R, Nicolini D, Troisi RI, Moccheggiani F, Vivarelli M

2949 MicroRNAs in the prognosis and therapy of colorectal cancer: From bench to bedside
To KK, Tong CW, Wu M, Cho WC

2974 Pathogenesis of non-alcoholic fatty liver disease in children and adolescence: From "two hit theory" to "multiple hit model"
Fang YL, Chen H, Wang CL, Liang L

MINIREVIEWS

2984 Role of aldehyde dehydrogenase 2 in ischemia reperfusion injury: An update
Panisello-Roselló A, Lopez A, Folch-Puy E, Carbonell T, Rolo A, Palmeira C, Adam R, Net M, Roselló-Catafau J

2995 Multiparametric analysis of colorectal cancer immune responses
Leman JK, Sandford SK, Rhodes JL, Kemp RA

ORIGINAL ARTICLE

Retrospective Study

3006 Push *vs* pull method for endoscopic ultrasound-guided fine needle aspiration of pancreatic head lesions: Propensity score matching analysis
Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Sato Y, Irie H, Watanabe K, Nakamura J, Kikuchi H, Waragai Y, Takasumi M, Hashimoto M, Hashimoto Y, Hikichi T, Ohira H

3013 Liver intravoxel incoherent motion diffusion-weighted imaging for the assessment of hepatic steatosis and fibrosis in children
Shin HJ, Yoon H, Kim MJ, Han SJ, Koh H, Kim S, Lee MJ

Clinical Trials Study

3021 New fecal test for non-invasive *Helicobacter pylori* detection: A diagnostic accuracy study
Iannone A, Giorgio F, Russo F, Riezzo G, Girardi B, Pricci M, Palmer SC, Barone M, Principi M, Strippoli GF, Di Leo A, Ierardi E

Observational Study

3030 Long-term outcomes of endoscopic resection for small (≤ 4.0 cm) gastric gastrointestinal stromal tumors originating from the muscularis propria layer
Zhang Y, Mao XL, Zhou XB, Yang H, Zhu LH, Chen G, Ye LP

SYSTEMATIC REVIEWS

3038 Systematic overview of hepatitis C infection in the Middle East and North Africa
Chaabna K, Cheema S, Abraham A, Alrouh H, Lowenfels AB, Maisonneuve P, Mamtani R

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, C. Mel Wilcox, MD, Doctor, Professor, Division of Gastroenterology and Hepatology, University of Alabama at Birmingham, Birmingham, AL 35294, United States

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORIAL OFFICE
Ze-Mao Gong, Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
July 21, 2018

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Gastroenterology

Submit a Manuscript: http://www.f6publishing.com

World J Gastroenterol 2018 July 21; 24(27): 2931-2948

DOI: 10.3748/wjg.v24.i27.2931

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Perioperative thromboprophylaxis in liver transplant patients

Lesley De Pietri, Roberto Montalti, Daniele Nicolini, Roberto Ivan Troisi, Federico Moccheggiani, Marco Vivarelli

Lesley De Pietri, Division of Anaesthesiology and Intensive Care Unit, Department of General Surgery, AUSL Reggio Emilia-IRCCS, Reggio Emilia 42123, Italy

Roberto Montalti, Daniele Nicolini, Federico Moccheggiani, Marco Vivarelli, Hepatobiliary and Abdominal Transplantation Surgery, Department of Experimental and Clinical Medicine, Polytechnic University of Marche, Ancona 60126, Italy

Roberto Ivan Troisi, Department of General, Hepatobiliary and Liver Transplantation Surgery, Ghent University Hospital Medical School, Ghent 185 3K3 9000, Belgium

Roberto Ivan Troisi, Department of Clinical Medicine, Federico II University Naples, Naples 80138, Italy

ORCID number: Lesley De Pietri (0000-0003-4925-9606); Roberto Montalti (0000-0002-3915-3851); Daniele Nicolini (0000-0002-5477-3346); Roberto Ivan Troisi (0000-0001-6280-810X); Federico Moccheggiani (0000-0002-8833-5360); Marco Vivarelli (0000-0003-0500-9461).

Author contributions: De Pietri L designed the literature review strategy, critically planned the article structure and wrote the paper; Montalti R, Nicolini D, Moccheggiani F, Troisi RI and Vivarelli M critically reviewed the article and contributed to the literature review.

Conflict-of-interest statement: All authors have no conflict of interest.

Manuscript source: Invited manuscript

Correspondence to: Lesley De Pietri, MD, Staff Physician, Division of Anaesthesiology and Intensive Care Unit, Department of General Surgery, AUSL Reggio Emilia-IRCCS, Viale Risorgimento 80, Reggio Emilia 42123, Italy. lesley.depietri@yahoo.it
Telephone: +39-522-296111

Received: March 25, 2018
Peer-review started: March 25, 2018
First decision: April 11, 2018
Revised: May 17, 2018
Accepted: June 22, 2018
Article in press: June 22, 2018
Published online: July 21, 2018

Abstract

Improvements in surgical and anesthetic procedures have increased patient survival after liver transplantation (LT). However, the perioperative period of LT can still be affected by several complications. Among these, thromboembolic complications (intracardiac thrombosis, pulmonary embolism, hepatic artery and portal vein thrombosis) are relatively common causes of increased morbidity and mortality. The benefit of thromboprophylaxis in general surgical patients has already been established, but it is not the standard of care in LT recipients. LT is associated with a high bleeding risk, as it is performed in a setting of already unstable hemostasis. For this reason, the role of routine perioperative prophylactic anticoagulation is usually restricted. However, recent data have shown that the bleeding tendency of cirrhotic patients is not an expression of an acquired bleeding disorder but rather of coexisting factors (portal hypertension, hypervolemia and infections). Furthermore, in cirrhotic patients, the new paradigm of "rebalanced hemostasis" can easily tip towards hypercoagulability because of the recently described enhanced thrombin generation, procoagulant changes in fibrin structure and platelet hyperreactivity. This new coagulation balance, along with improvements in surgical techniques and critical support, has led to a

dramatic reduction in transfusion requirements, and the intraoperative thromboembolic-favoring factors (venous stasis, vessels clamping, surgical injury) have increased the awareness of thrombotic complications and led clinicians to reconsider the limited use of anticoagulants or antiplatelets in the postoperative period of LT.

Key words: Anticoagulation; Liver transplantation; Antiplatelets; Thrombosis; Coagulation; Heparin; Thromboelastography; Thromboprophylaxis; Hepatic artery thrombosis; Portal vein thrombosis

Core tip: The improvements in surgical and anesthetic techniques during liver transplantation (LT) have led to such a reduction in transfusion requirements that bleeding risk is no longer the major concern. The increased knowledge of coagulation balance and the reported incidence of thrombotic complications (hepatic artery and portal vein thrombosis, intracardiac thrombosis, pulmonary embolism) in the LT setting have brought attention to perioperative thromboprophylaxis in an attempt to decrease the morbidity and mortality associated with these complications. The major concern of thromboprophylaxis is the risk of bleeding complications in a setting of already unstable hemostasis. Hence, monitoring its administration and the careful selection of the patients to be treated are of great importance.

De Pietri L, Montalti R, Nicolini D, Troisi RI, Moccheggiani F, Vivarelli M. Perioperative thromboprophylaxis in liver transplant patients. *World J Gastroenterol* 2018; 24(27): 2931-2948 Available from: URL: http://www.wjgnet.com/1007-9327/full/v24/i27/2931.htm DOI: http://dx.doi.org/10.3748/wjg.v24.i27.2931

INTRODUCTION

Cirrhosis has been traditionally conceived as a hypocoagulable condition, and bleeding is a feared complication of any invasive procedure. In patients with end-stage liver disease, significant coagulopathy (as defined by routine coagulation tests) has historically led clinicians to consider cirrhosis to be the prototype of acquired bleeding disorders, thus supporting the common practice of empirically transfusing patients with blood products or prohemostatic agents to correct standard laboratory test values to reduce the risk of bleeding[1,2]. In this review, we underline the concept of rebalanced hemostasis typical of cirrhotic patients (both in patients with cirrhosis and in patients with acute liver failure), as obtained by the parallel declines in pro- and antihemostatic drivers, resulting in a net hemostatic balance[3]. We also discuss the paradoxical pro-thrombotic tendency of cirrhotic patients. The new hemostatic balance, in fact, is thought to be much less stable compared with that of healthy patients and can easily tip it towards bleeding or thrombosis.

Prophylactic anticoagulation represents a routine practice to prevent thromboembolic complications [deep vein thrombosis (DVT) and pulmonary embolism (PE)] that can be potentially life-threatening in the postoperative course. Although the utility of thromboprophylaxis after general surgery has been established beyond doubt, in liver transplantation (LT), this opinion is not uniformly shared and does not represent a routine practice. LT is considered an operation with major bleeding risks. Transplanted livers may have delayed primary function, and coagulation does not improve immediately after transplantation, making hemorrhagic complications and transfusions not uncommon[4,5]. In contrast, although intraoperative thrombotic phenomena are uncommon, they are associated with an elevated mortality (ranging from 45% to 68% for PE and 50% for early hepatic artery thrombosis (HAT) and from 32% to 60% for portal vein thrombosis (PVT))[6-9].

Here, we reviewed the literature assessing thrombotic risks in cirrhotic patients and in the post-transplant period and evaluated whether empirical pharmacological thromboprophylaxis strategies and the use of global hemostasis assays may play a beneficial role in reducing this procedure-related thrombotic complications. We do not cover mechanical prophylaxis (intermittent pneumatic compression) because it must be considered and adopted in all abdominal surgery patients who are at a moderate or high risk for venous thromboembolism (VTE), who are, in turn, at a high risk for major bleeding complications[10].

NEW CONCEPT OF REBALANCED HEMOSTASIS AND THE UTILITY OF STANDARD LABORATORY TESTS

A marked reduction of both procoagulant factors (factors II, V, VII, IX, X, XI, XII), anticoagulant factors (antithrombin III, protein C, and protein S), an increase in von Willebrand factor (vWF) and a reduced level of ADAMTS13, a vWF-cleaving protease, are the specific features of cirrhosis and bring the patient to a new hemostatic balance[11]. vWF performs its hemostatic functions by binding to factor VIII and to constituents of connective tissue and by promoting platelet adhesion to endothelial surfaces and platelet aggregation under high shear stress[11].

Thrombocytopenia, as a consequence of hypersplenism in patients with portal hypertension, abnormal thrombopoietin metabolism, increased platelet destruction mediated by antiplatelet antibodies, and bone marrow suppression caused by alcohol, antiviral and immunosuppressive therapies, is another clinical feature of chronic liver disease[12]. Unless the platelet

Table 1 Balance of antihemostatic and prohemostatic drivers in the cirrhotic patient

	Anti-hemostatic drivers	Pro-hemostatic drivers
Primary hemostasis	Abnormal platelet function	Elevated vWF
	Thrombocytopenia	Reduced ADAMTS 13
	Decreased production of thrombopoietin	Platelet hyperreactivity
Coagulation	Reduced synthesis of factors II, V, VII, IX, X, and XI	Elevated factor VIII
	Vitamin K deficiency	Reduced anticoagulant protein C, protein S, antithrombin III
	Hypo-dysfibrinogenemia	Procoagulant changes in fibrin structure
Fibrinolysis	Low α2-antiplasmin,	Low plasminogen
	factor XIII, and TAFI	High PAI
	Elevated tPA	

vWF: Von Willebrand factor; TAFI: Thrombin-activatable fibrinolysis inhibitor; t-PA: Tissue plasminogen activator; PAI: Plasminogen activator inhibitor; ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.

count is severely low (< 50 × 10^9/L), thrombocytopenia does not represent an increased bleeding risk. Such a low platelet count is usually sufficient to guarantee a normal thrombin generation, and the low number of platelets is compensated by a higher level of vWF, which is responsible for greater platelet adhesion[13,14]. Hyperfibrinolysis is another described feature of end-stage liver disease, but its role in the coagulopathy of cirrhosis is still debated[15].

