Contrast-enhanced Ultrasound for Non-tumor Liver Diseases

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ABSTRACT

Contrast-enhanced ultrasound (CEUS) is a simple, safe and reliable technique for the clinical management of patients with various liver diseases. Although the major target of the technique may be focal hepatic lesions, it is also effective for the diagnosis of non-tumor liver diseases, such as grading hepatic fibrosis, characterization of chronic liver diseases and diagnosis of portal vein thrombosis. This review article aimed to overview the recent application of CEUS in the assessment of non-tumor liver diseases.

Keywords: *Cirrhosis, contrast agent, fibrosis, idiopathic portal hypertension, microbubble, portal vein thrombosis, ultrasound*

INTRODUCTION

Because of the simplicity, safety, and efficacy of using microbubble agent, CEUS has become popular worldwide [1, 2]. Contrast harmonic imaging has the advantages of fewer artifacts, less dependence with angle between US beam and vessel, and improved signal-to-noise ratio in comparison with Doppler sonography[3-5].

The major target of CEUS may be focal hepatic lesions; detection, characterization, treatment support, and evaluation of therapeutic response[6]. Recent studies have shown the remarkable improvement in the diagnostic abilities in the liver cancers such as hepatocellular carcinoma by using microbubble contrast agents[7]. Meanwhile, investigators have also proven the efficacy of CEUS in the diagnosis of non-tumor liver diseases[8-12]. There have been several attempts to quantify the contrast effect using parameters of time, intensity, and combination of them. These novel approaches may expand the application of ultrasound in the relevant field. This review article aimed to overview the recent application of CEUS in the diagnosis of non-tumor liver diseases.

1. Assessment of degree of hepatic fibrosis in chronic liver diseases

The severity of chronic liver disease depends on the grade of hepatic fibrosis. Clinical management of chronic liver disease should be implemented based on the stage of fibrosis, which determines the increased risk of developing hepatocellular carcinoma, portal hypertension, and/or hepatic failure in cirrhotic patients [13,15].

Although liver biopsy remains the gold standard for the evaluation of the grade of hepatic fibrosis, some shortcomings limit the clinical use, such as invasiveness in patients with impaired coagulation and the possibility of sampling error due to the heterogeneous distribution of fibrosis[16,17]. Against the background, non-invasive assessment of the grade of hepatic fibrosis has gained medical as well as social attention, imaging tools such as transient elastography, magnetic resonance elastography, and many serum markers[18-20]. These non-invasive techniques may have an advantage over liver biopsy in terms of possible repeated assessment of the grade of hepatic fibrosis during the management of a prolonged clinical course.

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Contrast-enhanced US with microbubble agents have become popular during the last two decades. This technique has also been reported to be useful for assessing severity of chronic liver disease[10] (Table). Application of US may be presumed reasonable as it is the modality most frequently used to evaluate chronic liver disease.

Contrast findings based on dynamic microbubble can be used to estimate the grade of hepatic fibrosis, in spite of the nature of an indirect assessment. The initial study was the transit-time analysis using first generation contrast agent "Levovist"[8]. That is, time-related intensity change analysis based on dynamic microbubble, moving from hepatic artery/portal vein to hepatic vein. They found that shortened transit-time may be the sign suggesting the presence of liver cirrhosis.

Table Comparison of diagnostic abilities in contrast parameters for grading hepatic fibrosis

Contrast agents	Parameter	Grade of fibrosis	Az	Authors	Years
SonoVue	Transit time*	Severe fibrosis	0.847	Staub et al [21]	2009
SonoVue	HTT**	Moderate - severe	0.71	Cobbold et al [22]	2010
		Cirrhosis	0.83		
SonoVue	Peak signal intensity	Severe fibrosis	0.88	Orlacchioet al [23]	2011
Sonazoid	Peak intensity/time***	F2	0.94	Ishibashi et al [12]	2010
		F3	0.96		
		F4	0.98		
Sonazoid	Intensity difference	F2	0.88	Ishibashi et al [25]	2012
		F3	0.95		
		F4	0.97		

