Front. Med. 2012, 6(4): 421–427
DOI 10.1007/s11684-012-0223-5

RESEARCH ARTICLE

Assessment of liver volume variation to evaluate liver function

Cong Tong[1]*, Xinsen Xu[1]*, Chang Liu (✉)[1], Tianzheng Zhang[2], Kai Qu[1]

[1]*Department of Hepatobiliary Surgery, the First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, Xi'an 710061, China;*
[2]*Department of Surgery, Shaanxi Xianyang 215 Hospital, Xianyang 712000, China*

Abstract **In order to assess the value of liver volumetry in cirrhosis and acute liver failure (ALF) patients, we explored the correlation between hepatic volume and severity of the hepatic diseases. The clinical data of 48 cirrhosis patients with 60 normal controls and 39 ALF patients were collected. Computed tomography-derived liver volume (CTLV) and body surface area (BSA) of normal controls were calculated to get a regression formula for standard liver volume (SLV) and BSA. Then CTLV and SLV of all patients were calculated and grouped by Child-Turcotte-Pugh classification for cirrhosis patients and assigned according to prognosis of ALF patients for further comparison. It turned out that the mean liver volume of the control group was 1 058 ± 337 cm^3. SLV was correlated with BSA according to the regression formula. The hepatic volume of cirrhosis patients in Child A, B level was not reduced, but in Child C level it was significantly reduced with the lowest liver volume index (CTLV/SLV). Likewise, in the death group of ALF patients, the volume index was significantly lower than that of the survival group. Based on volumetric study, we proposed an ROC (receiver operating characteristic) analysis to predict the prognosis of ALF patients that CTLV/SLV < 83.9% indicates a poor prognosis. In conclusion, the CTLV/SLV ratio, which reflects liver volume variations, correlates well with the liver function and progression of cirrhosis and ALF. It is also a very useful marker for predicting the prognosis of ALF.**

Keywords liver volume variation; cirrhosis; acute liver failure (ALF)

Introduction

Child-Turcotte-Pugh classification is a widely accepted empirical approach for assessment of severity of cirrhosis while the model for end-stage liver disease (MELD) score is widely-employed prognostic markers for acute liver failure (ALF). However, besides serologic indices and laboratory parameters, it has been reported that liver atrophy is also an important factor to evaluate liver function of cirrhosis and ALF. Saygili *et al*. [1] considered the radiologic evaluation as an important constituent in liver function evaluation and demonstrated the value of computed tomography (CT) and magnetic resonance imaging (MRI) for assessing severity of liver cirrhosis secondary to viral hepatitis. Similarly, with regard to ALF, Sekiyama *et al*. [2] also verified the value of liver volume measurement in ALF patients that the computed tomography-derived liver volume (CTLV) of survivors of ALF was significantly greater than that of non-survivors. Therefore it seems to be certain that liver volume associates with the liver function and progression of cirrhosis and ALF. However, CTLV alone cannot reflect individual physical differences such as body weight and height, and it is therefore necessary to standardize individual liver volume in the healthy state. Fortunately, Nicolas *et al*. [3] proposed a formula using body surface area (BSA) and body weight to predict total liver volume in western adults. Inspired by his idea, we collected the data of CTLV and BSA of normal adults to calculate a regression formula that would predict liver volume more accurately for Chinese, which was defined as standard liver volume (SLV). Then we measured the liver volume of both cirrhosis and ALF patients with CT, and explored the correlation between liver volume variations (CTLV/SLV) and liver function. We found that the CTLV/SLV ratio correlated well with Child classification in cirrhosis and was in accordance with the prognosis of ALF, based on which we established a CTLV/SLV prognostic formula for ALF utilizing the ROC (receiver operating characteristic) analysis.

Received February 28, 2012; accepted August 10, 2012
Correspondence: liuchangdoctor@163.com

*These authors contributed equally to this study and share first authorship.