Elevated tissue plasminogen activator and a deficiency of thrombin-activatable fibrinolysis inhibitor have been associated with laboratory changes typical of hyperfibrinolysis and an increased risk of bleeding[16]. However, cirrhosis has also been associated with reduced fibrinolysis, as shown by the decreased plasminogen and increased plasminogen activator inhibitor. The contrasting results explain the ongoing debate regarding the absence or presence of a hyperfibrinolytic state in patients with liver disease, even if the balance of fibrinolysis is probably restored by the parallel changes in profibrinolytic and antifibrinolytic drivers[17]. The decreased synthesis of both procoagulants and anticoagulants typical of cirrhosis usually restores a normal hemostatic balance (Table 1), which is so fragile that it can easily become unbalanced in a hemorrhagic or prothrombotic sense, depending on the presence of renal failure, infection, or upper gastrointestinal bleeding. The complexity of hemostatic balance in end-stage liver disease comes from the fact that a patient with cirrhosis and sepsis can be equally at risk for thrombosis, as a result of inflammation[18], and for bleeding, as a result of the release of anticoagulant endogenous heparinoids[19]. The new equilibrium described in stable patients with cirrhosis makes bleeding episodes related more to portal hypertension and hypervolemia than to defective hemostasis.

Despite this "balanced" hemostatic condition, cirrhosis results in the prolongation of standard coagulation tests, which usually do not analyze the complex interplay between pro- and anticoagulants and thus do not provide an accurate evaluation of the alteration in the *in vivo* hemostatic balance[11,20]. Prothrombin time (PT), activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) provide only a measure of procoagulant factors and are insensitive to the plasma levels of anticoagulant factors, so they are unreliable to depict the hemostatic status of patients with end-stage liver disease. The lack of reliability of standard plasma coagulation tests, as underlined in the Baveno VI guidelines[21], comes from the fact they are performed without thrombomodulin addition, which is the main protein C activator, and they only detect the first 5% of whole thrombin formation. The normal to increased thrombin generation shown by thrombomodulin-modified thrombin generation tests has further confirmed the unreliability of standard coagulation tests. Therefore, PT, aPTT and INR are untrustworthy in predicting bleeding risk or thrombotic risk and guiding perioperative hemostatic therapy[22]. Platelet number also poorly represents hemostatic capacity in cirrhotic patients, and thrombocytopenia is usually balanced by a marked increase in the plasma level of von Willebrand factor[13]. The defects in antifibrinolytic proteins balanced by decreased plasminogen[23], the decreased fibrinogen partially balanced by prothrombotic changes in the structure of the fibrin clot[24], and the increased factor VIII and reduced antithrombin and protein C constitute the basis for the recently recognized normo- or hypercoagulable state of cirrhosis, with a consequent risk of thromboembolic events.

THROMBOTIC COMPLICATIONS IN MEDICAL CIRRHOTIC PATIENTS AND POTENTIAL ROLE FOR ANTICOAGULATION

Traditionally, the endogenous coagulopathy and thrombocytopenia that characterize cirrhosis made bleeding complications the major concern while managing these patients. The increased knowledge of their coagulation balance and the reported incidence of thrombotic complications in end-stage liver disease patients have recently made the thrombotic risk more feared than

bleeding complications. In 2006, Northup *et al*[25] found that approximately 0.5% of all admissions involving cirrhosis patients resulted in a new thromboembolic event. Thus, despite the endogenous coagulopathy of cirrhosis, some patients experience venous thromboembolism, such as DVT or PE. Subsequent studies noted that liver cirrhosis per se represents a risk factor for VTE and that all the conditions that can favor any thrombotic complication are frequent in patients with end-stage liver disease. Platelet hyperreactivity, normal or enhanced thrombin generation, as shown by the thrombin generation test, endothelial dysfunction, hyperdynamic circulation, which can bring to circulation stasis, and the reduced mobility of the fragile cirrhotic patient are recognized prothrombotic conditions. Other authors have shown that this thrombophilia seems to worsen as the liver disease progresses, exposing the cirrhotic patients with more severe disease to a greater risk for VTE[26]. Hypoalbuminemia, as an expression of the severity of liver disease and the degree of portal hypertension, has been associated with an increased rate of VTE[27].

Recently, Ambrosino *et al*[28] conducted a systematic review and meta-analysis to evaluate the risk of VTE associated with cirrhosis, which was 3.7%. They confirmed a significantly increased VTE risk in 695012 cirrhotic patients compared with 1494660 non-cirrhotic controls (OR: 1.703; 95%CI: 1.333, 2.175; $P < 0.0001$). In particular, patients with cirrhosis experienced an increased prevalence of DVT compared to non-cirrhotic subjects. In contrast, more heterogeneity among studies has been found for PE risk, even if it has been shown to be higher in the cirrhotic population.

PVT, which is rare in the general population but relatively frequent in patients with cirrhosis, is another typical feature of chronic liver disease. Its prevalence increases with the severity of liver disease, ranging from 0.6% to 26%[29]. While patients with compensated cirrhosis are rarely affected, PVT is frequently detected in advanced stages, increasing to 25% in LT candidates and to 35% in cirrhotic patients with hepatocellular carcinoma (HCC)[30]. The main risk factors for PVT are the same as those described for thromboembolic disease in general: hypercoagulability, endothelial lesions, reduced portal blood flow and, when HCC is present, the neoplastic invasion of the portal vein. Because of the high prevalence of this thrombotic complication and the possible repercussions on LT[31], the available data suggest that prophylactic PVT treatment may be indicated in cirrhotic patients awaiting LT or after hepatic resection, even if this medical practice has not yet been included in international guidelines due to a lack of randomized controlled trials[32,33]. According to the Baveno VI consensus, anticoagulation should be considered in potential LT candidates with thrombosis of the main portal trunk or progressive PVT, with the goal of facilitating LT and reducing post-transplant morbidity and mortality[21].

THROMBOEMBOLIC EVENTS IN SURGICAL LIVER TRANSPLANT PATIENTS

Traditionally, perioperative bleeding complications, attributed to the endogenous coagulopathy and thrombocytopenia, represented the major concern during LT. In recent years, thanks to improvements in surgical techniques and anesthetic care, hemorrhagic complications have become less frequent, making transplants without intraoperative transfusion more common. The awareness of the new hemostatic balance that characterizes cirrhotic patients, together with the reduced bleeding complications during surgery, has redirected the attention to perioperative thrombotic complications, making surgeons and anesthetists more aware of the possibility of systemic venous or arterial thrombotic events. Recently, the idea of the occurrence of thrombotic complications associated with liver transplant as a consequence of an uncontrolled activation of coagulation rather than of surgical complications has become more common. Usually, thrombotic events associated with LT can be divided into systemic thrombotic complications and regional vascular events (*i.e.*, hepatic artery, portal vein, hepatic vein thrombosis). The incidence of early HAT, which may result in graft loss if arterial flow is not restored in the first 24 h after its occurrence, is approximately 3%-5% in adult patients, and the PVT incidence is approximately 2% in LT, with a very high mortality rate, ranging from 65% to 75%[34,35]. Hepatic vein thrombosis is instead considered a technical complication in case of a size mismatch of the grafts and in twisting and split liver transplant (*i.e.*, reconstruction of the middle hepatic vein in extended right splits or insufficient drainage of the anterolateral sector in full-right grafts). Such dangerous complications can have surgical causes (for HAT: Difficult and prolonged arterial reconstruction, kinking of the artery, prolonged surgical time, prolonged cold or warmed ischemia times, the use of an aortic jump graft[36]; for PVT: Prior PVT or splenectomy, small portal vein size, use of venous conduits, insufficient portal flow due to large collaterals or systemic shunts[34]). Nevertheless, there are increasing data suggesting that changes in the hemostatic system (genetic factors, end-stage renal disease, diabetes, and history of prior DVT/PE) as well as intra- and postoperative blood products transfusion (increased transfusions of cryoprecipitate or fresh-frozen plasma and factor VII) may contribute to the development of HAT[37,38]. Interestingly Stine *et al*[39] have recently showed that pre-transplant PVT is associated with increased risk of early graft loss from HAT suggesting that hypercoagulability, besides surgical factors, could be involved in the post-transplant HAT occurrence[39].

DVT is a rare post-transplant complication that has a reported incidence between 3.5% and 8.6% in recent series[40]. Intraoperative systemic thrombotic complications, which mainly occur as acute PE or intracardiac right atrial thrombosis, are other dangerous events described in the perioperative period whose incidence of approximately 1%-4% seems to be higher than that reported in other surgical operations[41,42]. VTE is a well-documented postoperative complication, and PE is the most common cause of preventable death in surgical patients. Several risk factors for the development of PE during LT have been suggested, including vascular clamping, veno-venous bypass, central venous catheters, anti-fibrinolytic drugs, tissue injury/ischemia, venous stasis and etiology of liver disease.

In recent years, it has been shown that the cirrhotic patients are in a new hemostatic balance that undergoes new changes during liver transplant. During this surgical procedure, vWF remains elevated[43], and its functional capacity increases during surgery, probably due to an enhanced release of vWF from the activated endothelial cells. In association with that finding, the plasmatic concentration of ADMTS13-cleaving protease decreases during transplant, leading to an imbalance between vWF and ADMATS13, which is possibly responsible for the thrombotic risk.

Thrombocytopenia, which is typical of end-stage liver disease and potentially worsened by hemodilution and consumption during liver transplant, is not associated with a reduction in platelet function[44]. The preserved platelet adhesion, together with an imbalanced vWF/ADAMTS13 ratio, could somehow explain the increased incidence of thrombotic complications in the liver transplant perioperative period[45].

For secondary hemostasis, in cirrhotic patients, the parallel decline in pro- and anticoagulation proteins leads to a new balance characterized by normal thrombin generation. In the perioperative liver transplant period, the reduction of protein C, protein S, antithrombin III, and heparin cofactor II and the persistent increase in factor VIII lead to increased thrombin generation and to a hypercoagulable status[45]. During surgical procedures, the fibrinolytic system, which is normally in equilibrium in cirrhotic patients, can move temporarily towards hyperfibrinolysis in the anhepatic phase and after reperfusion[46]. However, at the end of surgery, a hypofibrinolytic condition, related to a massive increase in plasminogen activator inhibitor type 1 (PAI-1), develops and usually lasts up to 5 d after surgery[47]. Even if the reduction in the fibrinolytic activity can justify the occurrence of some thrombotic complication, such a causal relation has not been demonstrated by scientific works. The recent clinical literature seems to underline the role of the perioperative hypercoagulable status in the genesis of thrombotic complications such as HAT, PVT and other systemic thrombotic events.

Although perioperative bleeding complications occur more often than thrombotic ones, postoperative thromboses are associated with high morbidity and, in some cases, with mortality. Independent of the real origin of the prothrombotic status observed in cirrhotic patients who undergo LT, more efforts on the prevention of such complications by means of different prophylactic antithrombotic therapies are necessary. A prophylactic antithrombotic treatment to prevent these complications may be clinically relevant, and because of the fear of bleeding complications in the postoperative period, it could be useful to have an instrument that can reflect the coagulation status of the transplanted patient better than the routine laboratory tests can, which have been unreliable in reflecting the *in vivo* physiology.

HEMOSTATIC STATUS IN THE TRANSPLANTED PATIENT AND DIAGNOSTIC TOOLS

Standard coagulation tests

Standard coagulation tests have long been the standard laboratory indicators of patients' coagulation status. According to the cell-based model of hemostasis, these tests do not account for the important interactions between platelets, clotting factors, and other cellular components in the generation of thrombin or for the balance between coagulation and fibrinolysis. Furthermore, PT and PTT give only one piece of information, *i.e.*, whether the thrombin generation has started, but they give no information of what occurs afterwards.

Viscoelastic tests

Because of the limits of conventional coagulation tests in recognizing significant coagulopathies or guiding transfusion, in recent years the viscoelastic tests has gained increasing importance. Viscoelastic tests give an "in vitro" picture of the growth of the clot and a measure of its stability until its physiological or pathological lysis. These viscoelastic coagulation tests performed bedside, including ROTEM® and TEG®, produce faster and more reliable results than conventional tests do. These two commercial devices function by slightly different mechanisms. The thromboelastometer (ROTEM-analyzer, TEM International, Munich, Germany) uses a fixed cup with a pin that rotates, while the thrombelastographer (TEG-analyzer, Haemonetics Corp., Braintree, MA, United States) uses a fixed pin and a rotating cup[48,49].

