# Hemostasis in patients with liver disease

J. van der Werf[1], R.J. Porte[2], T. Lisman[1,2]

(1) Surgical Research Laboratory, Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands ; (2) Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

## Abstract

**In patients with liver disease alterations in the hemostatic system frequently occur. Although it was generally believed that these changes result in a bleeding tendency, laboratory models and clinical data have shown evidence for a rebalanced hemostasis in liver disease, as a result of a concomitant decrease in both pro- and antihemostatic systems. The rebalanced system presumably has much narrower margins as compared to healthy individuals and therefore can more easily turn to either a hypo- or hypercoagulable state.**

**Bleeding does occur in patients with liver disease but this is frequently related to non-hematological factors, for example bleeding from ruptured esophageal varices. Further clinical data supporting the concept of rebalanced hemostasis include the lack of major blood loss in a great proportion of patients during liver transplantation and the fact that patients with liver disease are not fully protected from thromboembolic complications including venous thrombosis and thrombosis of the hepatic vessels.**

**It is still common practice to prophylactically treat patients with liver disease prior to invasive procedures to prevent bleeding. Because of a lack of data supporting the effectiveness of this management and the proven side-effects of transfusion of blood products, we believe transfusion of blood products can and should be restricted.**

**The most important thrombotic problem after liver transplantation is hepatic artery thrombosis, a potentially devastating complication. Since the bleeding tendency in patients with liver disease may not be primarily caused by a deranged hemostatic system, the restricted use of anticoagulant drugs in the post-transplant setting should be reconsidered.** (Acta gastroenterol. belg., **2009**, 72, **433-440**).

**Key words** : hemostasis, platelet, coagulation, fibrinolytic system, bleeding, thrombosis, transfusion.

## The hemostatic system

The hemostatic system consists of different components which work together to prevent blood loss in case of vessel wall damage. It starts with the exposure of collagen and other extracellular matrix proteins, which leads to the recruitment of circulating platelets to the site of the vessel wall injury. Subsequently platelets attach to the vessel wall by binding to collagen-bound von Willebrand factor (VWF), and the platelets aggregrate to one another. The platelet-platelet interaction is mediated by VWF or fibrinogen binding to the αIIβ 3 receptor on two adjacent platelets. This process is called primary hemostasis and results in the formation of a platelet plug (1-3).

Concomitantly with primary hemostasis, blood coagulation is initiated by tissue factor. Tissue factor is a transmembrane protein which is exposed to the bloodstream after vessel wall damage. The coagulation cascade, also referred to as secondary hemostasis, results in the generation of thrombin (factor IIa), which cleaves fibrinogen into fibrin. Fibrin forms an insoluble network which reinforces the platelet plug. The combined action of primary and secondary hemostasis thus leads to the formation of a clot composed of platelets in a meshwork of fibrin fibers running in all directions (1-3).

Under normal conditions the activation of hemostasis is controlled by anticoagulant factors including tissue factor pathway inhibitor (TFPI), antithrombin, and the protein C system. Moreover, the fibrinolytic system removes the clot once the vessel wall injury is healed. Fibrinolysis is initiated when vascular endothelium in the vicinity of the injury releases tissue plasminogen activator (tPA) which activates the pro-enzyme plasminogen to plasmin. Plasmin is a proteolytic enzyme capable of degrading fibrin into various degradation products and is in this way responsible for removing the blood clot. Fibrinolysis is not only regulated by activators such as tPA but also by different inhibitory proteins. Plasminogen activator inhibitor type I (PAI-I) is a direct inhibitor of tPA and plasmin inhibitor (PI) inactivates plasmin.

## The hemostatic system in liver disease

In patients with (severe) liver disease substantial changes in the hemostatic system are frequently observed. These alterations concern both the primary and secondary hemostasis as well as the fibrinolytic system.

### *Primary hemostasis ; thrombocytopenia, platelet function, and VWF*

Chronic liver disease is often characterized by a mild to moderate thrombocytopenia, which is related to different causes. One of the main causes is portal hypertension which is accompanied by increased platelet sequestration in the spleen as a result of congestive splenomegaly (4,5). In patients with severe disease up to 90% of the platelets may be stored in the spleen. In addition,

Correspondence to : Ton Lisman, Ph.D., Surgical Research Laboratory, Department of Surgery, University Medical Center Groningen, BA44, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. E-mail : j.a.lisman@chir.umcg.nl

Submission date : 08/10/2009
Acceptance date : 22/10/2009

patients with liver disease have a reduced thrombopoietin production by the liver (6). Other mechanisms responsible for thrombocytopenia are a reduced platelet half-life, which may be related to autoantibodies, and finally folic acid deficiency and defective platelet production as a result of toxic effects of alcohol on megakaryocytopoiesis in patients with alcohol-induced liver disease (7,8).

Besides thrombocytopenia, also platelet function defects are found in patients with liver disease (9). Platelet aggregation is diminished as a result of different factors such as impaired signal transduction (10), proteolysis of platelet membrane proteins by plasmin (11), and increased production of the endothelial-derived platelet inhibitor nitric oxide and prostacyclin (12). However, the results of different studies are conflicting. Ordinas *et al*. (13) reported that platelet function defects were also present under flow conditions but in different studies it was shown that the defective adhesion under flow was only due to thrombocytopenia and a low hematocrit (9,14). It thus may be that the intrinsic platelet defects observed in static laboratory assays are not relevant under flow conditions.

Substantially elevated levels of VWF are frequently found in patient with liver disease (15). Besides the important function in adhesion of platelets to the vessel wall VWF is also a carrier protein for blood clotting factor VIII. This interaction is required for normal factor VIII survival in the circulation. There may be different mechanisms responsible for the elevated levels of VWF. VWF is produced by the endothelium and it is suggested that as a result of endothelial damage, mediated by for example bacterial infection, VWF release is increased (15,16). Also, there may be enhancement of VWF protein expression in the diseased liver (17). The substantially elevated levels of VWF have been shown to compensate (in part) for thrombocytopenia and platelet function defects in laboratory models in which platelet adhesion and aggregation was studied under flow conditions (16).

Furthermore, VWF reactivity is regulated by a cleaving protease referred to as 'a disintegrin-like and metalloprotease with thrombospondin type 1 repeats' (ADAMTS-13), which is mainly synthesized by stellate cells in the liver (18). The production of ADAMTS-13 is reduced in patients with liver disease which may lead to a relative increase in VWF reactivity which may also compensate for thrombocytopenia and platelet function defects (16,18).