Peak signal intensity (dB), difference between peak intensity in the portal vein and in the liver parenchyma
Transit time*, difference between the arrival time of microbubble in the portal vein and in the hepatic vein
HTT(hepatic transit time)*, difference between the arrival time of microbubble in the hepatic artery and in the hepatic vein
Peak intensity/time***, the time to the maximum intensity ratio between the right portal vein and liver parenchyma from the onset of contrast enhancement in the portal vein
Intensity difference, difference in the late-phase parenchymal intensity before and after the high power emission of ultrasound Az, area under the receiver operating curve

Although the authors assumed four possible underlying mechanisms for this phenomenon, arterialization, intrahepatic shunt, pulmonary arteriovenous shunt, and hyperdynamic circulatory state, a subsequent study reported that intrahepatic, not extrahepatic, hemodynamic change account for the phenomenon [9]. Investigators followed to examine the efficacy of contrast parameters with the use of second generation contrast agent "Sonovue", area under the receiver operating curve (Az value) of 0.847 for severe fibrosis by transit time[21], 0.71 for moderate - severe fibrosis and 0.83 for cirrhosis by transit time[22], and 0.88 for severe fibrosis by analysis of intensity change between portal vein and liver parenchyma[23].

The other study examined the time-related intensity changes between intrahepatic portal vein and liver parenchyma so as to analyze the pattern of inflow and distribution of microbubble in the liver (Fig. 1)[12].

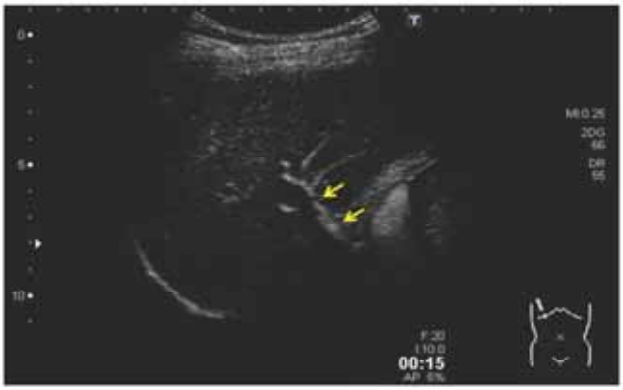

Figure 1A. 5s after the agent injection, early arterial phase Hepatic artery (arrows) was clearly enhanced without showing an enhancement in the portal vein or liver parenchyma.

The parameter, "time to the maximum intensity ratio between the right portal vein and liver parenchyma from the onset of contrast enhancement in the portal vein", may reflect the degree of the potential resistance against the inflow microbubble caused by hepatic fibrosis.

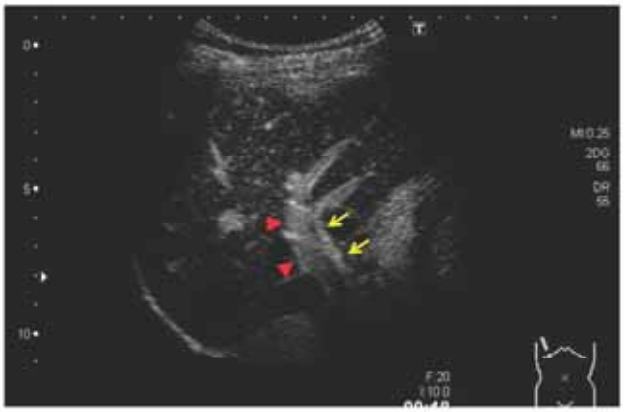

Figure 1B. 18s after the agent injection, arterio-portal phase. The image showed an enhancement in the hepatic artery (arrows) and portal vein (arrow heads).