TEG and rotational ROTEM are technologies that were previously applied in different surgical fields and are now applied to cirrhosis physiology. A more dynamic and targeted approach to the overall hemostatic process is at the basis of their success. They provide visual information on the coagulation process in terms

of maximal fibrin clot formation, fibrinolysis and tendency to hypercoagulability. These characteristics make these tests ideal for a rapid diagnosis of the type of coagulopathy and for an appropriate (and rational) choice of the therapeutic option in different fields, such as trauma care, cardiac surgery and LT[50]. Several studies have evaluated the effect of using TEG and ROTEM during LT on perioperative blood product transfusions, suggesting that a transfusion algorithm based on viscoelastic tests leads to reduced transfusions, but no survival benefit has been observed to date[51].

Actually, recent studies have noted that bleeding is no more the unique feared risk in liver cirrhosis. In the setting of liver surgery, several risk factors in addition to those previously described (vascular clamping, veno-venous bypass, central venous catheters, anti-fibrinolytic drugs, tissue injury/ischemia, venous stasis, etiology of liver disease, endothelial damages, ischemia time and vWF/ADAMT13 ratio imbalance) can increase the probability of thrombotic complications.

End-stage liver disease per se is a risk factor for VTE, and liver transplant surgery can improve the thrombotic condition. When dealing with cirrhotic patients, a test that could give information on hemorrhagic risk and the presence of normal clot stability or on the tendency to hypercoagulability would offer physicians an indication for prophylactic treatment without creating too much fear of the bleeding complications often associated with liver transplant. In the setting of liver disease and liver surgery, conventional coagulation tests give no or wrong information about hemostatic conditions, indicating hypocoagulability; in contrast, global viscoelastic tests show an enhanced hemostatic capacity or hypercoagulability.

TEG and ROTEM are seemingly superior tests of coagulation function in cirrhotic patients undergoing LT compared with traditional measures, but their capacity to recognize hypercoagulation status has yet to be demonstrated beyond much doubt.

In surgical settings, the study by Hincker and colleagues showed the encouraging results that ROTEM can predict thrombotic complications after major non-cardiac surgery[52]. Similarly, Kashuk and colleagues demonstrated that the presence of hypercoagulability identified by r-TEG is predictive of thromboembolic events in surgical patients[53]. When comparing TEG to INR in living-donor LT, TEG has been a useful tool to monitor for hypercoagulability in the perioperative period among liver donors, detecting a hypercoagulable state in some patients in spite of an elevated PT-INR[54].

Mallet *et al*[55] reported that several of the 124 liver recipients with end-stage liver disease presented with or developed a hypercoagulable thromboelastogram during liver transplant. Nevertheless, the 6 patients who developed early HAT had some TEG signs of hypercoagulability (increased cloth strength, high G, or shortened reaction time), though it was not clear what kind of influence these alterations could have on thrombotic complication. The authors also showed that standard laboratory tests did not succeed in diagnosing any signs of hypercoagulability. Although hypercoagulability on a viscoelastic device can be associated with an increased risk of thromboembolic events in different surgical fields, trauma setting and critical care[53,56,57], the same association in cirrhotic patients seems more difficult to demonstrate. In these patients, the definition of hypercoagulability based on viscoelastic parameters is not unique, and it has included a shortening of reaction time (R time), an increase in maximal amplitude (MA), an increase in net clot strength (G), or a combination of these parameters. However, emerging evidence suggests that hypercoagulability detected by ROTEM or TEG can increase the probability of venous or arterial thrombotic complications in certain patients, such as those who undergo liver transplant. Lerner *et al*[58], in a review of 27 case reports of thromboembolic events during LT, showed that TEG profiles were hypercoagulable in more than 70% of cases. The study by Zanetto and colleagues showed that in cirrhotic patients with hepatocellular carcinoma, thromboelastometry could detect hypercoagulability, as identified by the presence of a shorter clotting time and higher maximum clot firmness, which was associated with PVT presence. In particular, an increased baseline MCF FIBTEM (> 25 mm) was associated with a 5-fold higher risk of developing PVT in cirrhotic Child A patients[59]. Recently, Zahr and colleagues analyzed the native procoagulant state of 828 LT recipients by using pre-transplant thromboelastographic data to identify risk factors for early HAT and found that the MA value was significantly higher in patients diagnosed with early HAT compared with those who were not. Specifically, an MA value on preoperative TEG of 65 mm or greater was recorded in a total of 7% of patients who went on to develop early HAT (hazard ratio = 5.28; 95% CI: 2.10-12.29; $P < 0.001$), whereas only 1.2% of patients with an MA less than 65 mm experienced this complication. The authors concluded that preoperative TEG may reliably identify group of recipients at greater risk of developing early HAT[60]. The use of viscoelastic tests in detecting any hypercoagulability condition during liver transplant seems helpful in better managing blood product transfusion or, hypothetically, prophylactic therapy, but it remains unclear whether these tests during the course of the surgery would be of additional outcome benefit, and several doubts remain about the reliability of their measures. Compared with the thrombin generation test (TGT), ROTEM and TEG may not be appropriate for hemostasis assessment in patients with liver cirrhosis, and it could lead to the unnecessary transfusion of fresh-frozen plasma or to the wrong administration of a thromboprophylactic drug. Even though Blasi *et al*[61]

reported that "parameters from the first derivative of the ROTEM are similar to the thrombin generation assay, which is considered the gold standard marker of hyper/hypocoagulability", several papers underline the lack of correlation between the ROTEM and TGT results. Lentschener and colleagues showed that while thromboelastometry detected a hypocoagulable profile in decompensated cirrhotic patients, TGT showed a normal to increased thrombin generation, suggesting a preserved hemostasis and/or a procoagulant state[62].

In addition to the non-uniformity of results between thromboelastography and TGT, non-uniformity has been recorded within an individual test (ROTEM or TEG). Some of the discrepancies can be partially explained by the differences in test methods, the activators used and the lack of viscoelastic test reference ranges for cirrhotic patients. The current habit to define hypo- or hypercoagulability by referring to reference ranges obtained from healthy individuals may not provide a reliable estimation of the coagulation status and bleeding risks of cirrhotics[63]. Other limitations of the use of ROTEM and TEG need to be considered when analyzing the information they give. Platelet dysfunction, either drug-induced or inherited, is not detected. These devices are insensitive to the effects of vWF and factor XIII[49,64,65], and they lack activation of the anticoagulant protein C system. Other shortcomings of TEG and ROTEM are the lack of adequate standardization, low reproducibility of the results and sensitivity to preanalytic variables[66,67].

Thrombin generation test

TGT is a promising laboratory tool for investigating hemorrhagic coagulopathies, predicting the risk of recurrent VTE after a first event, and monitoring patients on parenteral or oral anticoagulants[68]. In contrast to TEG and ROTEM, TGT can be performed with or without thrombomodulin, thus allowing us to analyze the natural anticoagulant protein C pathway. Furthermore, TGT offers more information on the hemostatic capacity in total because in contrast to viscoelastic tests, it assesses not only fibrin formation but the generation of thrombin, which does not stop when the fibrin clot has been generated[69]. For this reason, TGT best mimics the *in vivo* balance of pro- and anticoagulant proteins in plasma and the dynamics of thrombin generated *in vivo*[70].

TGT measures specific parameters such as the lag-time (time to start), the time to peak, the peak height, and the endogenous thrombin potential[69], so when used to analyze cirrhotic patients, it has shown a preserved or even increased thrombin generation, indicating a normal or even increased coagulation capacity, while ROTEM, performed in the absence of thrombomodulin, has shown hypocoagulation in proportion to the level of liver impairment[62].

Although TGT seems to better describe the interactions between pro- and anticoagulant factors in the hemostatic process of patients with end-stage liver disease, this test is performed in platelet-poor plasma and/or platelet-rich plasma, which requires time to prepare and makes this method unsuitable for quick diagnosis and therefore impractical in a routine clinical setting.

Similar to TEG and ROTEM, this assay is not sufficiently standardized for broad clinical use, and the large variance of the preanalytic variables and the lack of standardized reference ranges prevent its routine clinical use[68]. Thrombin generation assays, although they are not readily available today, could provide a more effective tool for assessing the hemostatic system in patients with cirrhosis, but until further studies are performed, viscoelastic tests could be helpful for the clinical conditions associated with increased thrombotic risks by avoiding the overcorrection of the coagulation defects detected.

ROLE OF THROMBOPROPHYLAXIS

Review methodology

A systematic literature search was performed independently by two of the authors (LDP and RM) using PubMed, and the Cochrane Library Central. The search was limited to humans and articles reported in the English language. No restriction was set regarding the type of publication, date or publication status. Participants of adult age and any sex who underwent living transplantation or living donor liver transplantation procedures were considered. The search strategy was based on different combinations of words for each database. For the PubMed database, the following combination was used: ("liver transplantation" OR "liver transplant" OR "hepatic transplantation" OR "hepatic transplant") AND ("thromboprophylaxis" or "anticoagulation" or"antiplatelets" or "antithrombotic therapy" or "antithrombotic prophylaxis" or "prophylactic anticoagulation" or "anticoagulants" or "aspirin" or "heparin").

The same key words were inserted in the search manager fields of the Cochrane Library Central. The search was broadened by extensive cross-checking of reference lists of all retrieved articles fulfilling inclusion criteria. For all databases, the last search was run on March 28, 2018. The same two authors independently screened the title and abstract of the primary studies that were identified in the electronic search. The following inclusion criteria were set for inclusion in this systematic review: (1) studies reporting a thromboprophylactic therapy in liver transplant procedures; (2) studies reporting a description of the anticoagulation or antiplatelet therapy performed in liver transplant recipients; and (3) if more than one study was reported by the same institute, only the most recent or the highest quality study was included.

The following exclusion criteria were set: (1) letters, comments and case reports; and (2) studies where it was impossible to retrieve or calculate data of interest.

The same two authors extracted the following main data: (1) first author, year of publication and study type; (2) number and characteristics of patients; (3) effectiveness of the thromboprophylaxis performed in term of portal vein thrombosis, hepatic artery thrombosis, deep vein thrombosis and pulmonary embolism; and (4) complications of thromboprophylaxis. Bias of the individual studies was categorized based on study design. All relevant texts, tables and figures were reviewed for data extraction. Discrepancies between the two reviewers were resolved by consensus discussion.

The literature search yielded 634 articles; after the removal of all the articles that did not reflect the inclusion and exclusion criteria, a total of 11 articles[62,71-79] published between 1997 and 2018 were included in this systematic review. Three studies were prospective[71,76,80], only one was a prospective case control study[75] while all the others were retrospective[61,72,74] and four of these had control group[73,77-79]; No papers reported multicentric data. All these studies included a total of 5192 patients (adult and children).

Description of the studies

Despite the altered coagulation tests and thrombocytopenia, patients with end-stage liver disease are at a risk for thrombosis[28]. Several authors suggested that routine thromboprophylaxis should therefore not be withheld from hospitalized patients with liver disease[81] unless risk factors for bleeding are present. Recent advances in the understanding of the coagulopathy in chronic liver disease have provided strong support for anticoagulation as a new therapeutic paradigm for patients with cirrhosis, which would be able to decrease the progression of the liver disease[81].

Although the incidence of venous thrombosis after LT is similar to that reported in other types of major surgery, the fact that these complications occur despite hypocoagulable routine laboratory tests in the first postoperative days indicates that these routine tests probably do not reflect the *in vivo* physiology. The lack of reliable laboratory tests and the contraindications to thromboprophylaxis in cases of high hemorrhagic risk, such as that recognized in LT, make the management of anticoagulants complex in this surgical setting. After LT, patients may be hypercoagulable because of an imbalance between coagulation and fibrinolytic mechanisms, tipping towards a prothrombotic state in the early postoperative phase[82]. It has been established as well that after LT and partial hepatectomy, patients are hypercoagulable because of enhanced thrombin generating capacity, despite prolongations in the PT[83-85]. Furthermore, postoperative immunosuppressive drugs may play a role in increasing platelet aggregation and thrombogenicity[86]. However, usually physicians find several difficulties in administering thromboprophylaxis because they do not know if, in the postoperative period, the coagulopathy persists or the coagulation balance reverts to normality. In the light of the above mentioned observation thromboprophylaxis should not be withheld on basis of post-operative prolonged PT values, as in reality coagulation is hyperactive and standard coagulation test are not truly representative of the real coagulation status in these patients. Other difficulties come from the lack of effective predictors of VTE. INR, MELD score and platelet number have been unreliable to predict thromboembolic complications[25]. Due to the risks of bleeding and coagulopathy in the postoperative LT period, antithrombotic prophylaxis to prevent VTE is not routinely used, and no consensus exists.