### *Secondary hemostasis ; coagulation factors, fibrinogen and anticoagulation factors*

Hepatocytes are responsible for the synthesis of all coagulation factors involved in the coagulation cascade, with the exception of factor VIII. The main site of production of factor VIII in the liver is in the hepatic sinusoidal endothelial cells, although extrahepatic synthesis of factor VIII is presumably also of relevance (19). A diminished amount of coagulation factors V, VII, IX, X, XI and prothrombin is commonly found in patients with liver disease (20). However, an increased level of factor VIII is observed and probably this is related to the elevated level of its carrier protein VWF and to a decreased expression of the low-density-lipoprotein-related receptor by the liver. This receptor is involved in the process of clearing factor VIII from the circulation (17). Besides this, the hepatic sinusoidal endothelial cells maintain the capacity to produce factor VIII even when the liver function is severely deteriorated and in addition alternative pathways of factor VIII synthesis may be upregulated in patients with liver disease (21-23).

The quantitative defects of coagulation factors may be accompanied by qualitative defects of the vitamin K-dependent clotting factors VII, IX, X and prothrombin, as well as the vitamin K-dependent inhibitors protein C and S. Vitamin K is a cofactor for the gamma-glutamyl carboxylase, an enzyme produced in the liver, which is involved in essential post-translational modifications in the vitamin K-dependent clotting factors. As a result of vitamin K deficiency or a decreased production of carboxylase in patients with liver disease the function of the clotting factors may be impaired (24).

The level of fibrinogen in patients with liver disease depends on the type of the disease. It is in the normal range in patients with chronic liver disease but fibrinogen may be decreased in patients with decompensated cirrhosis or acute liver failure (25). However, a qualitative defect in fibrinogen is common in all types of liver disease due to an increased content of sialic acid (26). Hypersialisation of fibrinogen accounts for an impaired fibrinogen polymerization but does not affect the interaction of fibrinogen with platelets (27,28).

The liver is also involved in the production of anticoagulant proteins such as protein C and S, antithrombin, heparin cofactor II, and $\alpha_2$-macroglobulin. These inhibitors are frequently present in reduced levels as a consequence of the reduced synthetic capacity of the liver (29). The partial deficiencies in the anticoagulant systems may (in part) compensate for the defects in procoagulant factors (see section on rebalanced hemostatic system).

### *Fibrinolytic system ; profibrinolytics and antifibrinolytics*

All proteins involved in fibrinolysis are synthesized by the liver, with the exception of tissue plasminogen activator (tPA) and plasminogen activator inhibitor type I (PAI-I). As a consequence of liver disease, reduced amounts of both the profibrinolytic protein plasminogen and the antifibrinolytic proteins plasmin inhibitor (PI), factor XIII and thrombin-activatable fibrinolysis inhibitor (TAFI) are found (30-32). Plasma levels of tPA are increased as a result of enhanced release from endothelium and/or reduced clearance by the diseased

liver (33). PAI-I levels are also slightly increased but not to the same extent as the increase of tPA (34). Only in acute liver failure PAI-I levels are substantially elevated (35).

For decades, the net effects of the changes in the fibrinolytic system were described as hyperfibrinolysis with the exception of patients with acute hepatic failure in which the elevated levels of tPA are balanced by the antifibrinolytic protein PAI-I (35,36). However, recently we found that the evidence for the hyperfibrinolytic state in patients with liver disease was rather weak. Evidence was mainly based on elevated markers of fibrinolytic activation, such as D-dimers, but this elevation may simply reflect reduced clearance by the liver (1), and by several types of clot lysis assays which all have specific disadvantages (37-41). Using a novel, overall clot lysis assay, we found no evidence for hyperfibrinolysis in patients with cirrhosis and concluded that it is likely that the reduction in antifibrinolytic proteins is balanced by the concomitant reduction in profibrinolytic proteins (31). This is supported by the observation that patients with liver disease do not show a typical hyperfibrinolytic bleeding tendency, i.e. delayed bleeding after trauma or surgery (42). An exception to this is liver transplantation where t-PA may accumulate in the circulation during the anhepatic stage of the procedure, resulting in hyperfibrinolytic bleeding (43). Bleeding problems in patients with cirrhosis usually occur immediately (44).

## A rebalanced hemostatic system

As described above, liver disease results in alterations in both the pro- and antihemostatic pathways. The net effect of all these changes has long been unclear and it was generally believed that patients with liver disease have a bleeding tendency related to an impaired hemostasis. However, laboratory models and clinical data have showed evidence for a rebalanced hemostasis in liver disease, i.e. changes in prohemostatic pathways are counteracted by changes in antihemostatic pathways (2,45-48). In this way, a new 'rebalanced' hemostatic status occurs, which is balanced in a similar way as compared to healthy individuals (Fig. 1). However, this new hemostatic balance presumably has much narrower margins compared to healthy individuals, and can turn more easily to either hypocoagulation or hypercoagulation (47,49,50).

The concept of rebalanced hemostasis has been elegantly exemplified by Tripodi *et al*. (51), who used modern laboratory techniques to study thrombin generation in patients with liver disease. In this study, cirrhotic patients with abnormal standard coagulation tests (see section on conventional diagnostic tests) were tested for total thrombin generating capacity. In line with the prolonged prothrombin time (PT), thrombin generation was significantly lower in patients with stable cirrhosis than in controls. However, when thrombin generation was measured in the presence of thrombomodulin, an activator of protein C and thus also taking the reduction of anti-