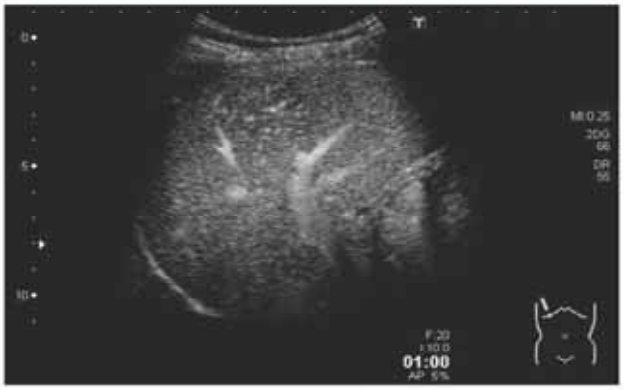

Figure 1C. 60s after the agent injection. The liver parenchyma was homogenously enhanced in this phase

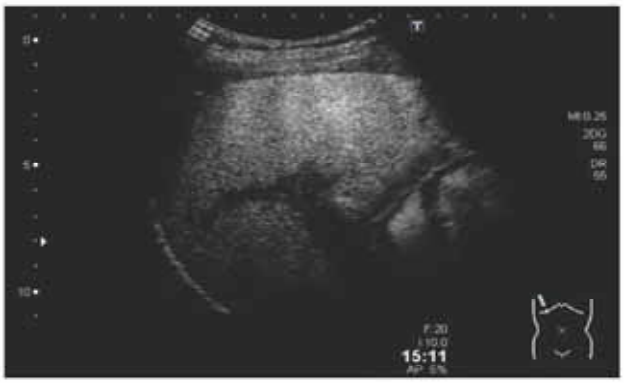

Figure 1D. 15m after the agent injection, late phase. The enhancement in the liver parenchyma remained positive in this phase.

The Az values of the parameter were 0.94 for marked fibrosis (≥F2), 0.96 for advanced fibrosis (≥F3) and 0.98 for cirrhosis. The effect of this contrast parameter was compared with other non-invasive parameters in the subsequent study: the order of the contrast parameter as a single model was second for marked fibrosis (≥F2) following FIB-4, second for advanced fibrosis (≥F3) following liver stiffness measurement (LSM), and fourth for cirrhosis (F4)[24]. However, for the combined models, the highest Az was 0.99 for cirrhosis and 0.89 for advanced fibrosis (≥F3), by the combination of contrast parameter with LSM. Even for marked fibrosis (≥F2), the best Az provided by the combination of the contrast parameter with FIB-4 was 0.87, which was better than the data in the previous report: 0.84 by LSM and APRI, 0.88 for LSM and Fibrotest, and 0.88 by LSM, Fibrotest, and APRI for marked fibrosis (≥F2)[18].

Some kinds of microbubble agents accumulate in the reticuloendothelial system[1,10]. By using this property, intensity analysis can estimate the amount of microbubble in the liver. This technique is applicable to predict the grade of hepatic fibrosis, which determines the sinusoidal space presented by the amount of intrahepatic microbubbles. Recent study investigated the relationship between contrast effect of a second generation microbubble agent "Sonazoid™ (GE Healthcare, Oslo, Norway)" with the property of being captured in the liver and the grade of hepatic fibrosis[25]. They found that the intensity difference at 15-minute phase showed most significant correlation with fibrosis grade ($\rho = 0.79$, $P < 0.0001$), and the best Az values are 0.88 for marked fibrosis, 0.95 for advanced fibrosis, and 0.97 for cirrhosis, which were significantly higher than those of FIB4, 0.85 for marked fibrosis, 0.89 for advanced fibrosis, and 0.90 for cirrhosis. Sensitivity, specificity and efficiency of the intensity difference were 88%, 72% and 81% for marked fibrosis, 85%, 91% and 89% for advanced fibrosis and 97%, 90% and 91% for cirrhosis, respectively.

1. Characterization of diffuse liver diseases between cirrhosis and IPH

Idiopathic portal hypertension (IPH) is relatively rare but a disorder which should be strictly distinguished from cirrhosis, both resulting in severe portal hypertensive manifestations[26-28]. IPH has less incidence of developing into hepatocellular carcinoma, a higher incidence of developing into portal vein thrombosis, and a better survival rate than cirrhosis[29, 30]. IPH should be strictly differentiated from cirrhosis because of differences in the clinical management.