Materials and methods

Patients

There were 48 cirrhosis patients who underwent serial abdominal CT at our institution between 2007 and 2011 included in this study. All patients were secondary to hepatitis B virus or C virus infection, which were proven by a viral antigen test and antibody titration. All patients had biopsy diagnosed cirrhosis. Patients with hepatic space-occupying lesions, thrombosis in the portal vein system, hepatic duct dilatation, or a history of alcoholism were excluded. We were able to determine Child classification from the available clinical records in all the cirrhotic patients, based on which they were grouped as follows: 10 cases were classified as class A, 26 cases as class B, and 12 cases as class C. The control group consisted of 60 patients who underwent upper abdominal helical CT for conditions unrelated to the hepatobiliary system at our institution during the same period. All patients had negative findings on hepatitis B or C surface antigen tests. Patients with abnormal liver function (ALB $<$ 35 g/L, ALT or AST $>$ 80 U/L, INR $>$ 11.2), with platelets $< 100 \times 10^9$ /L, with abnormities on abdominal CT or ultrasound findings, with conditions potentially affected by the biliary tree (e.g., pancreatic cancer) or associated with diffuse liver disease (e.g., lymphoma), and with a history of alcoholism or fatty liver were excluded. There were also 39 ALF patients who visited our institution during the same period included in this study. The diagnosis of ALF was made according to the diagnostic criteria of the Viral Hepatitis Prevention and Treatment Scheme in China [4]. They were assigned to two groups: group A consisted of 23 patients who recovered without surgical intervention, and group B consisted of 16 patients who died due to liver failure. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the appropriate institutional review committee.

Data collection

The data, which included age, body weight (BW), body height (BH), total bilirubin (TBIL), international normalized ratio (INR), serum creatinine (CREA), prothrombin time (PT), and albumin (ALB), were collected to determine Child classification of cirrhosis patients and to calculate MELD scores of ALF patients. We obtained informed consent from all patients or their families. All demographic and laboratory data were obtained at the time of the CT scan, when the diagnosis was made and intervention therapy was done immediately.

Volumetric analysis of the liver

The whole liver volume of all the patients and controls was measured using CT films according to the method of Heymsfield [5]. Serial abdominal transverse CT was taken at 5 mm- or 10 mm-intervals and the slice thickness was 8–10 mm. Each slice was traced with a cursor and the liver volume was calculated by adding the area of each slice from the most superior part to the most inferior part of the liver using the Myrian Expert program of Intrasense Corporation of France (Fig. 1).

Statistical analysis

Data were expressed as median and range and were analyzed by using correlation coefficient, Student's *t*-test, Chi-square test and survival analysis when appropriate with the help of SPSS software (Version 13.0) by Statistical Department, School of Medicine, Xi'an Jiaotong University. Linear

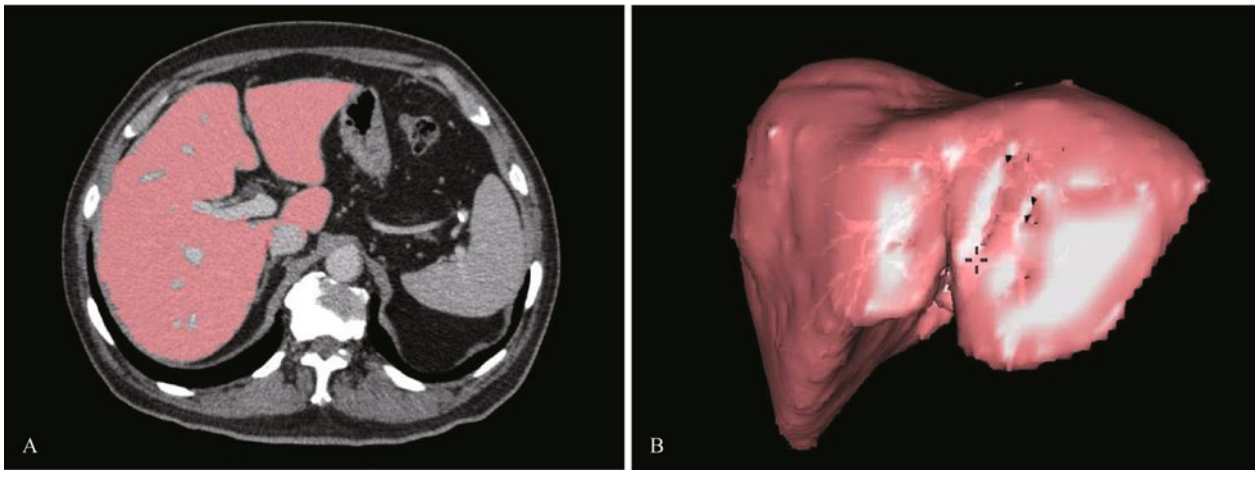

Fig. 1 Volumetric analysis of the liver. (A) To outline the edge of the liver on each slice of the CT films with a cursor**;** (B) Reconstruction of the liver by adding the area of each slice from the most superior part to the most inferior part.