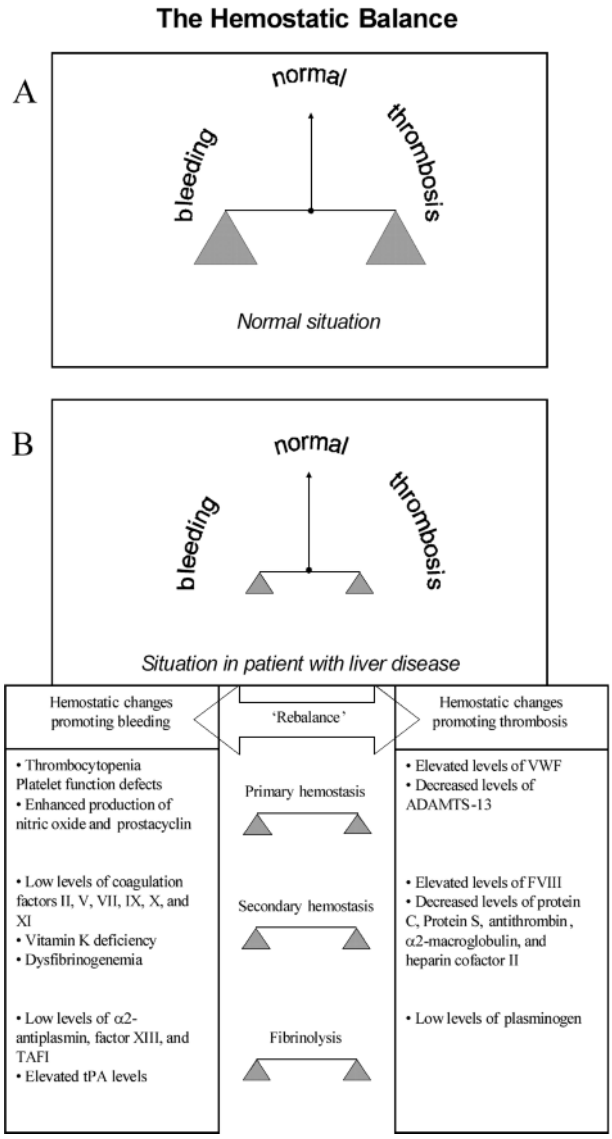


Fig. 1. — The rebalanced hemostatic system in patients with liver disease. Hemostatic alterations occur at both sides of the balance, resulting in a rebalanced system with much narrower margins which can turn more easily to either a hypo- or a hypercoagulable state.
Reprinted with permission from *Current Opinion in Organ Transplantation* (47). Copyright 2008, Wolters Kluwer Health.

coagulant factors in patients with liver disease into account, thrombin generation in patients was comparable to the thrombin generation in controls. Thus, when the coagulation system was tested in a physiologically relevant manner, no differences between patients and controls were detected, although the PT was clearly prolonged. In other words, although the PT suggests a hypocoagulable state in these patients, modern thrombin generation assays suggest otherwise.

Clinical data supporting the concept of rebalanced hemostasis include a lack of major blood loss in a great proportion of patients with end stage liver disease undergoing a major invasive procedure, e.g. liver transplantation (52,53). Although blood loss and transfusion

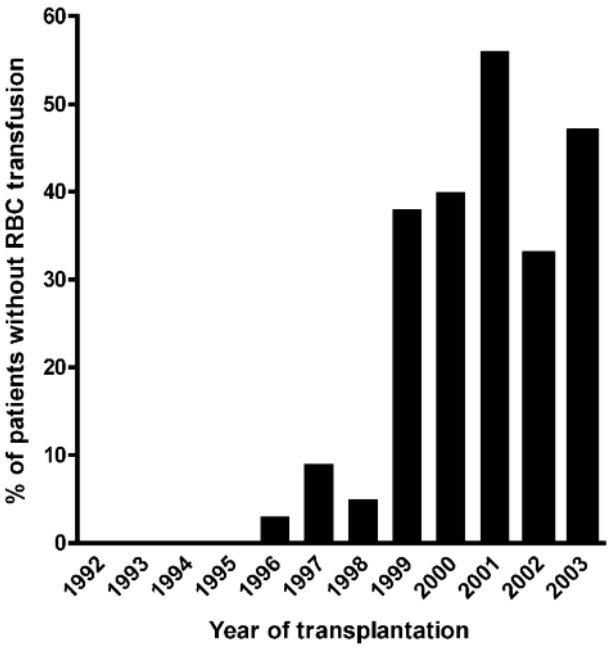


Fig. 2. — Percentage of adult patients who did not require red blood cell transfusion during a first orthotopic liver transplantation at the University Medical Center Groningen in the period 1992-2003. As shown, nowadays up to 50% of the patients transplanted does not require any transfusion.
Reprinted with permission from *Digestive Surgery* (52). Copyright 2004, S. Karger AG Basel.

requirements during liver transplantation used to be substantial, nowadays blood loss during transplantation is often rather limited and up to 50% of the patients transplanted, depending on the center, does not require any transfusion during the procedure (Fig. 2). The reduced transfusion requirements are possibly due to increased surgical experience, improvements in surgical techniques and improvement of anesthesiological care (52), but an important factor may also be that nowadays active attempts are made to perform the procedure under a low central venous pressure (CVP). A low CVP is accomplished by fluid restriction, which includes a very restricted use of prophylactic transfusion of plasma products, and in some centers even includes preoperative phlebotomy (53). It must be concluded that liver disease is not per definition associated with a severe hypocoagulation in this situation. Besides the lack of major blood loss multiple studies have shown that thromboembolic complications occur in patient with liver disease (49,54-56), demonstrating that these patients are not excluded from thromboembolic complications as was previously thought.

## Bleeding in patients with liver disease and during liver transplantation - treatment options

Although the hemostatic balance in patients with liver disease appears relatively well preserved, bleeding complications do occur. The most relevant bleeding problem in patients with liver disease is bleeding form ruptured esophageal varices (57). The role of an impaired hemostasis in variceal bleeding is doubtful and probably it has a mechanical cause, i.e. local vascular abnormalities and an increased splanchnic blood pressure (57).

Other bleeding complications may be hemostasis-related, and may be a result of poorly understood changes in the hemostatic balance resulting in a hypocoagulable state. These complications include bruising, epistaxis, mucosal bleeding (dental/oral), gastro-intestinal bleeding, and bleeding associated with invasive procedures. These problems are usually not life-threatening but there remain patients with severe bleeding in which no specific cause can be identified (1). The individual patient with severe hemostasis-related bleeding is usually not distinct from non-bleeding patients with liver failure, and the challenge for the future will be to develop hemostasis tests that predict these incidental severe bleeding complications in patients with liver failure. The most challenging invasive procedure for patients with liver disease is a liver transplantation. In the past this procedure required extensive blood transfusions but as stated before transfusion requirements have dropped tremendously (52). However, also during liver transplantation there remain patients that do require massive transfusion, which cannot be predicted from standard laboratory tests.

Factors that may aggravate bleeding in patients with liver disease are renal failure, which is common in advancing liver disease, and bacterial infections. Renal failure usually leads to a bleeding risk due to acquired platelet dysfunction, abnormal platelet-vessel wall interaction, endothelial abnormalities, and anemia (58,59). Endotoxins from bacteria can inhibit platelet function and coagulation. On the other hand, bacterial infections can also stimulate the coagulation process by increased endothelial activation (60,61).

Management of hemostatic disorders in patients with liver disease can be divided in prophylactic therapy versus rescue therapy. Traditional guidelines advise to use prophylactic strategies and not to perform invasive procedures when routine hemostatic tests are abnormal (45). Thus, a prolonged PT should be corrected by infusion of plasma, and a low platelet count should be corrected by administration of platelet concentrates. However, this strategy is doubtful for a number of reasons. As we have seen, conventional coagulation tests are probably not reliable in patients with liver disease (45). Besides this, normalisation of tests is rarely achieved by transfusions (62) and the effectiveness of prophylactic management has not been proven in clinical studies (63). In addition the awareness is rising that there are substantial side effects associated with plasma or platelet transfusion (64).