One of the major pathophysiologies of IPH may be intrahepatic portal vein occlusion and periportal fibrosis. This abnormality causes the unique vascular

structure of portal vein, paucity of medium-sized portal branches, irregular and often obtuse-angled division of the peripheral branches, their occasional abrupt interruptions, an avascular area beneath the liver surface, non-opacification of some of the large intrahepatic portal branches and of their periphery, and increase of very fine vasculature around large intrahepatic portal branches[31]. Against the characteristic features of portal system to help diagnose IPH, demonstration of portal vein images requires interventional techniques that are based on invasive procuedure and radiation exposure. To overcome these problems, recent study reported non-invasive visualization of intrahepatic portal vein structure. That is, contrast-enhanced 3DUS with Sonazoid may have the potential to discriminate IPH from cirrhosis by the portal vein appearances, under sufficient inter-reviewer and inter-operator agreement [32].

Efficacy of CEUS to diagnose IPH is also reported by other studies. One study examined dynamic behavior of microbubble in the liver parenchyma in 8 IPH, 47 cirrhosis and 36 controls, and found that delayed periportal enhancement may be a characteristic contrast finding of IPH[33]. Another study focused on the degree of captured microbubble in the liver parenchyma at the late phase[10]. The authors proved that IPH has dominant microbubble accumulation compared to cirrhosis probably due to preserved liver function supported by better prognosis[26-30]. The microbubble-based contrast US may be promising as a non-invasive diagnostic tool for IPH.

1. Portal vein thrombosis

Portal vein thrombosis is a clinically significant condition, as it can cause serious complications such as intestinal infarction and an increase of portal venous pressure [34, 35]. Studies have shown the clinical utility of CEUS in the diagnosis of portal vein thrombosis, improved detection of thrombus as a negative enhancement in the portal lumen[36], and differentiation of thrombosis between tumor thrombus and non-tumor thrombus [37]. These applications may contribute to improve the management of patients with liver cancer, for staging and determination of treatment direction.

Another study examined the efficacy of CEUS as a unique application to predict the therapeutic effect by anticoagulation[11]. The study reported that intra-thrombus positive enhancement demonstrated on contrast-enhanced sonograms has promise as a successful predictor of anticoagulation for the recent portal thrombosis. The sensitivity and specificity of positive contrast enhancement for the prediction of anticoagulation effect was 100%. More recent prospective study applied this technique to determine the safety and efficacy of anticoagulation treatment for portal vein thrombosis in 23 cirrhosis patients with acute variceal bleeding[38]. Five of 10 patients with active bleeding had portal vein thrombus, and all showed positive intra-thrombus enhancement on contrast ultrasonography. Anticoagulation treatment of these five patients resulted in complete recanalization of the portal vein within 2–11 days. They concluded that early anticoagulation treatment in cirrhosis patients with portal vein thrombosis and acute variceal bleeding may be safe, tolerated, and effective in cases with positive intra-thrombus enhancement on contrast ultrasonography.

Although early anticoagulation is a recommended treatment for recent portal vein thrombosis[39,40], complete recanalization is not guaranteed with the 30 to 40% success rate in the literatures[35, 40, 41]. Additionally, anticoagulation is associated with adverse events such as hemorrhage[40-44]. CEUS might help select candidates for anticoagulation, as a novel clinical marker predictive of the therapeutic effect.

SUMMARY

As described in this article, application of microbubble contrast agents in the liver disease has become more multifaceted. However, there are still some problems to be solved before usage of this technique become widespread. The high cost of high-end ultrasound equipment and limited availability of the microbubble agents in the limited countries are major concern. In addition, while many studies have shown the utility of this technique, it is undeniable that procedures in the analysis of enhancement effect became somewhat complicated. These issues should be overcome for the achievement of strong contribution of CEUS in clinical practice.

REFERENCES

1. Bouakaz A, de-Jong N. WFUMB Safety Symposium on Echo-Contrast Agents: nature and types of ultrasound contrast agents. Ultrasound Med Biol. 2007;33:187-96.

2. Shimada T, Maruyama H, Sekimoto T, Kamezaki H, Takahashi M, Yokosuka O. Heterogeneous staining in the liver parenchyma after the injection of perflubutane microbubble contrast agent. Ultrasound in Med Biol. 2012;38:1317-23.