regression analysis was made to predict SLV using body indices (weight and height) and the ROC analysis was performed for CTLV/SLV ratio and the prognosis of ALF. A P-value < 0.05 was considered statistically significant.

Results

The baseline characteristics of the patients

Background data of the patients in each group are shown in Table 1. The median age of the normal control group and the cirrhosis group did not show a significant difference, while in the ALF group, the median age of the death patients was significantly younger than the survival patients. The median height and weight of different groups did not differ significantly, either. In the normal control group, 40 of the 60 patients were males and 20 were females. Similarly, 31 patients in cirrhosis group (31/48) and 31 patients (31/39) in the ALF group were males. All patients received active therapy immediately at the onset of diagnosis.

The regression equation of SLV and BSA

BW and BH of normal controls were recorded to calculate BSA (BSA [m^2] = 0.006 1 × BH [cm] + 0.012 4 × BW [kg] − 0.009 9) [6]. CTLV and BSA of normal controls were collected to get a regression formula for SLV and BSA. The mean liver volume of the control group calculated from CT was 1 058 ± 337 cm^3. LV positively correlated with BSA: LV (cm^3) = 850.1 × BSA (m^2) − 305.3 ($r = 0.878$, $r^2 = 0.757$, $P < 0.05$).

Correlation of volume index and liver function in cirrhosis

The SLV calculated from BSA for the cirrhosis patients compared with that of the healthy control subjects did not show a statistically significant difference ($P > 0.05$). The CTLV was significantly smaller in Child C patients than in healthy control subjects ($P < 0.05$), whereas there was not a statistically significant difference between those values for Child A and B patients ($P > 0.05$). The volume index (CTLV/SLV) of Child C patients was 0.71 ± 0.20, which was significantly lower than that of Child A and B patients ($P < 0.05$) (Table 2, Fig. 2).

Correlation of volume index and prognosis in ALF

The SLV of ALF patients compared with that of the healthy control subjects did not show a statistically significant difference ($P > 0.05$). The CTLV was significantly smaller in death group patients than in survival group ($P < 0.05$), and there was a statistically significant difference between ALF patients and normal controls ($P < 0.05$). The volume index of the death group was 0.81 ± 0.10, which was significantly lower than that of the survival group, which was 0.95 ± 0.11 ($P < 0.05$) (Table 3, Fig. 3).

ROC analysis of the ALF volume index

The ROC curve analysis of the CTLV/SLV ratio of the ALF patients showed good diagnostic potential. AUC was 0.818 when the death group was set as positive (Fig. 4). The CTLV/SLV ratio cutoff point was determined based on the ROC

Table 1 Baseline characteristics of the patients

Diagnosis		Gender		Age (year)	Height (cm)	Weight (kg)
		Male	Female			
Normal controls		40	20	52±13	167.0±6.4	58.2±10.9
Cirrhosis	Child A	7	3	55±16	168.8±6.9	63.9±8.7
	Child B	15	11	49±13	168.0±7.5	59.8±10.5
	Child C	9	3	47±15	167.0±4.6	59.0±11.8
ALF	Death group	11	5	36±11	170.1±6.9	63.6±9.3
	Survival group	20	3	43±15	168.5±8.9	63.2±9.3

Table 2 Correlation between cirrhotic liver volume index and liver function

Child-Turcotte-Pugh classification	No. of patients	SLV (cm^3)	CTLV (cm^3)	Volume index[a]
Child A	10	1 231±120	1 156±258	0.94±0.18
Child B	26	1 189±140	1 054±430	0.87±0.31
Child C	12	1 174±129	814±169 [b]	0.71±0.20[b]

a. CTLV/ SLV.
b. Compared with Child A and B ($P<0.05$).