Side effects include transfusion reactions, risk of infection, transfusion-related acute long injury (TRALI) and even an increased bleeding risk by exacerbation of portal hypertension and intravascular volume over-

load (45,47,65). Moreover, transfusion of blood products may result in an increasing risk of postoperative morbidity and even mortality. For these reasons, we believe that hemostatic treatment in patients with liver disease should be aimed at reversal of clinically evident coagulopathy rather than laboratory evident coagulopathy (1). We advocate a 'wait and see' policy in which transfusions are mainly (if not exclusively) given on-demand, i.e., when bleeding occurs. Exceptions include very high-risk procedures e.g. intracranial pressure monitor placement in patients with acute liver failure. In this procedure bleeding could be detected too late resulting in irreversible damage.

Prohemostatic medications are frequently prophylactically used during liver surgery. They can be divided in synthetic antifibrinolytic agents (tranexamic acid, –aminocaproic acid and aprotinin), desmopressin (DDAVP) and recombinant factor VIIa (rFVIIa) (66). Antifibrinolytic agents have proven to be efficacious in reducing perioperative blood loss in liver transplant recipients (67,68). However, aprotinin has been taken of the market in 2008 due to an increased risk of morbidity and mortality following cardiac surgery (69), although little evidence for detrimental side effects of aprotinin in liver transplantation exists (70,71). Desmopressin is an analogue of the antidiuretic hormone vasopressin and increases secretion of VWF from endothelial cells. This results in a correction of the bleeding time (72), and a clinically relevant improvement of hemostasis in patients with von Willebrand's disease or mild hemophilia, but unfortunately no clinical effect in patients with liver disease has been proven (73-75). The role of rFVIIa in liver surgery is still unclear. Two large multicenter trials did not show a significant reduction of blood loss during liver transplantation (76,77).

It should be recalled that the earlier mentioned non-hematological factors are also of great importance in preventing and treating bleeding problems. Thus measures to reduce portal hypertension, to treat infection, and to improve renal function must not be forgotten (45).

## Thromboembolic complications in patients with liver disease and after liver transplantation – treatment options

Although traditionally patients with liver disease were considered to be 'auto-anticoagulated', it has recently been recognised that cirrhosis is often associated with hypercoagulation rather than hypocoagulation (50). Recent studies have shown that 0.5-1.8% of hospitalized patients with cirrhosis develop venous thrombosis. This number might even be an underestimation because in cirrhotic patients a venous thrombosis or pulmonary embolism may be difficult to diagnose (49,53-56). In addition to systemic venous thrombosis patient with liver disease may develop thrombosis in the portal and mesenteric veins. This is probably due to decreased levels of naturally occurring anticoagulants, portal hypertension which results in alterations in blood flow, and the risk may be enhanced by inherited thrombophilic mutations such as factor V Leiden (78,79).

After liver transplantation the most important liver-related thrombosis is hepatic artery thrombosis (HAT). It occurs in 1.6-8.9 % of the liver transplant recipients and is a severe complication sometimes requiring retransplantation (80). HAT may occur in the early phase after transplantation but can occur years after the procedure as well. Other types of liver-related thrombosis, including thrombosis of the portal vein or vena cava, are less common (81). The increased risk of thrombotic complications is probably due to transplantation-related triggers that stimulate coagulation or platelet adhesion, surgical factors, as well as non-surgical factors, including donor age (82). In addition, systemic thrombotic diseases (such as myocardial infarctions and stroke) have a higher prevalence in patients after transplantation, which may be related to the use of immunosuppressants which contribute to hypertension, dyslipedemia, and diabetes (83-86).

As a result of the classically described bleeding tendency of patients with liver disease, the use of anticoagulants to prevent thrombosis following a liver transplantation has long been limited. However, not only is there evidence that hemostasis prior to liver transplantation is relatively preserved, also evidence for a hypercoagulable state following liver transplantation exists (87,88) and therefore the use of anticoagulant drugs should be reconsidered. Because platelets play a central role in arterial thrombosis, antiplatelet therapy, for example using aspirin, seems an attractive method to prevent HAT and cardiovascular events (89,90).

Vivarelli *et al.* (91) investigated in a retrospective study the effect of long-term aspirin administration on the incidence of late HAT. They showed that aspirin reduced the risk of late HAT after liver transplantation in patients that had other risk factors for the development of HAT, i.e. donors who died from a cerebrovascular accident or the use of an arterial iliac conduit. These result might be of clinical relevance and require further investigation in prospective studies.

## Conventional diagnostic tests and their disadvantages

As described, liver disease may result in a rebalanced hemostasis which can turn more easily to either a hypo- or hypercoagulable state as compared to healthy individuals. Unfortunately the conventional diagnostic tests of platelets and coagulation are not capable of predicting bleeding or thromboembolic complications in patients with liver disease.

Diagnostic tests of platelets include platelet count, bleeding time and platelet aggregation tests. The platelet count in patients with liver disease is usually decreased but sufficiently high to support normal hemostasis. The bleeding time is often prolonged but a correlation with

bleeding symptoms has not been found. The same is true for platelet aggregation tests which are frequently abnormal, but the clinical significance is unclear.

The coagulation cascade is tested by the prothrombin time (PT) and activated partial thromboplastin time (APTT). These tests measure the generation of thrombin as a function of procoagulant factors (1,2). In patients with liver disease the PT and APTT are often prolonged, which is suggestive of a bleeding tendency. However, both tests are insensitive to changes in the anticoagulant system. The interpretation of prolonged screening tests of coagulation in complex disorders of hemostasis should be different from the interpretation of prolonged tests in patient with defects only in the procoagulant system, such as hemophilia. (92). As mentioned before, Tripodi *et al*. modified the PT into a more sophisticated thrombin generation test, which included anticoagulant factors by adding thrombomodulin. This test indicated a normal thrombin generation in patients with liver disease, which suggests that the prolonged PT in patients with liver disease may not indicate a bleeding risk (51).

It is common practice to use the international normalized ratio (INR) instead of the PT in patients with liver disease (93). However, the INR system is developed to monitor anticoagulant therapy with vitamin K antagonists and may not be suitable for patients with liver disease. The use in patients with liver disease leads to substantial inter-laboratory variation of the INR due to differences in laboratory methods, which affects the MELD score (94-96). The MELD score (Model of End stage Liver Disease) is used to prioritise the candidates for a liver transplantation and the INR is an important determinant of the MELD score. Trotter *et al.* (94) showed 26% variability in INR results between three different laboratories, and these results were confirmed in a recent European multicenter study (96). These variations in INR profoundly affect the MELD score. The MELD score in a single patient may differ up to 12 points (mean of 4.8 points in our study) when the tests are performed in different laboratories. A patients' chance on receiving a donor liver may thus in part also be related to the laboratory in which the INR used to calculate the score was determined (96).