Recently, Mukerji and colleagues advised delaying anticoagulation until the post-transplant INR was above 1.5 to 2.0 and the platelet count was below 50000[9]. Similarly, Blasi and colleagues suggested administering thromboprophylaxis with low-molecular-weight heparin to patients with Child A cirrhosis and in patients who undergo intraoperative thrombectomy, avoiding its administration if the platelet count is under 30×10^9/L or in cases of significant intraoperative blood loss[61].

Even if thromboprophylaxis in the early postoperative period of cadaveric liver transplant recipients is not routinely administered and the reports on the usage of heparin are very limited, more surgeons have begun to implement thromboprophylaxis therapy to reduce the risk of vessel thrombosis (Table 2). Most liver transplant centers have developed their own protocols for heparin infusion and the monitoring of its activity, even though bleeding remains the most feared complication associated with anticoagulation therapy, especially in cases of delayed graft function and marginal graft. For instance, Kaneko *et al*[71] reported a high incidence (9%) of surgical revision for hemorrhagic complications in their living related liver recipients who received unfractionated heparin (UFH). They suggested that the dose of heparin should be adjusted to maintain activated clotting time (ACT) levels lower than the previously settled ones during the early postoperative period. Mori *et al*[80] declared that their basic protocol after living donor LT for the patients who underwent portal reconstruction for PVT did not include anticoagulation therapy. Only patients with good coagulation (PT-INR < 1.5) or slow portal flow were administered intravenous heparin at the dose of 5 U/kg/h during the first week after the LT and only then shifted to warfarin[80]. Similarly, Stange and colleagues suggested to administer low-dose heparin as a continuous infusion of 5.000 IE over 24 h, beginning 6 h postoperatively, for 14 d only in case of split-liver transplantation or complex arterial reconstruction[72].

In contrast to Kaneko and Mori, Yip and colleagues[73] implemented a standardized prophylactic regimen in LT recipients with subcutaneous heparin

Table 2 Different thromboprophylaxis protocols for postoperative arterial and venous thrombosis in liver transplant patients

Authors	Type of study	Drug used	Target population	Number Pts	PVT	HAT	Bleeding	Observations
Blasi 2016[61]	Retrospective study No controls	Enoxaparin not routinely, unless intraoperative. thrombectomy or the patient was under anticoagulant treatment before LT. No thromboprophylaxis if the platelets are under 30 × 10^9/L.	Adult LT	328	8 (2.4%)	NA	Not reported	5/8 patients with PVT did not receive prophylaxis, and the other 3 received it days after LT or in only a few doses
Kaneko 2005[71]	Prospective study No controls	Dalteparin administration adjusted with reference to the ACT (130-160 s)	Adult Living-donor LT	128	1 PVT (0.78%) and 1 (0.78%) PVT + HAT	2 HAT (1.5%) and 1 HAT + PVT (0.78%)	11 (8.5%) surgical revisions and 8 (6.25%) patients with hemorrhages complications treated conservatively	High hemorrhage complication rate in this series indicates that a lower target ACT range may be preferable in the second post-operative week.
Gad 2016[74]	Retrospective study No controls	Heparin infusion up to 180-200 units/kg/day adjusted with reference to the ACT (target levels, 180-200 s) and/or the aPTT (target levels, 50-70 s).	Adult and pediatric living-donor LT	186	5 (2.3%)	4 HAT (1.8%) 4 HAT and PVT (1.8%)	4 (1.8%)	Pre-LT PVT may deserve more intensive anticoagulation therapy
Sugawara 2002[76]	Prospective study No Controls	LMWH, ATIII, prostaglandin E1 (0.01 g/kg/h) and a protease inhibitor	Adult Living-donor LT	172	4 (2.3%) both PVT + HAT	7 (4.0%)	Not considered	The authors' strategy against HAT is aimed to correct the imbalance between the coagulation and anticoagulation systems
Mori 2017[80]	Prospective study No controls	Heparin infusion at the dose of 5 U/kg/h during the first week after LT	Adult Living-donor LT	282 total patients; 48 patients with pre-existing PVT; number of patient with thromboprophylaxis not cited	8 (17%)	NA	Not considered	The basic protocol after LDLT does not provide anticoagulant therapy. Only patients with good coagulation (INR) < 1.5 or slow portal flow (velocity < 10 cm/s) and intraoperative portal reconstruction for PVT were administered intravenous heparin. The aim of this study was to determine the risk factors that influence the incidence of DVT/PE and the effectiveness of prophylaxis
Yip 2016[73]	Retrospective case control study	Subcutaneous heparin (5000 U) every 8 h	Adult LT	999 total patients; 288 patients with thromboprophylaxis from 2011	Not considered	Not considered	NA	The aim of this study was to determine the risk factors that influence the incidence of DVT/PE and the effectiveness of prophylaxis

Uchikawa 2009[75]	Prospective case control study	Continuous i.v. Dalteparin infusion administered in the anhepatic phase to maintain the ACT levels from 140 to 150 seconds (Gr.A) *vs* continuous i.v Dalteparin infusion administered immediately after the operation and adjusted depending on clinical findings (Gr.B)	Adult Living-donor LT	42 total patients (10 *vs* 32)	0 % in Gr. B 5 (15.6%) in Gr. A	0 % in Gr. B 5 (15.6%) in Gr. A	0% in Gr. B 1 (3.1%) in Gr. A	The study evaluated the advantage of ACT as a reliable tool for bedside monitoring of LMWH anticoagulant effects during and following LDLT
Stange 2003[72]	Retrospective study No controls	UFH 5000 IU over 24 h beginning 6 h postoperatively, for 14 d	Adult Living-donor LT	1192	Not evaluated	14 (1.17%)	3 (0.2%) bleeding episodes not apparently related to UFH	The authors analyzed the incidence, clinical presentation, therapeutic options, and outcome of hepatic artery thrombosis (HAT)
Wolf DC, 1997[77]	Retrospective case control study	81 mg oral aspirin in adult and 40 mg in children from postoperative day 1	Adult and pediatric LT	499 total patients (354 *vs* 175)	Not evaluated	10 (2.9%) *vs* 6 (3.6%) in the not treated group	89 (16.8%) gastrointestinal bleeding 66 treated *vs* 23 not treated patients	The spontaneous or invasive maneuver-related bleeding episodes were more frequent in the treated group
Vivarelli 2007[78]	Retrospective case control study	100 mg aspirin	Adult LT	838 total patients (236 treated *vs* 592 not treated)	Not evaluated	1/236 (0.4%) treated patients *vs* 13/592 (2.2%) not treated patients	0%	The aim of this study was to determine the safety and efficacy of aspirin therapy on late HAT
Shay 2013[79]	Retrospective case control study	325 mg aspirin	Adult LT	469 total patients (165 treated *vs* 304 not treated)	6/304 (2%) not treated patients *vs* 1/165 patients treated (0.6%)	15/304 patients (4.9%) *vs* 5/165 (3%) patients overall HAT (early and late) in the control and treated group	Similar bleeding rates between the two groups	The aim of this study was to determine the safety and efficacy of early aspirin therapy on clinical outcomes

LT: Liver transplant; PVT: Portal vein thrombosis; HAT: Hepatic artery thrombosis; ACT: Activated clotting time; aPTT: Activated partial thromboplastin time; DVT: Deep vein thrombosis; PE: Pulmonary embolism; LMWH: Low-molecular-weight heparin; UFH: Unfractionated heparin.

(5000 U) every 8 h, demonstrating that this therapy significantly reduces VTE events without increasing bleeding risks. In support of this kind of thromboprophylaxis, other studies have found that unfractionated heparin did not increase the risk of bleeding in patients with cirrhosis[87,88]. Gad and colleagues[74], in a retrospective work on 222 adult and pediatric living-donor LTs, reported their standard prophylactic therapy (heparin infusion up to 180-200 units/kg per day adjusted with reference to the ACT and/or the aPTT) and concluded that a more intensive anticoagulation therapy could be one option, especially when dealing with preoperative PVT. Uchikawa *et al*[75], fearing bleeding complications associated with UFH administration, proposed a thromboprophylactic regimen with dalteparin, a relatively selective inhibitor of factor Xa activity. In their prospective case-control group, they showed that anticoagulation therapy, based on ACT, reduces thrombotic complications without increasing bleeding[75]. Similarly, Sugawara *et al*[76] demonstrated the efficacy of intensive anticoagulation obtained with low-molecular-weight heparin (LMWH) administration.

In addition to LMWH and UFH, antiplatelet drugs have been proposed for prophylaxis after LT because of the important role of platelets in thrombotic complication. Wolf and colleagues in 1997 showed no benefit of prophylactic low-dose aspirin therapy in the prevention of early HAT after liver transplantation[77]. Differently, Vivarelli *et al*[78], in a single-center retrospective study, examined the effect of long-term aspirin administration (100 mg) on the incidence of late HAT in a large number of patients. They found a relative risk reduction of 82% without any recorded bleeding episodes throughout the follow-up period. Unfortunately, one of the major limitations of the

Table 3 Possible conditions warranting thromboprophylaxis in the postoperative period of liver transplant recipients

Living-donor liver transplant and split liver
Surgical difficulties and complex vessel reconstruction
Presurgical portal vein thrombosis
Intraoperative portal or hepatic artery thrombectomy
Hypoplastic portal vein
Jump graft artery reconstruction
Cholestatic recipient diseases and Budd-Chiari disease
Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis
Small or multiple recipient arteries
Low portal or arterial blood flow intraoperatively

study was the inability to verify the effect of aspirin on early HAT because of authors' inability to start aspirin immediately after LT in all patients with known impaired coagulative function or with a high risk of bleeding[78]. In contrast to Vivarelli, Shay *et al*[79] showed that aspirin prophylaxis is safe and effective in decreasing early HAT in adult recipients, making the HAT incidence decrease from 3.6% to 0% in the treated group. There was no difference in bleeding complications between the groups, regardless of the dosage of aspirin (325 mg) used.

There are emerging data on the safety of anti-coagulants in patients with cirrhosis[81,89]. Several groups recommend thromboprophylaxis in the absence of clear contraindications in the clinical, but not surgical, setting[87,90]. A different situation is represented by LT, where guidelines for VTE prophylaxis are lacking from both safety and efficacy standpoints. In this setting, a careful risk stratification, a wise drug choice and a reliable monitoring of drug effects may orient the choice on whether cirrhotic patients could benefit from prophylaxis (Table 3).

DRUG CHARACTERISTICS AND MONITORING ASSAY

In general, liver transplant surgery guidelines regarding VTE prophylaxis are lacking from both safety and efficacy standpoints. However, consideration should be given to using both mechanical and chemical prophylaxis after LT. Some studies, in fact, have reported rates as high as 79.6% of transplants being undertaken without transfusion[91] and a risk of developing a DVT after LT with mechanical prophylaxis alone ≥ 9%[40]. The growing evidence from clinical studies of the normal or even increased coagulation status in patients with cirrhosis, which has replaced the old dogma of the "auto-anticoagulated patient", has oriented most physicians to a more frequent postoperative thromboprophylaxis administration. Therefore, several warnings must be considered before implementing a more liberal use of anticoagulants in patients who have undergone liver transplant, and the risks and benefits of anticoagulation in these patients must be carefully weighed. Some of these warnings regard the chosen drug. Unfractionated heparin and LMWH are the most frequently used drugs, although there are several concerns and a lack of consensus on the required doses, the efficacy of treatment and the best way to monitor the pharmacologic effects achieved.