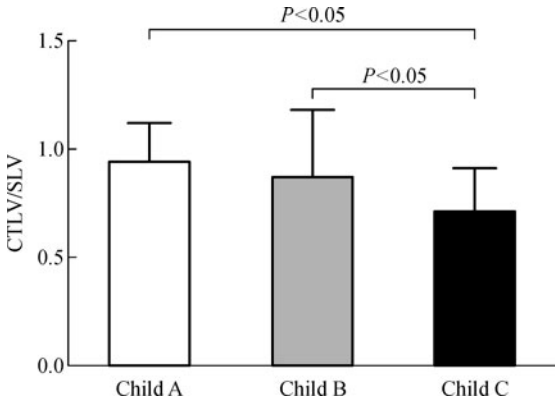

Fig. 2 Difference of the volume index between different cirrhosis Child classes.

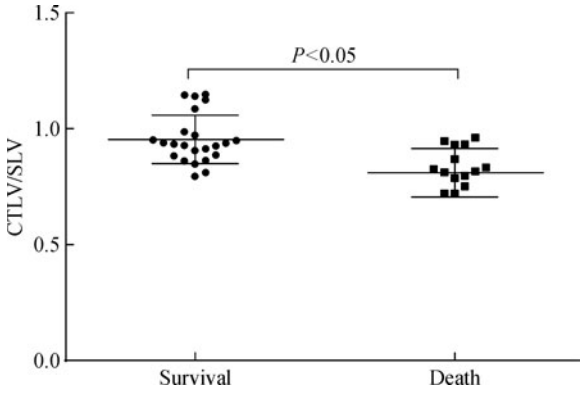

Fig. 3 Difference of the volume index between different ALF prognosis.

analysis. The difference between the death and the survival group was greatest at the probability cutoff point of 0.839 for the CTLV/SLV ratio, with the sensitivity of 91.3%, the specificity of 68.7%, the positive predictive value of 87.9%, and the negative predictive value of 75.9%, suggesting a probability of poor prognosis when CTLV/SLV < 0.839.

Discussion

CT-determined liver volume measurement

Child classification and MELD scoring system for the assessment of liver function and prognosis are widely accepted. Extensive attention has been put on the study of liver volume since Heymsfield *et al.* [5] first measured the volume of a cadaver's liver using CT in 1979. Researchers have reported that the difference between CT measured liver volume and the actual liver volume is minor [7,8]. Although numbers of shortcomings of CT volume calculation, which include partial volume effect, respiratory phase motion, and interobserver variation, have been pointed out by different researchers [5], thanks to its faster speed of data collecting and image processing, thinner slice thickness, and fewer artifacts from respiratory motion, CT is now able to create more precise images even in patients with significant ascites and to provide more accurate liver volume measurement [9,10].

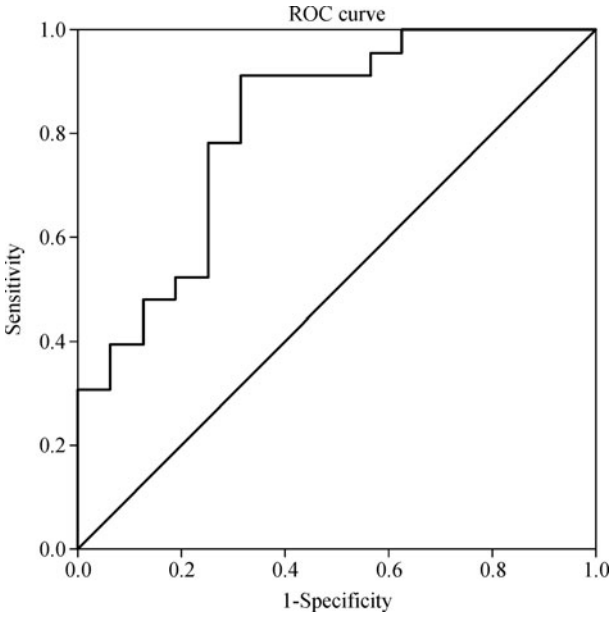

Fig. 4 ROC analysis of the ALF volume index.