## Conclusion

There may be no causal relationship between changes in classical laboratory hemostasis tests in patients with liver disease and bleeding. Accumulating evidence suggest that the hemostatic system in these patients is rebalanced, albeit with narrower margins. Therefore, minor alterations in this delicate balance may lead to hypo- or hypercoagulation, which could become clinically evident as bleeding or thrombosis. This concept of a rebalanced hemostatic system in patients with liver disease is based on an expanding amount of laboratory studies and clinical data which are confirmed by multiple centers, but further investigation is required to definitively prove the concept of rebalanced hemostasis in patients with liver disease. Moreover, additional research should focus on the relevance of individual hemostatic defects.

In the view that the bleeding tendency in patients with liver disease is not primarily caused by an impaired hemostasis, we have to improve our understanding of the bleeding diathesis in patients with liver disease. The challenge for the future will be to develop hemostasis tests that predict the incidental severe bleeding complications in patients with liver disease, and also tests to identify patients at risk for thrombosis are urgently required. Furthermore, randomised clinical studies should evaluate the safety and efficacy of a restricted transfusion policy in patients with liver disease undergoing invasive procedures, such as liver transplantation. Finally, prospective, multicenter and randomized studies to evaluate safety and efficacy of different anticoagulant strategies to prevent thrombosis in liver transplant patients should be initiated.

## References


1. LISMAN T., LEEBEEK F.W.G. Hemostatic alterations in liver disease : a review on pathophysiology, clinical consequences, and treatment. *Dig. Surg.*, 2007, **24** : 250-258.
2. TRIPODI A., MANNUCCI P.M. Abnormalities of hemostasis in chronic liver disease : reappraisal of their clinical significance and need for clinical and laboratory research. *J. Hepatol.*, 2007, **46** : 727-733.
3. FURIE B., FURIE B.C. Mechanisms of thrombus formation. *N. Engl. J. Med.*, 2008, **359** : 938-949.
4. ASTER R.H. Pooling of platelets in the spleen : role in the pathogenesis of 'hypersplenic' thrombocytopenia. *J. Clin. Invest.*, 1966, **45** : 645-657.
5. SCHMIDT K.G., RASMUSSEN J.W., BEKKER C., MADSON P.E. Kinetics and in vivo distribution of 111-In-labeled autologous platelets in chronic hepatic disease : mechanisms of thrombocytopenia. *Scan. J. Haematol.*, 1985, **34** : 39-46.
6. GOULIS J., CHAU T.N., JORDAN S., MEHTA A.B., WATKINSON A., ROLLES K., BURROUGHS A.K. Thrombopoietin concentrations are low in patients with cirrhosis and thrombocytopenia and are restored after orthotopic liver transplantation. *Gut*, 1999, **44** : 754-758.
7. KAJIHARA M., KATO S., OKAZAKI Y., KAWAKAMI Y., ISHII H., IKEDA Y., KUWANA M. A role of autoantibody-mediated platelet destruction in thrombocytopenia in patients with cirrhosis. *Hepatology*, 2003, **37** : 1267-1276.
8. LEVINE R.F., SPIVAK J.L., MEAGHER R.C., SIEBER F : Effect of ethanol on thrombopoiesis. *Br. J. Haematol.*, 1986, **62** : 345-354.
9. ESCOLAR G., CASES A., VIÑAS M., PINO M., CALLS J., CIRERA I., ORDINAS A. Evaluation of acquired platelet dysfunctions in uremic and cirrhotic patients using the platelet function analyzer (PFA-100) : influence of hematocrit elevation. *Haematologica*, 1999, **84** : 614-619.
10. LAFFI G., MARRA F., FAILLI P., RUGGIERO M., CECCHI E., CARLONI V., GIOTTI A., GENTILINI P. Defective signal transduction in platelets from cirrhotics is associated with increased cyclic nucleotides. *Gastroenterology*, 1993, **105** : 148-156.
11. PASCHE B., OUIMET H., FRANCIS S., LOSCALZO J. Structural changes in platelet glycoprotein IIb/IIIa by plasmin : determinants and functional consequences. *Blood*, 1994, **83** : 404-414.
12. TURITTO V.T., BAUMGARTNER H.R. Platelet interaction with subendothelium in a perfusion system : physical role of red blood cells. *Microvasc. Res.*, 1975, **9** : 335-344.
13. ORDINAS A., ESCOLAR G., CIRERA I., VIÑAS M., COBO F., BOSCH J., TERÉS J., RODÉS J. Existence of a platelet-adhesion defect in patients with cirrhosis independent of hematocrit : studies under flow conditions. *Hepatology*, 1996, **24** : 1137-1142.
14. LISMAN T., ADELMEIJER J., DE GROOT P.G., JANSSEN H.L., LEEBEEK F.W. No evidence for an intrinsic platelet defect in patients with liver cirrhosis - studies under flow conditions. *J. Thromb. Haemost.*, 2006, **4** : 2070-2072.
15. FERRO D., QUINTARELLI C., LATTUADA A., LEO R., ALESSANDRONI M., MANNUCCI P.M., VIOLI F. High plasma levels of