Unfractionated heparin

Heparin is used to reduce the incidence of HAT after liver transplantation. The anti-coagulatory effect of UFH comes mainly from its capacity to enhance the endogenous anticoagulant antithrombin III activity, from its effects on platelets, platelet factor 4, the fibrinolytic system and thrombin[92,93]. In liver cirrhosis or liver failure, the hepatic synthesis of coagulation factors, including antithrombin, is impaired, affecting anti-Xa testing and the predictability of UFH's anticoagulation effect[94]. In cirrhotic patients, a discrepancy has been reported between the anti-Xa level and the activated partial thromboplastin time while monitoring UFH therapy[95]. The anti-Xa tests underestimate the UFH levels, whereas the aPTT gives an overestimation[96]. Neither of these tests assesses drug levels directly; rather, they estimate the drug levels starting from the anticoagulant action of the drug.

When monitoring unfractionated heparin's effects by aPTT modifications, physicians must address an already prolonged aPTT value in many patients with cirrhosis, making the aPTT target ranges for these patients unclear. The aPTT test has not been assessed in cirrhotic patients, and its targeted range is unclear given that aPTT is prolonged at baseline in patients with cirrhosis. In this case, the level of ant-Xa is usually decreased, and that of aPTT is increased. This condition brings into question whether the augmentation of UFH doses based on anti-Xa level could expose patients to a higher risk of bleeding or if decreasing the UFH dose based on aPTT values could predispose patients to subtherapeutic therapy.

The fluctuating liver graft synthetic capacity and the consequently variable antithrombin level in the plasma of the transplanted patients make the heparin anticoagulation activity extremely variable during the postoperative period, requiring continuous monitoring and dose adjustment. Thus, understandable fears of bleeding are common in the post-liver transplant period.

Hemorrhagic complication can occur with the poorly monitored use of heparin. Kaneko *et al*[71] reported that 9% of their living related liver recipients who used UFH developed hemorrhagic complications that required surgical treatment. Other authors[74] noted the safety profile of heparin infusion in a liver transplant setting, underlining the necessity to obtain several samples to monitor its activity.

The ACT monitors the activity of the intrinsic pathway in the coagulation system and has been used after liver transplant to assess heparin anticoagulation.

Different target levels, depending on the clinical study, have been described and range from 130-160 s[71] and 180-200 s[74]. Most liver transplant centers have developed their own protocols for heparin infusions and heparin activity monitoring based on empirical rules. Because of the lack of consensus on the target ranges to be reached to obtain anticoagulation without increasing the hemorrhagic risk too much, authors have chosen the target limit arbitrarily, and surprisingly, the same target range has been both associated and not associated with bleeding complications in different clinical papers.

Another limit of UFH administration is heparin-induced thrombocytopenia (HIT), which is an adverse immune-mediated reaction to heparin that results in platelet count decreases of more than 50% within 5 to 10 d after heparin administration. The prevalence of HIT or HIT antibody in the liver recipient population seems to be very low[97], with the exception of Budd-Chiari syndrome patients, in whom the HIT prevalence is significantly higher than the general population[98]. Nevertheless, the careful monitoring of platelet count and possible thrombosis is necessary when heparin therapy is prolonged or patients have a history of heparin therapy.

Despite these limitations, UFH pharmacokinetics, especially if administered at low doses, characterized by a rapid short-term action, poor bioavailability, and a rapidly reversible anticoagulant effect in case of hemorrhagic complications, makes UFH a good anticoagulant in liver transplant patients with concomitant renal failure. Because of the limitations of both anti-Xa and aPTT tests in estimating the drug levels in plasma, thrombin generation testing could represent a valid alternative that offers information about the true anticoagulant effect of this drug; unfortunately, this test is not available for routine clinical use[96].

Low-molecular-weight heparin

LMWH selectively inhibits clotting factor X and, augments antithrombin III activity[71]. Despite being considered a drug with less risk of bleeding[99] than unfractionated heparin due to its selective inhibition of coagulation factor X, and because of its reduced ability to bind to platelet factor 4 and von Willebrand factor, its anticoagulation activity may be difficult to predict[99]. The anticoagulation efficacy in the presence of both graft and renal dysfunction may be extremely variable, and a reduction in the dosage of LMWH is recommended because it has increased anticoagulant potency in patients with cirrhosis[100]. Hence, in patients with impaired renal function, which is commonly seen following LT, monitoring and dose adjustments according to the degree of renal injury are required. For this reason, in patients with a high bleeding tendency, such as liver transplant recipients, an adjustable continuous infusion of LMWH may be recommended to avoid peak plasma levels and to better manage the continuous changes in the coagulation cascade related to the graft functionality[75]

While LMWH reduces ischemia-reperfusion-associated liver damage, which may make it more advantageous than UFH for intraoperative and postoperative anticoagulant therapy in LT, continuous monitoring and dose adjustments according to the degree of renal function are required. The most widely used test that correlates with the administered LMWH dose is the anti-FXa activity in plasma, which measures the inhibitory activity of LMWH-antithrombin (AT) complexes towards FXa. However, the assay is prone to several pitfalls that need to be considered when it is used to monitor the cirrhotic patient[101]. The low levels of antithrombin typical of cirrhotic patients limit the formation of LMWH-AT-FXa complexes and lower the ability of the anti-FXa activity assay to guide LMWH dosage[96]. Potze and colleagues found that the anti-FXa assay underestimated the LMWH dose administered in vitro to plasma of cirrhotic patients and had dangerous clinical consequences[96]. The low reliability of the anti-FXA assay, which underlines a persistently low anti-FXA activity, can lead to dangerous LMWH dose escalation in the postoperative period in liver transplant recipients[102]. To overcome this limitation of the assay at low AT levels, some authors propose the addition of AT before monitoring LMWH, which is not the standard practice in most routine diagnostic laboratories[81]. Another alternative could be represented by the ACT, which is the most commonly used and sensitive monitoring method to verify UFH' s effects. Some reports have documented that ACT is not reliable in monitoring LMWH's effect[103,104], and the ACT cannot usually monitor the activity of factor Xa. However, in other clinical papers, ACT did monitor the anticoagulatory effect of LMWH in coronary intervention procedures[105] and in living-donor LT[75]. Uchikawa *et al*[75] showed that ACT measurement is a simple, reliable method for bedside monitoring of LMWH's (dalteparin's) anticoagulant effects for living-donor LT.

The usefulness of the conventional ACT for LMWH monitoring is still under debate. TGT could represent a valid alternative[106]. However, this test is still impractical in a routine clinical setting, as it requires time to prepare and is not suitable for quick diagnosis.

Antiplatelet

The constant activation of platelets in the perioperative period of liver transplant, which can lead to platelet consumption and sequestration in the liver following graft reperfusion, has been associated with the occurrence of arterial thrombosis and graft failure[44]. Because of the significant role of platelets in the development of thrombosis, antiplatelet therapy has come to be seen as an attractive preventive therapy. Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of

the cyclooxygenase (COX) enzyme, which leads to an interference with platelet aggregation and to an endothelial cell-mediated inhibition of the coagulation cascade[107]. Although the widespread use of aspirin seems attractive, the traditional fear of hemorrhagic complication in the postoperative period of the liver transplant patient is responsible for the general avoidance of anticoagulant medication in these patients and for the very few studies performed on the efficacy and safety of antiplatelet drugs after liver transplantation. The literature on antiplatelet administration in the post-transplant period is controversial. Wolf and colleagues (1997) found no benefit of prophylactic low-dose aspirin therapy in the prevention of early HAT after liver transplantation, and even if aspirin administration did not seem to be associated with postoperative bleeding complications, a trend toward an increased incidence of gastrointestinal bleeding was seen[77]. In contrast, Vivarelli *et al*[78]. reported the efficacy and safety of long-term aspirin administration for the occurrence of late HAT, without hemorrhagic complications associated with aspirin administration. Similarly, Shay *et al*[79], who used a higher dosage of aspirin immediately after surgery, showed that aspirin prophylaxis was safe and effective in decreasing early HAT in adult recipients, with no evidence of significant bleeding. These recent works seem to suggest that thromboprophylactic anticoagulation with aspirin in selected high-risk LT patients may be considered carefully.

Antiplatelet agents, in contrast to other anti-coagulants, could offer the advantage of not requiring laboratory monitoring for dose adjustments. No tests are usually performed to avoid excessive inhibition of platelet function, and the issues regarding monitoring in the use of other anticoagulants cannot be applied to antiplatelet drugs. Unfortunately, laboratory tests of platelet function are frequently abnormal in patients with cirrhosis, and it may be challenging to detect the efficacy of anti-platelet agents in a category of patients with thrombocytopenia and platelet function alterations[108]. Furthermore, despite the clinical evidence for the efficacy of aspirin for early and late HAT, the use of aspirin has been associated with an increased risk of a first variceal bleeding in patients with established varices[109] and with acute renal failure, hyponatremia, and diuretic resistance in patients with ascites[110], occasionally making preventive aspirin administration in liver recipients difficult.

Clopidogrel

P2Y12 blockers such as clopidogrel, which has an active metabolite that irreversibly inhibits the ADP P2Y12 receptor, have been proposed to prevent post-transplant arterial thrombosis, but the risk of thrombosis vs bleeding must be wisely considered when choosing this drug in the postoperative period[7].

Perioperative management of antiplatelet therapy in patients who undergo surgery with a high hemorrhagic risk is difficult and should be formulated by a team of experts (surgeon, anesthesiologist), who should weigh the relative risk of bleeding with that of thrombosis. The risk of bleeding complications in the perioperative period has been increased 1.5-fold under low-dose aspirin[111], and when clopidogrel is not discharged within 7 d prior to the operation, this risk increases to 30%[112]. Clopidogrel is correlated with increased bleeding and is usually interrupted in the postoperative period until the risk has been reduced. Clopidogrel's hemorrhagic risk, the lack of established reversal agents, the fact that it is widely metabolized by the liver and excreted in urine, and the risk of excessive anticoagulation in the immediate postoperative period have made this drug barely manageable and, thus, not indicated for postoperative antithrombotic prophylaxis.

Direct oral anticoagulant agents

Direct oral anticoagulant agents (DOACs) have been proposed as an attractive alternative to heparin and LMWH for the prevention of post-transplant thrombotic complications. Moreover, preliminary data show that the use of DOAC is safe in cirrhotics[113]. These drugs have the advantages of oral administration, fixed dose and no need for laboratory monitoring. Moreover, their mechanism of action is independent of antithrombin, which is necessary for LMWH be effective but may be severely impaired in cirrhosis patients. However, we know of no DOAC study in postoperative liver transplant patients. The experience with DOACs is still limited, their anticoagulation effect is not quickly reversible, their elimination route is through the kidney and liver, and excessive drug accumulation could be associated with bleeding issues in the postoperative period. In liver transplant recipients, renal and liver function are often impaired, and excessive anticoagulation effects could develop, making DOACs of scarce interest for postoperative thromboprophylaxis.

CONCLUSION

The widespread fear of postoperative bleeding after LT has been partly reduced by the awareness of the real coagulation balance of cirrhotic patients and by the increasing number of transplants performed without the need for transfusion. The old concept of the cirrhotic patient as an anticoagulated patient and the idea that the normal coagulation tests are able to represent the real coagulation balance of the patient have now been replaced. With this new knowledge, the attention towards thromboembolic complications of the liver transplant patients has become increasingly pressing. An unbalanced coagulation system toward hypercoagulability may persist for a variable period of time after the liver transplant. The delayed recovery of the anticoagulant factors and the reaching of normal activity among almost all of the procoagulant proteins not before day 1 to 3 postoperatively have been

widely described[82]. The increasing awareness that hypercoagulability can represent a serious risk in the perioperative period of the liver recipient, together with the lack of reliable tests to verify the presence of this condition, should increase the awareness of physicians of the need for adequate thromboprophylaxis therapy. Literature on this matter is scarce, and the degree of anticoagulation to be achieved or the tests to monitor anti-coagulation are not the result of common consensus. Thromboprophylaxis should be used more often. From the literature available, we infer that the most commonly used drugs for antithrombotic purposes in patients undergoing LT are UFH, LMWH and cardioaspirin. The use of DOAC and clopidogrel in this category of patients is still limited, due in particular to their slowly reversible effect and the excessive anticoagulation effect they can cause because of their elimination route. Likewise, the possibility of hemorrhagic complications in transplanted patients remains a real fear. Pharmacological prophylaxis is probably beneficial in reducing the incidence of thromboembolic complications in the perioperative period, but a careful patient selection and a reliable coagulation test to monitor the pharmacological prophylaxis are needed. Thrombin-generation assays are the most reliable tests to represent the net amount of thrombin that can be generated as a result of the pro- and anticoagulant drivers and is a promising laboratory tool for investigating hemorrhagic and thrombotic coagulopathies. However, this test is still impractical in a routine clinical setting because it requires time to prepare and is not suitable for quick diagnosis. While waiting for this test to be readily available for bedside testing, viscoelastic tests, with all their limitations, could be helpful for the clinical conditions associated with increased thrombotic risks by avoiding the overcorrection of coagulation defects.