Hepatic functional reserve is highly related to the quantity and quality of liver cells, which could be reflected by the liver volume and shape. However, although laboratory parameters that compose the Child classification and MELD scoring system could reflect liver function more directly and

Table 3 Correlation between ALF liver volume index and liver function

Groups	Prognosis	No. of patients	SLV (cm^3)	CTLV (cm^3)	Volume index[a]
A	Survival	23	1 227±127	1 164±137	0.95±0.11
B	Death	16	1 219±116	981±110	0.81±0.10 [b]

a. CTLV / SLV.
b. Compared with patients in the survival group ($P<0.05$).

accurately, they are more susceptible to the influence of clinical intervention and could fluctuate dramatically in a short time [11]. So compared with laboratory parameters, liver volume is a more stable and consistent indicator, which is difficult to be influenced. It not only reflects the number of the liver cells, but also indicates the blood perfusion and metabolic situation of the liver [12,13], which is equally valuable with Child classification and MELD scoring system, especially in case of preoperative assessment of liver function.

Joyeux *et al.* [14] investigated the CT volume of the liver with the measurement of 50 healthy livers using CT and obtained a mean total liver volume of 1 497 cm^3, which is not very close to the mean total liver volume of the control group in our study (1 058 $\pm$ 337 cm^3), but is acceptable if considering differences in measuring methods and race. The SLV formula has already been intensively investigated, and together with CTLV, they have been applied to evaluate the possibility of liver resection in liver cancer patients before surgery and to match donor-recipient pairs before liver transplantation [10]. The standard LV calculations (LV [cm^3] = 850.1 $\times$ BSA [m^2] – 305.3) used in our study might be easily applied since body height and body weight could be easily obtained to calculate BSA in the clinic. Then we could compare SLV with CTLV so that we can quantitatively calculate hepatic volume index, which could be helpful for evaluating liver reserve function, selecting an appropriate treatment, and determining the prognosis.

Cirrhotic liver volume measurement

In our study, we found a significant correlation between liver volume index as calculated on CT and severity of cirrhosis according to the Child classification. The mean total liver volume of Child A, B, and C patients was 1 156 $\pm$ 258 cm^3, 1 054 $\pm$ 430 cm^3, and 814 $\pm$ 169 cm^3, respectively, of which the Child C group was significantly smaller than that of the healthy control subjects. It paralleled the procedure of cirrhosis that fibrosis progresses until the hypertrophy reaches a maximum and then the hypertrophied liver regions begin to atrophy, which is clinically considered to be decompensated cirrhosis [15–18]. With respect to volume index, we can see that the liver of Child C patients not only shrank in size in general, but also varied the most in volume, a significantly higher volume change than seen in Child A and B patients. All of these data directly reflect the deduction that the lowest amount of liver cells in Child C patients led to the disturbance of the pathophysiologic state and the worst clinical manifestations of the condition. Therefore, we suspect that the correlation between CT-determined liver volume index and Child classification reflects the close relationship between functional capacity and volume changes in the liver in patients with cirrhosis.

However, even in the same Child level, there were some differences in the variation of the liver volume that would overlap the boundaries between different Child levels. For example, a significantly higher volume change rate was detected in some Child A patients rather than in some patients in Child B or C, which perhaps explained the reason why massive ascites and severe hepatic encephalopathy occurred in some Child A patients while some Child C patients were in a relatively good condition. Therefore the combination of Child classification and CT-determined liver volume measurement is valuable in evaluating liver functional reserve and helpful in choosing the appropriate time for surgical treatment.