3. Maruyama H, Ebara M. Recent applications of ultrasound: diagnosis and treatment of hepatocellular carcinoma. Int J Clin Oncol. 2006;11:258-67.
4. Mitchell DG. Color Doppler Imaging: Principles, Limitations, and Artifacts. Radiology. 1990;177:1-10.
5. Foley WD, Erickson SJ. Color Doppler Flow Imaging. Am J Roentgenol. 1991;156:3-13.
6. Lencioni R, Piscaglia F, Bolondi L. Contrast-enhanced ultrasound in the diagnosis of hepatocellular carcinoma. J Hepatol. 2008;48:848-57.
7. Maruyama H, Yoshikawa M, Yokosuka O. Current role of ultrasound for the management of hepatocellular carcinoma. World J Gastroenterol. 2008;14:1710-9.
8. Albrecht T, Blomley MJK, Cosgrove DO, Taylor-Robinson SD, Jayaram V, Eckersley R, et al. Non-invasive diagnosis of hepatic cirrhosis by transit-time analysis of an ultrasound contrast agent. Lancet. 1999;353:1579-83.
9. Sugimoto H, Kaneko T, Hirota M, Tezel E, Nakao A. Earlier hepatic vein transit-time measured by contrast ultrasonography reflects intrahepatic hemodynamic changes accompanying cirrhosis. J Hepatol. 2002;37:578-83.
10. Maruyama H, Ishibashi H, Takahashi M, Imazeki F, Yokosuka O. Impact of Signal Intensity from Accumulated Microbubbles in the Liver for the Differentiation of Idiopathic Portal Hypertension from Liver Cirrhosis. Radiology. 2009;252:587-94.
11. Maruyama H, Ishibashi H, Takahashi M, Shimada T, Kamesaki H, Yokosuka O. The prediction of the therapeutic effects of anticoagulation for recent portal vein thrombosis: a novel approach with contrast-enhanced ultrasound. Abdom Imaging. 2012;37:431-8.
12. Ishibashi H, Maruyama H, Takahashi M, Fujiwara K, Imazeki F, Yokosuka O. Assessment of Hepatic Fibrosis by Analysis of the Dynamic Behavior of Microbubbles during Contrast Ultrasonography. Liver Int. 2010;30:1355-63.
13. Tandon P, Garcia-Tsao G. Portal hypertension and hepatocellular carcinoma: prognosis and beyond. Clin Gastroenterol Hepatol. 2006;4:1318-9.
14. Nissen NN, Martin P. Hepatocellular carcinoma: the high-risk patient. J Clin Gastroenterol. 2002;35:S79-85.
15. Williams R. Global challenges in liver disease. Hepatology. 2006;44:521-6.
16. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol. 2002;97:2614-8.
17. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology. 2003;38:1449-57.
18. 18. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology. 2005;128:343-50.
19. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunqa J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology. 2008;134:960-74.
20. Asbach P, Klatt D, Schlosser B, Biermer M, Muche M, Rieger A, et al. Viscoelasticity-based staging of hepatic fibrosis with multifrequency MR elastography. Radiology. 2010;257:80-6.
21. Staub F, Tournoux-Facon C, Roumy J, Chaigneau C, Morichaut-Beauchant M, Levillain P, et al. Liver fibrosis staging with contrast-enhanced ultrasonography: prospective multicenter study compared with METAVIR scoring. Eur Radiol. 2009;19:1991-7.
22. Cobbold JFL, Crossey MME, Colman P, Goldin RD, Murphy PS, Patel N, et al. Optimal combinations of ultrasound-based and serum markers od disease severity in patients with chronic hepatitis C. J Viral Hepat. 2010;17:537-45.
23. Orlacchio A, Bolacchi F, Petrella MC, Pastorelli D, Bazzocchi G, Angelico M, et al. Liver contrast enhanced ultrasound perfusion imaging in the evaluation of chronic hepatitis C fibrosis: preliminary results. Ultrasound Med Biol. 2011;37:1-6.
24. Tawada A, Maruyama H, Kamezaki H, Shimada T, Ishibashi H, Takahashi M, et al. Magnitude of contrast-enhanced ultrasonography as a noninvasive predictor for hepatic fibrosis: comparison with liver stiffness measurement and serum-based models. Hepatol Int.Forthcoming.
25. Ishibashi H, Maruyama H, Takahashi M, Shimada T, Kamesaki H, Fujiwara K, et al. Demonstration of intrahepatic accumulated microbubble on ultrasound represents the grade of hepatic fibrosis. Eur Radiol. 2012;22:1083-90.
26. Hillaire S, Valla DC, Lebrec D. Non cirrhotic portal hypertension. Clin Liver Dis. 1997;1:1223–40.
27. Sarin SK, Kapoor D. Non-cirrhotic portal fibrosis: Current concepts and management. J Gastroenterol Hepatol. 2002;17:526-34.
28. Dhiman RK, Chawla Y, Vasishta RK, Kakkar N, Dilawari JB, Trehan MS, et al. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): Experience with 151 patients and a review of the literature. J Gastroenterol Hepatol. 2002;17:6-16.
29. Benhamou JP, Valla DC. Intrahepatic portal hypertension. In: Bircher J, Benhamou JP, McIntyre N, et al, editors. Oxford textbook of clinical hepatology, 2nd edn. Oxford: Oxford University Press; 1999. 661–70.