Unfortunately, because of the lack of a coagulation test that reliably predicts the risk of bleeding or thrombosis in the perioperative LT period, strong recommendations on thromboprophylaxis in this setting cannot be made, in particular in patients with delayed graft function. More well-designed clinical studies on the efficacy, safety, and tolerability of anticoagulant drugs for the prevention of thrombotic events in transplanted patients are needed.

REFERENCES

1 **Lisman T**, Caldwell SH, Burroughs AK, Northup PG, Senzolo M, Stravitz RT, Tripodi A, Trotter JF, Valla DC, Porte RJ; Coagulation in Liver Disease Study Group. Hemostasis and thrombosis in patients with liver disease: the ups and downs. *J Hepatol* 2010; **53**: 362-371 [PMID: 20546962 DOI: 10.1016/j.jhep.2010.01.042]

2 **Runyon BA**; AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology* 2013; **57**: 1651-1653 [PMID: 23463403 DOI: 10.1002/hep.26359]

3 **Lisman T**, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood* 2010; **116**: 878-885 [PMID: 20400681 DOI: 10.1182/blood-2010-02-261891]

4 **Liang TB**, Bai XL, Li DL, Li JJ, Zheng SS. Early postoperative hemorrhage requiring urgent surgical reintervention after orthotopic liver transplantation. *Transplant Proc* 2007; **39**: 1549-1553 [PMID: 17580186 DOI: 10.1016/j.transproceed.2007.01.080]

5 **Hendriks HG**, van der Meer J, de Wolf JT, Peeters PM, Porte RJ, de Jong K, Lip H, Post WJ, Slooff MJ. Intraoperative blood transfusion requirement is the main determinant of early surgical re-intervention after orthotopic liver transplantation. *Transpl Int* 2005; **17**: 673-679 [PMID: 15717214 DOI: 10.1007/s00147-004-0793-5]

6 **Ishitani M**, Angle J, Bickston S, Caldwell S, Isaacs R, Pruett T. Liver transplantation: incidence and management of deep venous thrombosis and pulmonary emboli. *Transplant Proc* 1997; **29**: 2861-2863 [PMID: 9365593]

7 **Feltracco P**, Barbieri S, Cillo U, Zanus G, Senzolo M, Ori C. Perioperative thrombotic complications in liver transplantation. *World J Gastroenterol* 2015; **21**: 8004-8013 [PMID: 26185371 DOI: 10.3748/wjg.v21.i26.8004]

8 **Qi X**, Dai J, Jia J, Ren W, Yang M, Li H, Fan D, Guo X. Association between portal vein thrombosis and survival of liver transplant recipients: a systematic review and meta-analysis of observational studies. *J Gastrointestin Liver Dis* 2015; **24**: 51-59, 4 p following 59 [PMID: 25822434 DOI: 10.15403/jgld.2014.1121.qix]

9 **Mukerji AN**, Karachristos A, Maloo M, Johnson D, Jain A. Do postliver transplant patients need thromboprophylactic anticoagulation? *Clin Appl Thromb Hemost* 2014; **20**: 673-677 [PMID: 24917126 DOI: 10.1177/1076029614538490]

10 **Guyatt GH**, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: 7S-47S [PMID: 22315257 DOI: 10.1378/chest.1412S3]

11 **Tripodi A**. Hemostasis abnormalities in cirrhosis. *Curr Opin Hematol* 2015; **22**: 406-412 [PMID: 26203733 DOI: 10.1097/MOH.0000000000000164]

12 **Violi F**, Basili S, Raparelli V, Chowdary P, Gatt A, Burroughs AK. Patients with liver cirrhosis suffer from primary haemostatic defects? Fact or fiction? *J Hepatol* 2011; **55**: 1415-1427 [PMID: 21718668 DOI: 10.1016/j.jhep.2011.06.008]

13 **Lisman T**, Bongers TN, Adelmeijer J, Janssen HL, de Maat MP, de Groot PG, Leebeek FW. Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology* 2006; **44**: 53-61 [PMID: 16799972 DOI: 10.1002/hep.21231]

14 **Tripodi A**, Primignani M, Chantarangkul V, Clerici M, Dell'Era A, Fabris F, Salerno F, Mannucci PM. Thrombin generation in patients with cirrhosis: the role of platelets. *Hepatology* 2006; **44**: 440-445 [PMID: 16871542 DOI: 10.1002/hep.21266]

15 **Leebeek FW**, Rijken DC. The Fibrinolytic Status in Liver Diseases. *Semin Thromb Hemost* 2015; **41**: 474-480 [PMID: 26049070 DOI: 10.1055/s-0035-1550437]

16 **Caldwell SH**, Hoffman M, Lisman T, Macik BG, Northup PG, Reddy KR, Tripodi A, Sanyal AJ; Coagulation in Liver Disease Group. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. *Hepatology* 2006; **44**: 1039-1046 [PMID: 17006940 DOI: 10.1002/hep.21303]

17 **Colucci M**, Binetti BM, Branca MG, Clerici C, Morelli A, Semeraro N, Gresele P. Deficiency of thrombin activatable fibrinolysis inhibitor in cirrhosis is associated with increased plasma fibrinolysis. *Hepatology* 2003; **38**: 230-237 [PMID: 12830006 DOI: 10.1053/jhep.2003.50277]

18 **Levi M**, van der Poll T. Coagulation and sepsis. *Thromb Res* 2017; **149**: 38-44 [PMID: 27886531 DOI: 10.1016/j.thromres.2016.11.007]

19 **Senzolo M**, Agarwal S, Zappoli P, Vibhakorn S, Mallett S, Burroughs AK. Heparin-like effect contributes to the coagulopathy in patients with acute liver failure undergoing liver transplantation.

Liver Int 2009; **29**: 754-759 [PMID: 19220741 DOI: 10.1111/j.1478-3231.2009.01977.x]
20 **Tripodi A**, Caldwell SH, Hoffman M, Trotter JF, Sanyal AJ. Review article: the prothrombin time test as a measure of bleeding risk and prognosis in liver disease. *Aliment Pharmacol Ther* 2007; **26**: 141-148 [PMID: 17593061 DOI: 10.1111/j.1365-2036.2007.03369.x]
21 **de Franchis R**; Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**: 743-752 [PMID: 26047908 DOI: 10.1016/j.jhep.2015.05.022]
22 **Haas T**, Fries D, Tanaka KA, Asmis L, Curry NS, Schöchl H. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? *Br J Anaesth* 2015; **114**: 217-224 [PMID: 25204698 DOI: 10.1093/bja/aeu303]
23 **Lisman T**, Leebeek FW, Mosnier LO, Bouma BN, Meijers JC, Janssen HL, Nieuwenhuis HK, De Groot PG. Thrombin-activatable fibrinolysis inhibitor deficiency in cirrhosis is not associated with increased plasma fibrinolysis. *Gastroenterology* 2001; **121**: 131-139 [PMID: 11438502]
24 **Hugenholtz GC**, Macrae F, Adelmeijer J, Dulfer S, Porte RJ, Lisman T, Ariëns RA. Procoagulant changes in fibrin clot structure in patients with cirrhosis are associated with oxidative modifications of fibrinogen. *J Thromb Haemost* 2016; **14**: 1054-1066 [PMID: 26833718 DOI: 10.1111/jth.13278]
25 **Northup PG**, McMahon MM, Ruhl AP, Altschuler SE, Volk-Bednarz A, Caldwell SH, Berg CL. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. *Am J Gastroenterol* 2006; **101**: 1524-8; quiz 1680 [PMID: 16863556 DOI: 10.1111/j.1572-0241.2006.00588.x]
26 **Vukovich T**, Teufelsbauer H, Fritzer M, Kreuzer S, Knoflach P. Hemostasis activation in patients with liver cirrhosis. *Thromb Res* 1995; **77**: 271-278 [PMID: 7740519]
27 **Gulley D**, Teal E, Suvannasankha A, Chalasani N, Liangpunsakul S. Deep vein thrombosis and pulmonary embolism in cirrhosis patients. *Dig Dis Sci* 2008; **53**: 3012-3017 [PMID: 18443906 DOI: 10.1007/s10620-008-0265-3]
28 **Ambrosino P**, Tarantino L, Di Minno G, Paternoster M, Graziano V, Petitto M, Nasto A, Di Minno MN. The risk of venous thromboembolism in patients with cirrhosis. A systematic review and meta-analysis. *Thromb Haemost* 2017; **117**: 139-148 [PMID: 27761574 DOI: 10.1160/TH16-06-0450]
29 **Tsochatzis EA**, Senzolo M, Germani G, Gatt A, Burroughs AK. Systematic review: portal vein thrombosis in cirrhosis. *Aliment Pharmacol Ther* 2010; **31**: 366-374 [PMID: 19863496 DOI: 10.1111/j.1365-2036.2009.04182.x]
30 **Chawla YK**, Bodh V. Portal vein thrombosis. *J Clin Exp Hepatol* 2015; **5**: 22-40 [PMID: 25941431 DOI: 10.1016/j.jceh.2014.12.008]
31 **Fouzas I**, Paul A, Becker C, Vernadakis S, Treckmann JW, Máthé Z, Gerken G, Sotiropoulos GC. Orthotopic liver transplantation in patients with portal vein thrombosis in the absence of hepatocellular carcinoma. *Transplant Proc* 2012; **44**: 2734-2736 [PMID: 23146508 DOI: 10.1016/j.transproceed.2012.09.024]
32 **Senzolo M**, M Sartori T, Rossetto V, Burra P, Cillo U, Boccagni P, Gasparini D, Miotto D, Simioni P, Tsochatzis E, A Burroughs K. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. *Liver Int* 2012; **32**: 919-927 [PMID: 22435854 DOI: 10.1111/j.1478-3231.2012.02785.x]
33 **Yamashita Y**, Bekki Y, Imai D, Ikegami T, Yoshizumi T, Ikeda T, Kawanaka H, Nishie A, Shirabe K, Maehara Y. Efficacy of postoperative anticoagulation therapy with enoxaparin for portal vein thrombosis after hepatic resection in patients with liver cancer. *Thromb Res* 2014; **134**: 826-831 [PMID: 25156238 DOI: 10.1016/j.thromres.2014.07.038]
34 **Duffy JP**, Hong JC, Farmer DG, Ghobrial RM, Yersiz H, Hiatt JR, Busuttil RW. Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. *J Am Coll Surg* 2009; **208**: 896-903; discussion 903-5 [PMID: 19476857 DOI: 10.1016/j.jamcollsurg.2008.12.032]
35 **Oh CK**, Pelletier SJ, Sawyer RG, Dacus AR, McCullough CS, Pruett TL, Sanfey HA. Uni- and multi-variate analysis of risk factors for early and late hepatic artery thrombosis after liver transplantation. *Transplantation* 2001; **71**: 767-772 [PMID: 11330540]
36 **Yang Y**, Zhao JC, Yan LN, Ma YK, Huang B, Yuan D, Li B, Wen TF, Wang WT, Xu MQ, Yang JY. Risk factors associated with early and late HAT after adult liver transplantation. *World J Gastroenterol* 2014; **20**: 10545-10552 [PMID: 25132774 DOI: 10.3748/wjg.v20.i30.10545]
37 **Silva MA**, Jambulingam PS, Gunson BK, Mayer D, Buckels JA, Mirza DF, Bramhall SR. Hepatic artery thrombosis following orthotopic liver transplantation: a 10-year experience from a single centre in the United Kingdom. *Liver Transpl* 2006; **12**: 146-151 [PMID: 16382467 DOI: 10.1002/lt.20566]
38 **Salami A**, Qureshi W, Kuriakose P, Moonka D, Yoshida A, Abouljoud M. Frequency and predictors of venous thromboembolism in orthotopic liver transplant recipients: a single-center retrospective review. *Transplant Proc* 2013; **45**: 315-319 [PMID: 23267811 DOI: 10.1016/j.transproceed.2012.06.060]
39 **Stine JG**, Pelletier SJ, Schmitt TM, Porte RJ, Northup PG. Pre-transplant portal vein thrombosis is an independent risk factor for graft loss due to hepatic artery thrombosis in liver transplant recipients. *HPB* (Oxford) 2016; **18**: 279-286 [PMID: 27017168 DOI: 10.1016/j.hpb.2015.10.008]
40 **Annamalai A**, Kim I, Sundaram V, Klein A. Incidence and risk factors of deep vein thrombosis after liver transplantation. *Transplant Proc* 2014; **46**: 3564-3569 [PMID: 25498090 DOI: 10.1016/j.transproceed.2014.09.113]
41 **Warnaar N**, Molenaar IQ, Colquhoun SD, Slooff MJ, Sherwani S, de Wolf AM, Porte RJ. Intraoperative pulmonary embolism and intracardiac thrombosis complicating liver transplantation: a systematic review. *J Thromb Haemost* 2008; **6**: 297-302 [PMID: 18005235 DOI: 10.1111/j.1538-7836.2007.02831.x]
42 **Sakai T**, Matsusaki T, Dai F, Tanaka KA, Donaldson JB, Hilmi IA, Wallis Marsh J, Planinsic RM, Humar A. Pulmonary thromboembolism during adult liver transplantation: incidence, clinical presentation, outcome, risk factors, and diagnostic predictors. *Br J Anaesth* 2012; **108**: 469-477 [PMID: 22174347 DOI: 10.1093/bja/aer392]
43 **Pereboom IT**, Adelmeijer J, van Leeuwen Y, Hendriks HG, Porte RJ, Lisman T. Development of a severe von Willebrand factor/ADAMTS13 dysbalance during orthotopic liver transplantation. *Am J Transplant* 2009; **9**: 1189-1196 [PMID: 19422343 DOI: 10.1111/j.1600-6143.2009.02621.x]
44 **Pereboom IT**, Lisman T, Porte RJ. Platelets in liver transplantation: friend or foe? *Liver Transpl* 2008; **14**: 923-931 [PMID: 18581510 DOI: 10.1002/lt.21510]
45 **Arshad F**, Lisman T, Porte RJ. Hypercoagulability as a contributor to thrombotic complications in the liver transplant recipient. *Liver Int* 2013; **33**: 820-827 [PMID: 23490221 DOI: 10.1111/liv.12140]
46 **Porte RJ**, Bontempo FA, Knot EA, Lewis JH, Kang YG, Starzl TE. Tissue-type-plasminogen-activator-associated fibrinolysis in orthotopic liver transplantation. *Transplant Proc* 1989; **21**: 3542 [PMID: 2500761]
47 **Lisman T**, Leebeek FW, Meijer K, Van Der Meer J, Nieuwenhuis HK, De Groot PG. Recombinant factor VIIa improves clot formation but not fibrolytic potential in patients with cirrhosis and during liver transplantation. *Hepatology* 2002; **35**: 616-621 [PMID: 11870375 DOI: 10.1053/jhep.2002.31771]
48 **Ganter MT**, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. *Anesth Analg* 2008; **106**: 1366-1375 [PMID: 18420846 DOI: 10.1213/ane.0b013e318168b367]
49 **Lancé MD**. A general review of major global coagulation assays: thrombelastography, thrombin generation test and clot waveform analysis. *Thromb J* 2015; **13**: 1 [PMID: 25937820 DOI: 10.1186/1477-9560-13-1]