von Willebrand factor as a marker of endothelial perturbation in cirrhosis : relationship to endotoxemia. *Hepatology*, 1996, **23** : 1377-1383.
16. LISMAN T., BONGERS T.N., ADELMEIJER J., JANSSEN H.L., DE MAAT M.P., DE GROOT P.G., LEEBEEK F.W. Elevated levels of von Willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology*, 2006, **44** : 53-61.
17. HOLLESTELLE M.J., GEERTZEN H.G.M., STRAATSBURG I.H., VAN GULIK T.M., VAN MOURIK J.A. Factor VIII expression in liver disease. *Thromb. Haemost.*, 2004, **91** : 267-275.
18. MANNUCCI PM., CANCIANI MT., FORZA I., LUSSANA F., LATTUADA A., ROSSI E. Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. *Blood*, 2001, **98** : 2730-2735.
19. MADEIRA C.L., LAYMAN M.E., DE VERA R.E., FONTES P.A., RAGNI M.V : Extrahepatic factor VIII production in transplant recipient of hemophilia donor liver. *Blood*, 2009, **113** : 5364-5365.
20. KERR R., NEWSOME P., GERMAIN L., THOMSON E., DAWSON P., STIRLING D., LUDLAM C.A. Effects of acute liver injury on blood coagulation. *J. Thromb. Haemost.*, 2003, **1** : 754-759.
21. HOLLESTELLE M.J., THINNES T., CRAIN K., STIKO A., KRUIJT J.K., VAN BERKEL T.J., LOSKUTOFF D.J., VAN MOURIK J.A. Tissue distribution of factor VIII gene expression in vivo – a closer look. *Thromb. Haemost.*, 2001, **86** : 855-861.
22. HOLLESTELLE M.J., POYCK P.P., HOLLESTELLE J.M., MARSMAN H.A., MOURIK J.A., GULIK T.M. Extrahepatic factor VIII expression in porcine fulminant hepatic failure. *J. Thromb. Haemost.*, 2005, **3** : 2274-2280.
23. JACQUEMIN M., NEYRINCK A., HERMANNS M.I., LAVEND'HOMME R., REGA F., SAINT-REMY J.M., PEERLINCK K., VAN RAEMDONCK D., KIRKPATRICK C.J. FVIII production by human lung microvascular endothelial cells. *Blood*, 2006, **108** : 515-517.
24. BLANCHARD R.A., FURIE B.C., JORGENSEN M., KRUGER S.F., FURIE B. Acquired vitamin K-dependent carboxylation deficiency in liver disease. *N. Engl. J. Med.*, 1981, **305** : 242-248.
25. DE MAAT M.P., NIEUWENHUIZEN W., KNOT E.A., VAN BUUREN H.R., SWART G.R. Measuring plasma fibrinogen levels in patients with liver cirrhosis. The occurrence of proteolytic fibrin(ogen) degradation products and their influence on several fibrinogen assays. *Thromb. Res.*, 1995, **78** : 353-362.
26. FRANCIS J.L., ARMSTRONG D.J. Acquired dysfibrinogenaemia in liver disease. *J. Clin. Pathol.*, 1982, **35** : 667-672.
27. MARTINEZ J., MACDONALD K.A., PALASCAK J.E. The role of sialic acid in the dysfibrinogenemia associated with liver disease : distribution of sialic acid on the constituent chains. *Blood*, 1983, **61** : 1196-1202.
28. HARFENIST E.J., PACKHAM M.A., MUSTARD J.F. Effects of variant gamma chains and sialic acid content of fibrinogen upon its interactions with ADP-stimulated human and rabbit platelets. *Blood*, 1984, **64** : 1163-1168.
29. LISMAN T., LEEBEEK F.W.G., DE GROOT P.G. Haemostatic abnormalities in patients with liver disease. *J. Hepatol.*, 2002, **37** : 280-287.
30. STEIN S.F., HARKER L.A. Kinetic and functional studies of platelets, fibrinogen, and plasminogen in patients with hepatic cirrhosis. *J. Lab. Clin. Med.*, 1982, **99** : 217-230.
31. LISMAN T., LEEBEEK F.W., MOSNIER L.O., BOUMA B.N., MEIJERS J.C., JANSSEN H.L., NIEUWENHUIS H.K., DE GROOT P.G. Thrombin-activatable fibrinolysis inhibitor deficiency in cirrhosis is not associated with increased plasma fibrinolysis. *Gastroenterology*, 2001, **121** : 131-139.
32. BILAND L., DUCKERT F., PRISENDER S., NYMAN D. Quantitative estimation of coagulation factors in liver disease. The diagnostic and prognostic value of factor XIII, factor V and plasminogen. *Thromb. Haemost.*, 1978, **39** : 646-656.
33. LEIPER K., CROLL A., BOOTH N.A., MOORE N.R., SINCLAIR T., BENNETT B. Tissue plasminogen activator, plasminogen activator inhibitors, and activator-inhibitor complex in liver disease. *J. Clin. Pathol.*, 1994, **47** : 214-217.
34. LEEBEEK F.W.G., KLUFT C., KNOT E.A.R., DE MAAT M.P.M., WILSON J.H.P. A shift in balance between profibrinolytic and antifibrinolytic factors causes enhanced fibrinolysis in cirrhosis. *Gastroenterology*, 1991, **101** : 1382-1390.
35. PERNAMBUCO J.R., LANGLEY P.G., HUGHES R.D., IZUMI S., WILLIAMS R. Activation of the fibrinolytic system in patients with fulminant liver failure. *Hepatology*, 1993, **18** : 1350-1356.
36. LEEBEEK F.W.G. Hyperfibrinolysis in liver cirrhosis. *In* : GREENWALDT P. (ed). Fibrinolysis in Disease. Boca Raton, CRC Press, 1995, pp, 194-201.