ALF liver volume measurement

In our study, we also found a significant correlation between liver volume index as calculated on CT and the prognosis of ALF patients. The mean total liver volume of death group and survival group was 981 $\pm$ 110 cm^3, and 1 164 $\pm$ 137 cm^3, respectively, of which the death group was significantly smaller than the survival group. Shakil *et al*. [19] suggested that once liver volume declined below 1 000 ml, recovery with medical management was unlikely, which is in accordance with our result. They also recommended that liver volume measurement could be a useful prognostic tool and a decline of liver volume below 1 000 ml was indicative of the need for emergency transplantation. With respect to volume index we can see that the death group also got a significantly higher volume change rate than the survival group. It corresponded well with the pathological process of ALF that hepatic regenerative changes and cell necrosis took place at the same time. When regenerative changes overcame the damages caused by liver cell necrosis, patients were more likely to recover. On the contrary, a lack of regenerative activity and the necrosis involving a greater part of the hepatic parenchyma, which would perhaps result in an atrophied liver volume eventually, was associated with a poor outcome. Therefore, we speculate that the CT-determined liver volume index is able to reflect the functional capacity of ALF livers and predict the prognosis of ALF. Based on the data collected from the patients, we also proposed a ROC analysis to predict the prognosis of patients with ALF that a poor prognosis had significantly lower CTLV/SLV ratios. Patients with CTLV/SLV < 0.839 at the time of ALF diagnosis indicates a poor prognosis that probably liver transplantation and advance preparation for the procedure is needed while other cases may possibly be treated conservatively. The CTLV/SLV ratio in our formula may not be affected by medical therapy or intensive therapy and only needs body height, body weight and CTLV for analyzing, which is very convenient. Therefore, the formula of CTLV/SLV ratio in evaluation at the onset of encephalopathy is a simple and useful method for predicting the prognosis of ALF cases that it may greatly assist decision making based on the CTLV/SLV ratio, in particular regarding the need for emergency liver transplantation.

Application scope of liver volume measurement

Although we have demonstrated the clinical value of liver volume measurement in liver function evaluation of cirrhosis and ALF patients, we have to point out some limitations on the use of liver volume measurement in clinical practice. Since our conclusion of liver function evaluation is depended on the liver volume variations, there are absolutely specific conditions when liver volume was significantly interfered, which limit the use of liver volume measurement. For instance, there are causes for liver enlargement such as concurrent right heart failure, alcoholics, steatohepatitis and some other storage diseases. Under these circumstances, it is of great possibility that CTLV is larger than SLV, which is very likely to result in the misjudgement of liver function and the real function is worse than expected. On the contrary, there are also circumstances for liver atrophy such as liver surgery, which should also be excluded from the scope of liver volume application. It is also noteworthy that when liver tumor occurs, it might also affect the accuracy of liver volume measurement that whether to include the tumor volume in liver function evaluation is still controversial. To sum up, when utilizing liver volume measurement in clinical practice, we should be aware of the limitations of this method and take advantage of the measures appropriately to avoid the unnecessary misjudgement.

Limitations

It should be noted that there are a few limitations in our study. The main limitation is that only a small number of patients were included in our study because this study was undertaken at a single institution. The second limitation is that all cirrhosis patients were secondary to viral hepatitis B or C that other causes were excluded from our study population. However, liver volume may differ on the basis of the cause. Finally, we didn't perform a MR scanner to evaluate cirrhosis and ALF although it might offer a more extensive and comprehensive evaluation of the diseases and made perhaps more accurate volume measurements. Therefore, a larger scale prospective study is necessary to compare CT and MRI volume measurements and to further explore the prognostic value of the liver volume index.

Summary

In conclusion, the Child classification and MELD scoring system are now widely used in China for evaluation of liver functional reserve. Indicators that composing the Child classification and MELD scoring system are susceptible to the influence of clinical intervention and could fluctuate dramatically in a short time, which disturbs the strict correspondence with liver function. Under the circumstances of increasingly widespread use of CTLV measurement, the combination of traditional scoring system and liver volume assessment would be able to evaluate the function reserve of the liver more accurately.