50 **Wikkelsø A**, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database Syst Rev* 2016; : CD007871 [PMID: 27552162 DOI: 10.1002/14651858.CD007871.pub3]

51 **Forkin KT**, Colquhoun DA, Nemergut EC, Huffmyer JL. The Coagulation Profile of End-Stage Liver Disease and Considerations for Intraoperative Management. *Anesth Analg* 2018; **126**: 46-61 [PMID: 28795966 DOI: 10.1213/ANE.0000000000002394]

52 **Hincker A**, Feit J, Sladen RN, Wagener G. Rotational thromboelastometry predicts thromboembolic complications after major non-cardiac surgery. *Crit Care* 2014; **18**: 549 [PMID: 25292221 DOI: 10.1186/s13054-014-0549-2]

53 **Kashuk JL**, Moore EE, Sabel A, Barnett C, Haenel J, Le T, Pezold M, Lawrence J, Biffl WL, Cothren CC, Johnson JL. Rapid thrombelastography (r-TEG) identifies hypercoagulability and predicts thromboembolic events in surgical patients. *Surgery* 2009; **146**: 764-72; discussion 772-4 [PMID: 19789037 DOI: 10.1016/j.surg.2009.06.054]

54 **Cerutti E**, Stratta C, Romagnoli R, Schellino MM, Skurzak S, Rizzetto M, Tamponi G, Salizzoni M. Thromboelastogram monitoring in the perioperative period of hepatectomy for adult living liver donation. *Liver Transpl* 2004; **10**: 289-294 [PMID: 14762869 DOI: 10.1002/lt.20078]

55 **Krzanicki D**, Sugavanam A, Mallett S. Intraoperative hypercoagulability during liver transplantation as demonstrated by thromboelastography. *Liver Transpl* 2013; **19**: 852-861 [PMID: 23696318 DOI: 10.1002/lt.23668]

56 **McCrath DJ**, Cerboni E, Frumento RJ, Hirsh AL, Bennett-Guerrero E. Thromboelastography maximum amplitude predicts postoperative thrombotic complications including myocardial infarction. *Anesth Analg* 2005; **100**: 1576-1583 [PMID: 15920177 DOI: 10.1213/01.ANE.0000155290.86795.12]

57 **Rafiq S**, Johansson PI, Ostrowski SR, Stissing T, Steinbrüchel DA. Hypercoagulability in patients undergoing coronary artery bypass grafting: prevalence, patient characteristics and postoperative outcome. *Eur J Cardiothorac Surg* 2012; **41**: 550-555 [PMID: 22011771 DOI: 10.1093/ejcts/ezr001]

58 **Lerner AB**, Sundar E, Mahmood F, Sarge T, Hanto DW, Panzica PJ. Four cases of cardiopulmonary thromboembolism during liver transplantation without the use of antifibrinolytic drugs. *Anesth Analg* 2005; **101**: 1608-1612 [PMID: 16301227 DOI: 10.1213/01.ANE.0000184256.28981.2B]

59 **Zanetto A**, Senzolo M, Vitale A, Cillo U, Radu C, Sartorello F, Spiezia L, Campello E, Rodriguez-Castro K, Ferrarese A, Farinati F, Burra P, Simioni P. Thromboelastometry hypercoagulable profiles and portal vein thrombosis in cirrhotic patients with hepatocellular carcinoma. *Dig Liver Dis* 2017; **49**: 440-445 [PMID: 28109767 DOI: 10.1016/j.dld.2016.12.019]

60 **Zahr Eldeen F**, Roll GR, Derosas C, Rao R, Khan MS, Gunson BK, Hodson J, Mergental H, Ferraz-Neto BH, Isaac J, Muiesan P, Mirza DF, Iqbal A, Perera MT. Preoperative Thromboelastography as a Sensitive Tool Predicting Those at Risk of Developing Early Hepatic Artery Thrombosis After Adult Liver Transplantation. *Transplantation* 2016; **100**: 2382-2390 [PMID: 27780186 DOI: 10.1097/TP.0000000000001395]

61 **Blasi A**, Molina V, Sanchez-Cabús S, Balust J, Garcia-Valdecasas JC, Taura P. Prediction of thromboembolic complications after liver resection for cholangiocarcinoma: is there a place for thromboelastometry? *Blood Coagul Fibrinolysis* 2018; **29**: 61-66 [PMID: 29045240 DOI: 10.1097/MBC.0000000000000672]

62 **Lentschener C**, Flaujac C, Ibrahim F, Gouin-Thibault I, Bazin M, Sogni P, Samama CM. Assessment of haemostasis in patients with cirrhosis: Relevance of the ROTEM tests?: A prospective, cross-sectional study. *Eur J Anaesthesiol* 2016; **33**: 126-133 [PMID: 26258657 DOI: 10.1097/EJA.0000000000000322]

63 **De Pietri L**, Bianchini M, Rompianesi G, Bertellini E, Begliomini B. Thromboelastographic reference ranges for a cirrhotic patient population undergoing liver transplantation. *World J Transplant* 2016; **6**: 583-593 [PMID: 27683637 DOI: 10.5500/wjt.v6.i3.583]

64 **Lang T**, von Depka M. [Possibilities and limitations of thrombelastometry/-graphy]. *Hamostaseologie* 2006; **26**: S20-S29 [PMID: 16953288]

65 **Jámbor C**, Reul V, Schnider TW, Degiacomi P, Metzner H, Korte WC. In vitro inhibition of factor XIII retards clot formation, reduces clot firmness, and increases fibrinolytic effects in whole blood. *Anesth Analg* 2009; **109**: 1023-1028 [PMID: 19762725 DOI: 10.1213/ANE.0b013e3181b5a263]

66 **Kitchen DP**, Kitchen S, Jennings I, Woods TA, Fitzmaurice DA, Murray ET, Walker ID. Point of Care INR testing devices: performance of the Roche CoaguChek XS and XS Plus in the UK NEQAS BC external quality assessment programme for healthcare professionals: four years' experience. *J Clin Pathol* 2012; **65**: 1119-1123 [PMID: 23038688 DOI: 10.1136/jclinpath-2012-201049]

67 **MacDonald SG**, Luddington RJ. Critical factors contributing to the thromboelastography trace. *Semin Thromb Hemost* 2010; **36**: 712-722 [PMID: 20978992 DOI: 10.1055/s-0030-1265288]

68 **Tripodi A**. Thrombin Generation Assay and Its Application in the Clinical Laboratory. *Clin Chem* 2016; **62**: 699-707 [PMID: 26955824 DOI: 10.1373/clinchem.2015.248625]

69 **Hemker HC**, Al Dieri R, De Smedt E, Béguin S. Thrombin generation, a function test of the haemostatic-thrombotic system. *Thromb Haemost* 2006; **96**: 553-561 [PMID: 17080210]

70 **Dielis AW**, Castoldi E, Spronk HM, van Oerle R, Hamulyák K, Ten Cate H, Rosing J. Coagulation factors and the protein C system as determinants of thrombin generation in a normal population. *J Thromb Haemost* 2008; **6**: 125-131 [PMID: 17988231 DOI: 10.1111/j.1538-7836.2007.02824.x]

71 **Kaneko J**, Sugawara Y, Tamura S, Togashi J, Matsui Y, Akamatsu N, Kishi Y, Makuuchi M. Coagulation and fibrinolytic profiles and appropriate use of heparin after living-donor liver transplantation. *Clin Transplant* 2005; **19**: 804-809 [PMID: 16313329 DOI: 10.1111/j.1399-0012.2005.00425.x]

72 **Stange BJ**, Glanemann M, Nuessler NC, Settmacher U, Steinmüller T, Neuhaus P. Hepatic artery thrombosis after adult liver transplantation. *Liver Transpl* 2003; **9**: 612-620 [PMID: 12783404 DOI: 10.1053/jlts.2003.50098]

73 **Yip J**, Bruno DA, Burmeister C, Kazimi M, Yoshida A, Abouljoud MS, Schnickel GT. Deep Vein Thrombosis and Pulmonary Embolism in Liver Transplant Patients: Risks and Prevention. *Transplant Direct* 2016; **2**: e68 [PMID: 27500259 DOI: 10.1097/TXD.0000000000000578]