37. BEN ARI Z., OSMAN E., HUTTON R.A., BURROUGHS A.K. Disseminated intravascular coagulation in liver cirrhosis : fact or fiction ? *Am. J. Gastroenterol.*, 1999, **94** : 2977-2982.
38. VUKOVICH T., TEUFELSBAUER H., FRITZER M., KREUZER S., KNOFLACH P. Hemostasis activation in patients with liver cirrhosis. *Thromb. Res.*, 1995, **77** : 271-278.
39. FRANCIS R.B., FEINSTEIN D.I. Clinical significance of accelerated fibrinolysis in liver disease. *Haemostasis*, 1984, **14** : 460-465.
40. COLUCCI M., BINETTI B.M., BRANCA M.G., 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.
41. WILDE J.T., KITCHEN S., KINSEY S., GREAVES M., PRESTON F.E. Plasma D-dimer levels and their relationship to serum fibrinogen/fibrin degradation products in hypercoagulable states. *Br. J. Haematol.*, 1989, **71** : 65-70.
42. LEE M.H., VOSBURGH E., ANDERSON K., MC DONAGH J. Deficiency of plasma plasminogen activator inhibitor 1 results in hyperfibrinolytic bleeding. *Blood*, 1993, **81** : 2357-2362.
43. PORTE R.J., BONTEMPO F.A., KNOT E.A., LEWIS J.H., KANG Y.G., STARZL T.E. Systemic effects of tissue plasminogen activator-associated fibrinolysis and its relation to thrombin generation in orthotopic liver transplantation. *Transplant.*, 1989, **47** : 978-984.
44. PICCININO F., SAGNELLI E., PASQUALE G., GIUSTI G. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. *J. Hepatol.*, 1986, **2** : 165-173.
45. CALDWELL S.H., HOFFMAN M., LISMAN T., MACIK B.G., NORTHUP P.G., REDDY K.R., TRIPODI A., SANYAL A.J. ; COAGULATION IN LIVER DISEASE GROUP. Coagulation disorders and hemostasis in liver disease : pathophysiology and critical assessment of current management. *Hepatology*, 2006, **44** : 1039-1046.
46. LISMAN T., CALDWELL S.H., LEEBEEK F.W.G., PORTE R.J. Hemostasis in chronic liver disease - Is chronic liver disease associated with a bleeding diathesis ? *J. Thromb. Haemost.*, 2006, **4** : 2059-2060.
47. WARNAAR N., LISMAN T., PORTE R.J. The two tales of coagulation in liver transplantation. *Curr. Opin. Organ. Transplant.*, 2008, **13** : 298-303.
48. MANNUCCI P.M. Abnormal hemostasis tests and bleeding in chronic liver disease : Are they related ? No. *J. Thromb. Haemost.*, 2006, **4** : 721-723.
49. NORTHUP P.G., MCMAHON M.M., RUHL A.P., ALTSCHULER S.E., VOLK-BEDNARZ A., CALDWELL S.H., BERG C.L. Coagulopathy does not fully protect hospitalized cirrhosis patients form peripheral venous thromboembolism. *Am. J. Gastroenterol.*, 2006, **101** : 1524-1528.
50. NORTHUP P.G., SUNDARAM V., FALLON M.B., REDDY K.R., BALOGUN R.A., SANYAL A.J., ANSTEE Q.M., HOFFMAN M.R., IKURA Y., CALDWELL S.H. ; COAGULATION IN LIVER DISEASE GROUP. Hypercoagulation and thrombophilia in liver disease. *J. Thromb. Haemost.*, 2008, **6** : 2-9.
51. TRIPODI A., SALERNO F., CHANTARANGKUL V., CLERICI M., CAZZANIGA M., PRIMIGNANI M., MANNUCCI P.M. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology*, 2005, **41** : 553-558.
52. DE BOER M.T., MOLENAAR I.Q., HENDRIKS HG., SLOOFF M.J., PORTE R.J. Minimizing blood loss in liver transplantation : progress through research and evolution of techniques. Dig Surg, 2005, **22** : 265-275.
53. MASSICOTTE L., LENIS S., THIBEAULT L., SASSINE MP., SEAL R.F., ROY A. Effect of low central venous pressure and phlebotomy on blood product transfusion requirements during liver transplantation. *Liver transplant.*, 2006, **12** : 117-123.
54. SØGAARD K.K., HORVATH-PUHO E., GRØNBAEK H., JEPSEN P., VILSTRUP H., SØRENSEN H.T. Risk of venous thromboembolism in patients with liver disease : a nationwide population-based case-control study. *Am. J. Gastroenterol.*, 2009, 104 : 96-101.
55. GARCIA-FUSTER M.J., ABDILLA N., FABIA M.J., FORNER M.J., CUÑAT A : Venous thromboembolism and liver cirrhosis. Rev Esp Enferm Dig, 2008, **100** : 259-262.
56. 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.
57. SHARARA A.I., ROCKEY D.C. Gastroesophageal variceal hemorrhage. *N. Engl. J. Med.*, 2001, **345** : 669-681.
58. NORIS M., REMUZZI G. Uremic bleeding : closing the circle after 30 years of controversies ? *Blood*, 1999, **94** : 2569-2574.
59. JOIST J.H., GEORGE J.N. Hemostatic abnormalities in liver and renal disease. *In* : COLMAN R.W., HIRSH J., MARDER V.J., CLOWES A.E., GEORGE J.N. (eds). Hemostasis and Thrombosis. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 955-973.
60. THALHEIMER U., TRIANTOS C.K., SAMONAKIS D.N., PATCH D., BURROUGHS A.K. Infection, coagulation, and variceal bleeding in cirrhosis. *Gut*, 2005, **54** : 556-563.