References

1. Saygili OB, Tarhan NC, Yildirim T, Serin E, Ozer B, Agildere AM. Value of computed tomography and magnetic resonance imaging for assessing severity of liver cirrhosis secondary to viral hepatitis. Eur J Radiol 2005; 54(3): 400–407
2. Sekiyama K, Yoshiba M, Inoue K, Sugata F. Prognostic value of hepatic volumetry in fulminant hepatic failure. Dig Dis Sci 1994; 39 (2): 240–244
3. Vauthey JN, Abdalla EK, Doherty DA, Gertsch P, Fenstermacher MJ, Loyer EM, Lerut J, Materne R, Wang X, Encarnacion A, Herron D, Mathey C, Ferrari G, Charnsangavej C, Do KA, Denys A. Body surface area and body weight predict total liver volume in Western adults. Liver Transpl 2002; 8(3): 233–240
4. Chinese Medical Association. Viral Hepatitis Prevention and Treatment Scheme in China. Chin J Hepatol (Zhonghua Gan Zang Bing Za Zhi) 2000; 8(6): 324–329 (in Chinese)
5. Heymsfield SB, Fulenwider T, Nordlinger B, Barlow R, Sones P, Kutner M. Accurate measurement of liver, kidney, and spleen volume and mass by computerized axial tomography. Ann Intern Med 1979; 90(2): 185–187
6. Kardel T, Holm HH, Rasmussen SN, Mortensen T. Ultrasonic determination of liver and spleem volumes. Scand J Clin Lab Invest 1971; 27(2): 123–128
7. Kalkmann J, Forsting M, Stattaus J. Liver volume variations as a parameter to assess therapy response in advanced metastatic liver disease. Onkologie 2011; 34(1–2): 30–34
8. Dubus L, Gayet M, Zappa M, Abaleo L, De Cooman A, Orieux G, Vilgrain V. Comparison of semi-automated and manual methods to measure the volume of liver tumours on MDCT images. Eur Radiol 2011; 21(5): 996–1003
9. Müller SA, Bläuer K, Kremer M, Thorn M, Mehrabi A, Meinzer HP, Hinz U, Metzger J, Büchler MW, Schmied BM. Exact CT-based liver volume calculation including nonmetabolic liver tissue in three-dimensional liver reconstruction. J Surg Res 2010; 160(2): 236–243
10. Zhou XP, Lu T, Wei YG, Chen XZ. Liver volume variation in patients with virus-induced cirrhosis: findings on MDCT. AJR Am J Roentgenol 2007; 189(3): W153–159
11. Du WB, Pan XP, Li LJ. Prognostic models for acute liver failure. Hepatobiliary Pancreat Dis Int 2010; 9(2): 122–128
12. Li YM, Lv F, Xu X, Ji H, Gao WT, Lei TJ, Ren GB, Bai ZL, Li Q. Evaluation of liver functional reserve by combining D-sorbitol clearance rate and CT measured liver volume. World J Gastroenterol 2003; 9(9): 2092–2095
13. Tu R, Xia LP, Yu AL, Wu L. Assessment of hepatic functional reserve by cirrhosis grading and liver volume measurement using CT. World J Gastroenterol 2007; 13(29): 3956–3961
14. Joyeux H, Berticelli J, Chemouny S, Masson B, Borianne P. Semi-automatic measurements of hepatic lobes. Application to study of liver volumes. Analysis of 50 computed tomography of normal liver. Ann Chir 2003; 128(4): 251–255 (in French)

15. Dodd GD 3rd, Baron RL, Oliver JH 3rd, Federle MP. Spectrum of imaging findings of the liver in end-stage cirrhosis: Part II, focal abnormalities. AJR Am J Roentgenol 1999; 173(5): 1185–1192
16. Wang JH, Changchien CS, Hung CH, Eng HL, Tung WC, Kee KM, Chen CH, Hu TH, Lee CM, Lu SN. FibroScan and ultrasonography in the prediction of hepatic fibrosis in patients with chronic viral hepatitis. J Gastroenterol 2009; 44(5): 439–446
17. Shim JH, Yu JS, Chung JJ, Kim JH, Kim KW. Segmental difference of the hepatic fibrosis from chronic viral hepatitis due to hepatitis B versus C virus infection: comparison using dual contrast material-enhanced MRI. Korean J Radiol 2011; 12(4): 431–438
18. Krinsky GA, Lee VS, Theise ND. Focal lesions in the cirrhotic liver: high resolution ex vivo MRI with pathologic correlation. J Comput Assist Tomogr 2000; 24(2): 189–196
19. Shakil AO, Jones BC, Lee RG, Federle MP, Fung JJ, Rakela J. Prognostic value of abdominal CT scanning and hepatic histopathology in patients with acute liver failure. Dig Dis Sci 2000; 45 (2): 334–339