74 **Gad EH**, Abdelsamee MA, Kamel Y. Hepatic arterial and portal venous complications after adult and pediatric living donor liver transplantation, risk factors, management and outcome (A retrospective cohort study). *Ann Med Surg* (Lond) 2016; **8**: 28-39 [PMID: 27257483 DOI: 10.1016/j.amsu.2016.04.021]

75 **Uchikawa Y**, Ikegami T, Masuda Y, Ohno Y, Mita A, Urata K, Nakazawa Y, Terada M, Miyagawa S. Administration of dalteparin based on the activated clotting time for prophylaxis of hepatic vessel thrombosis in living donor liver transplantation. *Transplant Proc* 2009; **41**: 3784-3790 [PMID: 19917388 DOI: 10.1016/j.transproceed.2009.04.011]

76 **Sugawara Y**, Kaneko J, Akamatsu N, Imamura H, Kokudo N, Makuuchi M. Anticoagulant therapy against hepatic artery thrombosis in living donor liver transplantation. *Transplant Proc* 2002; **34**: 3325-3326 [PMID: 12493462]

77 **Wolf DC**, Freni MA, Boccagni P, Mor E, Chodoff L, Birnbaum A, Miller CM, Schwartz ME, Bodenheimer HC Jr. Low-dose aspirin therapy is associated with few side effects but does not prevent hepatic artery thrombosis in liver transplant recipients. *Liver Transpl Surg* 1997; **3**: 598-603 [PMID: 9404960]

78 **Vivarelli M**, La Barba G, Cucchetti A, Lauro A, Del Gaudio M, Ravaioli M, Grazi GL, Pinna AD. Can antiplatelet prophylaxis reduce the incidence of hepatic artery thrombosis after liver transplantation? *Liver Transpl* 2007; **13**: 651-654 [PMID: 17457885 DOI: 10.1002/lt.21028]

79 **Shay R**, Taber D, Pilch N, Meadows H, Tischer S, McGillicuddy J, Bratton C, Baliga P, Chavin K. Early aspirin therapy may reduce

hepatic artery thrombosis in liver transplantation. *Transplant Proc* 2013; **45**: 330-334 [PMID: 23267805 DOI: 10.1016/j.transproceed.2012.05.075]
80 **Mori A**, Iida T, Iwasaki J, Ogawa K, Fujimoto Y, Uemura T, Hatano E, Okajima H, Kaido T, Uemoto S. Portal vein reconstruction in adult living donor liver transplantation for patients with portal vein thrombosis in single center experience. *J Hepatobiliary Pancreat Sci* 2015; **22**: 467-474 [PMID: 25755116 DOI: 10.1002/jhbp.235]
81 **Hugenholtz GC**, Northup PG, Porte RJ, Lisman T. Is there a rationale for treatment of chronic liver disease with antithrombotic therapy? *Blood Rev* 2015; **29**: 127-136 [PMID: 25468718 DOI: 10.1016/j.blre.2014.10.002]
82 **Stahl RL**, Duncan A, Hooks MA, Henderson JM, Millikan WJ, Warren WD. A hypercoagulable state follows orthotopic liver transplantation. *Hepatology* 1990; **12**: 553-558 [PMID: 2401460]
83 **Lisman T**, Bakhtiari K, Pereboom IT, Hendriks HG, Meijers JC, Porte RJ. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. *J Hepatol* 2010; **52**: 355-361 [PMID: 20132999 DOI: 10.1016/j.jhep.2009.12.001]
84 **Mallett SV**, Sugavanam A, Krzanicki DA, Patel S, Broomhead RH, Davidson BR, Riddell A, Gatt A, Chowdary P. Alterations in coagulation following major liver resection. *Anaesthesia* 2016; **71**: 657-668 [PMID: 27030945 DOI: 10.1111/anae.13459]
85 **Potze W**, Alkozai EM, Adelmeijer J, Porte RJ, Lisman T. Hypercoagulability following major partial liver resection - detected by thrombomodulin-modified thrombin generation testing. *Aliment Pharmacol Ther* 2015; **41**: 189-198 [PMID: 25382796 DOI: 10.1111/apt.13022]
86 **Remuzzi G**, Bertani T. Renal vascular and thrombotic effects of cyclosporine. *Am J Kidney Dis* 1989; **13**: 261-272 [PMID: 2650537]
87 **Gómez Cuervo C**, Bisbal Pardo O, Pérez-Jacoiste Asín MA. Efficacy and safety of the use of heparin as thromboprophylaxis in patients with liver cirrhosis: a systematic review and meta-analysis. *Thromb Res* 2013; **132**: 414-419 [PMID: 23993900 DOI: 10.1016/j.thromres.2013.08.001]
88 **Intagliata NM**, Henry ZH, Shah N, Lisman T, Caldwell SH, Northup PG. Prophylactic anticoagulation for venous thromboembolism in hospitalized cirrhosis patients is not associated with high rates of gastrointestinal bleeding. *Liver Int* 2014; **34**: 26-32 [PMID: 23758818 DOI: 10.1111/liv.12211]
89 **Intagliata NM**, Northup PG. Anticoagulant Therapy in Patients with Cirrhosis. *Semin Thromb Hemost* 2015; **41**: 514-519 [PMID: 26049069 DOI: 10.1055/s-0035-1550436]
90 **Intagliata NM**, Maitland H, Caldwell SH. Direct Oral Anticoagulants in Cirrhosis. *Curr Treat Options Gastroenterol* 2016; **14**: 247-256 [PMID: 27020266 DOI: 10.1007/s11938-016-0092-0]
91 **Massicotte L**, Denault AY, Beaulieu D, Thibeault L, Hevesi Z, Nozza A, Lapointe R, Roy A. Transfusion rate for 500 consecutive liver transplantations: experience of one liver transplantation center. *Transplantation* 2012; **93**: 1276-1281 [PMID: 22617090 DOI: 10.1097/TP.0b013e318250fc25]
92 **Agnelli G**, Borm J, Cosmi B, Levi M, ten Cate JW. Effects of standard heparin and a low molecular weight heparin (Kabi 2165) on fibrinolysis. *Thromb Haemost* 1988; **60**: 311-313 [PMID: 2851195]
93 **Padilla A**, Gray E, Pepper DS, Barrowcliffe TW. Inhibition of thrombin generation by heparin and low molecular weight (LMW) heparins in the absence and presence of platelet factor 4 (PF4). *Br J Haematol* 1992; **82**: 406-413 [PMID: 1329921]
94 **Ha NB**, Regal RE. Anticoagulation in Patients With Cirrhosis: Caught Between a Rock-Liver and a Hard Place. *Ann Pharmacother* 2016; **50**: 402-409 [PMID: 26861989 DOI: 10.1177/1060028016631760]
95 **Fuentes A**, Gordon-Burroughs S, Hall JB, Putney DR, Monsour HP Jr. Comparison of anti-Xa and activated partial thromboplastin time monitoring for heparin dosing in patients with cirrhosis. *Ther Drug Monit* 2015; **37**: 40-44 [PMID: 24901494 DOI: 10.1097/FTD.0000000000000105]
96 **Potze W**, Arshad F, Adelmeijer J, Blokzijl H, van den Berg AP, Porte RJ, Lisman T. Routine coagulation assays underestimate levels of antithrombin-dependent drugs but not of direct anticoagulant drugs in plasma from patients with cirrhosis. *Br J Haematol* 2013; **163**: 666-673 [PMID: 24219333 DOI: 10.1111/bjh.12593]
97 **Assfalg V**, Hüser N. Heparin-induced thrombocytopenia in solid organ transplant recipients: The current scientific knowledge. *World J Transplant* 2016; **6**: 165-173 [PMID: 27011914 DOI: 10.5500/wjt.v6.i1.165]
98 **Zaman S**, Wiebe S, Bernal W, Wendon J, Czuprynska J, Auzinger G. Increased prevalence of heparin-induced thrombocytopenia in patients with Budd-Chiari syndrome: a retrospective analysis. *Eur J Gastroenterol Hepatol* 2016; **28**: 967-971 [PMID: 27015137 DOI: 10.1097/MEG.0000000000000632]
99 **Weitz JI**. Low-molecular-weight heparins. *N Engl J Med* 1997; **337**: 688-698 [PMID: 9278467 DOI: 10.1056/NEJM199709043371007]
100 **Senzolo M**, Rodriguez-Castro KI, Rossetto V, Radu C, Gavasso S, Carraro P, Zerbinati P, Sartori MT, Simioni P. Increased anticoagulant response to low-molecular-weight heparin in plasma from patients with advanced cirrhosis. *J Thromb Haemost* 2012; **10**: 1823-1829 [PMID: 22712870 DOI: 10.1111/j.1538-7836.2012.04824.x]
101 **Bounameaux H**, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. *J Thromb Haemost* 2004; **2**: 551-554 [PMID: 15102007 DOI: 10.1111/j.1538-7933.2004.00648.x]
102 **Bechmann LP**, Sichau M, Wichert M, Gerken G, Kröger K, Hilgard P. Low-molecular-weight heparin in patients with advanced cirrhosis. *Liver Int* 2011; **31**: 75-82 [PMID: 20958919 DOI: 10.1111/j.1478-3231.2010.02358.x]
103 **Linkins LA**, Julian JA, Rischke J, Hirsh J, Weitz JI. In vitro comparison of the effect of heparin, enoxaparin and fondaparinux on tests of coagulation. *Thromb Res* 2002; **107**: 241-244 [PMID: 12479885]
104 **Henry TD**, Satran D, Knox LL, Iacarella CL, Laxson DD, Antman EM. Are activated clotting times helpful in the management of anticoagulation with subcutaneous low-molecular-weight heparin? *Am Heart J* 2001; **142**: 590-593 [PMID: 11579347 DOI: 10.1067/mhj.2001.117317]
105 **Marmur JD**, Anand SX, Bagga RS, Fareed J, Pan CM, Sharma SK, Richard MF. The activated clotting time can be used to monitor the low molecular weight heparin dalteparin after intravenous administration. *J Am Coll Cardiol* 2003; **41**: 394-402 [PMID: 12575965]
106 **Potze W**, Arshad F, Adelmeijer J, Blokzijl H, van den Berg AP, Meijers JC, Porte RJ, Lisman T. Differential in vitro inhibition of thrombin generation by anticoagulant drugs in plasma from patients with cirrhosis. *PLoS One* 2014; **9**: e88390 [PMID: 24505487 DOI: 10.1371/journal.pone.0088390]
107 **Fritsma GA**, Ens GE, Alvord MA, Carroll AA, Jensen R. Monitoring the antiplatelet action of aspirin. *JAAPA* 2001; **14**: 57-58, 61-62 [PMID: 11523339]
108 **Hugenholtz GG**, Porte RJ, Lisman T. The platelet and platelet function testing in liver disease. *Clin Liver Dis* 2009; **13**: 11-20 [PMID: 19150305 DOI: 10.1016/j.cld.2008.09.010]
109 **De Lédinghen V**, Heresbach D, Fourdan O, Bernard P, Liebaert-Bories MP, Nousbaum JB, Gourlaouen A, Becker MC, Ribard D, Ingrand P, Silvain C, Beauchant M. Anti-inflammatory drugs and variceal bleeding: a case-control study. *Gut* 1999; **44**: 270-273 [PMID: 9895389]
110 **European Association for the Study of the Liver.**. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946 DOI: 10.1016/j.jhep.2010.05.004]
111 **Burger W**, Chemnitius JM, Kneissl GD, Rücker G. Low-dose aspirin for secondary cardiovascular prevention - cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation - review and meta-analysis. *J Intern Med* 2005; **257**: 399-414 [PMID: 15836656 DOI: 10.1111/j.1365-2796.2005.01477.x]

112 **Chernoguz A**, Telem DA, Chu E, Ozao-Choy J, Tammaro Y, Divino CM. Cessation of clopidogrel before major abdominal procedures. *Arch Surg* 2011; **146**: 334-339 [PMID: 21422366 DOI: 10.1001/archsurg.2011.23]

113 **Hum J**, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis. *Eur J Haematol* 2017; **98**: 393-397 [PMID: 28009449 DOI: 10.1111/ejh.12844]

P- Reviewer: Ikura Y, Lisman T, Matowicka-Karna J, Nava A
S- Editor: Wang JL **L- Editor**: A **E- Editor**: Huang Y

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

ISSN 1007-9327