61. REITSMA P.H., BRANGER J., VAN DEN B.B., WEIJER S., VAN DER P.T., MEIJERS J.C. Procoagulant protein levels are differentially increased during human endotoxemia. *J. Thromb. Haemost.*, 2003, **1** : 1019-1023.
62. YOUSSEF W.I., SALAZAR F., DASARATHY S., BEDDOW T., MULLEN K.D. Role of fresh-frozen plasma infusion in correction of coagulopathy of chronic liver disease : a dual phase study. *Am. J. Gastroenterol.*, 2003, **98** : 1391-1394.
63. SEGAL J.B., DZIK W.H. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures : an evidence-based review. *Transfusion*, 2005, **45** : 1413-1425.
64. ALTER H.J., KLEIN H.G. The hazards of blood transfusion in historical perspective. *Blood*, 2008, **112** : 2617-2626.
65. PEREBOOM I.T.A., DE BOER M.T., HAAGSMA E.B., HENDRIKS H.G.D., LISMAN T., PORTE R.J. Platelet transfusion during liver transplantation is associated with increased postoperative mortality due to acute long injury. Anesth analg, 2009, **108** : 1083-1091.
66. MANNUCCI P.M., LEVI M. Prevention and treatment of major blood loss. *N. Engl. J. Med.*, 2007, **356** : 2301-2311.
67. PORTE R.J., MOLENAAR I.Q., BEGLIOMINI B., GROENLAND T.H., JANUSZKIEWICZ A., LINDGREN L., PALARETI G., HERMANS J., TERPSTRA O.T. Aprotinin and transfusion requirements in orthotopic liver transplantation : a multicentre randomised double-blind study. EMSALT Study Group. Lancet, 2000, **355** : 1303-1309.
68. BOYLAN J.F., KLINCK J.R., SANDLER A.N., ARELLANO R., GREIG P.D., NIERENBERG H., ROGER S.L., GLYNN M.F. Tranexamic acid reduces blood loss, transfusion requirements, and coagulation factor use in primary orthotopic liver transplantation. Anesthesiology, 1996, **85** : 1043-1048.
69. FERGUSSON D.A., HÉBERT P.C., MAZER C.D., FREMES S., MAC ADAMS C., MURKIN J.M., TEOH K., DUKE P.C., ARELLANO R., BLAJCHMAN M.A., BUSSIÈRES J.S., CÔTÉ D., KARSKI J., MARTINEAU R., ROBBLEE J.A., RODGER M., WELLS G., CLINCH J., PRETORIUS R., BART INVESTIGATORS. A comparison of apoprotinin and lysine analogues in high-risk cardiac surgery. *N. Engl. J. Med.*, 2008, **358** : 2319-2331.
70. WARNAAR N., MALLET S.V., DE BOER M.T., ROLANDO N., BURROUGHS A.K., NIJSTEN M.W., SLOOFF M.J., ROLLES K., PORTE R.J. The impact of aprotinin on renal function after liver transplantation : an analysis of 1,043 patients. *Am. J. Transplant.*, 2007, **7** : 2378-2387.
71. PORTE R.J. Aprotinin and lysine analogues in high-risk cardiac surgery. *N. Engl. J. Med.*, 2008, 359-1181.
72. BURROUGHS A.K., MATTHEWS K., QADIRI M., THOMAS N., KERNOFF P., TUDDENHAM E., MC INTYRE N : Desmopressin and bleeding time in patients with cirrhosis. *Br. Med. J.* (Clin. Res. Ed.), 1985, **291** : 1377-1381.
73. DE FRANCHIS R., ARCIDIACONO P.G., CARPINELLI L., ANDREONI B., CESTARI L., BRUNATI S., ZAMBELLI A., BATTAGLIA G., MANNUCCI P.M. Randomized controlled trial of desmopressin plus terlipressin versus terlipressin alone for the treatment of acute variceal hemorrhage in cirrhotic patients : a multicenter, double-blind study. New Italian Endoscopic Club. *Hepatology*, 1993, **18** : 1102-1107.
74. WONG A.Y., IRWIN M.G., HUI T.W., FUNG S.K., FAN S.T., MA E.S. Desmopressin does not decrease blood loss and transfusion requirements in patients undergoing hepatectomy. *Can. J. Anaesth.*, 2003, **50** : 14-20.
75. PIVALIZZA E.G., WARTERS R.D., GEBHARD R. Desmopressin before liver transplantation. *Can. J. Anaesth.*, 2003, **50** : 748-749.
76. PLANINSIC R.M., VAN DER MEER J., TESTA G., TESTA G., GRANDE L., CANDELA A., PORTE R.J., GHOBRIAL R.M., ISONIEMI H., SCHELDE P.B., ERHARDTSEN E., KLINTMALM G., EMRE S. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transpl.*, 2005, **11** : 895-900.
77. LODGE J.P., JONAS S., JONES R.M., OLAUSSON M., MIR-PALLARDO J., SOEFELT S., GARCIA-VALDECASAS J.C., MC ALISTER V., MIRZA D.F. ; rFVIIa OLT STUDY GROUP. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transpl.*, 2005, **11** : 973-979.
78. OKUDA K., OHNISHI K., KIMURA K., MATSUTANI S., SUMIDA M., GOTO N., MUSHA H., TAKASHI M., SUZUKI N., SHINAGAWA T. *et al.* Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. *Gastroenterology*, 1985, **89** : 279-286.
79. FRANCOZ C., BELGHITI J., VILGRAIN V., SOMMACALE D., PARADIS V., CONDAT B., DENNINGER M.H., SAUVANET A., VALLA D., DURAND F. Splanchnic vein thrombosis in candidates for liver transplantation : usefulness of screening and anticoagulation. *Gut*, 2005, **54** : 691-697.
80. SILVA M.A., JAMBULINGAM P.S., GUNSON B.K., MAYER D., BUCKELS J.A., MIRZA D.F., BRAMHALL S.R. Hepatic artery thrombosis following orthotopic liver transplantation : a 10-year experience from a single centre in the United Kingdom. *Liver transplant.*, 2006, **12** : 146-151.
81. QUIROGA S., SEBASTIÀ M.C., MARGARIT C., CASTELLS L., BOYE R., VAREZ-CASTELLS A. Complications of orthotopic liver transplantation : spectrum of findings with helical CT. Radiograph, 2001, **21** : 1085-1102.
82. LISMAN T., PORTE R.J. Hepatic artery thrombosis after liver transplantation : more than just a surgical complication ? *Transpl. Int.*, 2009, **22** : 162-164.
83. OJO A.O. Cardiovascular complication after renal transplantation and their prevention. *Transplant.*, 2006, **82** : 603-611.
84. JOHNSTON S.D., MORRIS J.K., CRAMB R., GUNSON B.K., NEUBERGER J. Cardiovascular morbidity and mortality after orthotopic liver transplantation. *Transplant.*, 2002, **73** : 901-906.
85. BORG M.A., VAN DER WOUDEN E.J., SLUITER W.J., SLOOFF M.J., HAAGSMA E.B., VAN DEN BERG A.P. Vascular events after liver transplantation : a long-term follow-up study. *Transpl. Int.*, 2008, **21** : 74-80.
86. MILLER L.W. Cardiovascular toxicities of immunosuppressive agents. *Am. J. Transplant.*, 2002, **2** : 807-818.
87. PEREBOOM I.T.A., ADELMEIJER J., VAN LEEUWEN Y., HENDRIKS H.G., PORTE R.J., LISMAN T. Development of severe von Willebrand factor/ADAMTS13 dysbalance during orthotopic liver transplantation. *Am. J. Transplant.*, 2009, **9** : 1189-1196.
88. STAHL R.L., DUNCAN A., HOOKS M.A., HENDERSON J.M., MILLIKAN W.J., WARREN W.D. A hypercoagulable state follows orthotopic liver transplantation. *Hepatology*, 1990, **12** : 553-558.
89. PEREBOOM I.T.A., LISMAN T., PORTE R.J. Platelets in liver transplantation : friend or foe ? *Liver Transpl.*, 2008, **14** : 923-931.
90. LISMAN T., PORTE J.R. Antiplatelet medication after liver transplantation : does it affect outcome ? *Liver Transpl.*, 2007, 13 : 644-646.
91. VIVARELLI M., LA BARBA G., CUCCHETTI A., LAURO A., DEL GAUDIO M., RAVAIOLI M., GRAZI G.L., PINNA A.D. Can antiplatelet prophylaxis reduce the incidence of hepatic artery thrombosis after liver transplantation ? *Liver Transpl.*, 2007, 13 : 651-654.
92. THACHIL J. Relevance of clotting tests in liver disease. *Postgrad. Med.*, 2008, **84** : 177-181.
93. REVERTER J.C. Abnormal hemostasis tests and bleeding in chronic liver disease : are they related ? Yes. *J. Thromb. Haemost.*, 2006, **4** : 717-720.
94. TROTTER J.F., BRIMHALL B., ARJAL R., PHILLIPS C. Specific laboratory methodologies achieve higher model for end-stage liver disease (MELD) scores for patients listed for liver transplantation. *Liver Transpl.*, 2004, **10** : 995-1000.
95. ROBERT A., CHAZOUILLERES O. Prothrombin time in liver failure : time, ratio, activity percentage, or international normalized ratio ? *Hepatology*, 1996, **24** : 1392-1394.
96. LISMAN T., VAN LEEUWEN Y., ADELMEIJER J., PEREBOOM I.T., HAAGSMA E.B., VAN DEN BERG A.P., PORTE R.J. Interlaboratory variability in assessment of the model of end-stage liver disease score. *Liver Int.*, 2008, **28** : 1344-1351.