30. Okuda K, Obata H. Idiopathic portal hypertension (hepatoportal sclerosis). In: Okuda K, Benhamou JP, editors. Portal Hypertension. Clinical and Physiological Aspects. Tokyo: Springer; 1992. 271-87 p.

31. Futagawa S, Fukazawa M, Horisawa M, Musha H, Ito T, Sugiura M, et al. Portographic liver changes in idiopathic noncirrhotic portal hypertension. Am J Roentgenol 1980;134:917-23.

32. Maruyama H, Okugawa H, Kobayashi S, Yoshizumi H, Takahashi M, Ishibashi H, et al. Non-invasive portography: a microbubble-induced three-dimensional sonogram for discriminating idiopathic portal hypertension from cirrhosis. Br J Radiol. 2012;85:587-95.

33. Maruyama H, Shimada T, Ishibashi H, Takahashi M, Kamesaki H, Yokosuka O. Delayed periportal enhancement: a characteristic finding on contrast ultrasound in idiopathic portal hypertension. Hepatol Int. 2012;6:511-9.

34. Kumar S, Sarr MG, Kamath PS. Mesenteric venous thrombosis. N Engl J Med. 2001;45:1683-8.

35. Chawla Y, Duseja A, Dhiman RK. Review article: the modern management of portal vein thrombosis. Aliment Pharmacol. 2009;30:881-94.

36. Rossi S, Rosa L, Ravetta V, Cascina A, Quaretti P, Azzaretti A, et al. Contrast-enhanced versus conventional and color Doppler sonography for the detection of thrombosis of the portal and hepatic venous systems. AJR Am J Roentgenol. 2006;186:763–73.

37. Rossi S, Ghittoni G, Ravetta V, Torello-Viera F, Rosa L, Serassi M, et al. Contrast-enhanced ultrasonography and spiral computed tomography in thedetection and characterization of portal vein thrombosis complicating hepatocellular carcinoma. Eur Radiol. 2008;18:1749–56.

38. Maruyama H, Takahashi M, Shimada T, Yokosuka O. Emergency anticoagulation treatment for cirrhosis patients with portal vein thrombosis and acute variceal bleeding. Scand J Gastroenterol. 2012;47:686-91.

39. deFranchis R, on behalf of the Baveno V Faculty. Revising consensus in portal hypertension: Report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2010;53:762-8.

40. Plessier A, Darwish-Murad S, Hernandez-Guerra M, Consigny Y, Fabris F, Trebicka J, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology. 2010;51:210-8.

41. Condat B, Pessione F, Denninger MH, Denninger MH, Guillin MC, Poliquin M, et al. Recent portal or mesenteric venous thrombosis: increased recognition and frequent recanalization on anticoagulant therapy. Hepatology. 2000;32:466-70.

42. Condat B, Pessione F, Hillaire S, Denninger MH, Guilin MC, Poliquin M, et al. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology. 2001;120:490-7.

43. Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manqusa F, Iannaccone L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40:736-41.

44. Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut. 2005;54:691–7.