Int J Clin Exp Med 2020;13(9):6909-6915
www.ijcem.com /ISSN:1940-5901/IJCEM0114515

Original Article

The diagnostic value of Gd-EOB-DTPA-enhanced MRI scans in small hepatocellular carcinoma in patients with liver cirrhosis

Yingning Wu[1,2], Lina Huang[1], Baosheng Li[1], Hengguo Li[2]

[1]Department of Radiology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, Guangxi Zhuang Autonomous Region, China; [2]Medical Imaging Center, The First Affiliated Hospital of Ji'nan University, Guangzhou, Guangdong Province, China

Received May 18, 2020; Accepted June 12, 2020; Epub September 15, 2020; Published September 30, 2020

Abstract: Objective: To explore the diagnostic value of gadolinium-ethoxybenzyl-diethylenetriamine (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) scanning in small hepatocellular carcinoma in patients with liver cirrhosis. Methods: The selected liver cirrhosis patients were divided into the plain scan (PS) group and the Gd-EOB-DTPA-enhanced (GE) group according to the different detection methods, with 60 cases in each group. The patients in both groups underwent surgery to take biopsy specimens, by which the pathological results were finally determined. The biopsy results and the final diagnosis, the incidences of breathing artifacts in the early and late arterial phases, and the differences in the receiver operator characteristic (ROC) curves in each group were analyzed and compared to explore the diagnostic value of Gd-EOB-DTPA-enhanced MRI scanning in small hepatocellular carcinoma in patients with liver cirrhosis. Results: In the PS group, there were 23 cases diagnosed with hyperplastic nodules, 25 with small hepatocellular carcinoma, and 12 with regenerative nodules. Compared with the final diagnosis of 16 cases with hyperplastic nodules, 39 with small hepatocellular carcinoma and 5 with regenerative nodules, there was a significant difference within the group ($P<0.05$). In the GE group, there were 6 cases diagnosed with hyperplastic nodules, 49 with small hepatocellular carcinoma and 5 with regenerative nodules. Compared with the final diagnosis of 4 cases with hyperplastic nodules, 50 with small hepatocellular carcinoma, and 6 with regenerative nodules, there was little difference within the groups ($P>0.05$). There were 6 cases in the PS group and 4 cases in the GE group who presented with breathing artifacts in the early arterial phase, for incidence rates of 10.00% and 6.67%, respectively ($P>0.05$). Meanwhile, in the late arterial phase, there were 19 cases in the PS group and 8 cases in the GE group who presented with breathing artifacts, for incidence rates of 31.67% and 13.33%, respectively. The incidence of breathing artifacts in the late arterial phase in the PS group was significantly higher than it was in the GE group ($P<0.05$). The area under the curve (AUC) of the Gd-EOB-DTPA-enhanced MRI scan was 0.806 in patients with small hepatocellular carcinoma, and the diagnostic sensitivity and specificity were 76.64% and 88.32%, respectively. The AUC of the MRI plain scan was 0.791 in patients with small hepatocellular carcinoma, and the diagnostic sensitivity and specificity were 77.74% and 75.35%, respectively ($P=0.016$). Conclusion: Compared with the MRI plain scan, the Gd-EOB-DTPA-enhanced MRI scan had a higher diagnostic rate and a better diagnostic value in small hepatocellular carcinoma in patients with liver cirrhosis.

Keywords: MRI, liver cirrhosis, diagnostic value, Gd-EOB-DTPA-enhanced, hepatocellular carcinoma

Introduction

Liver cirrhosis is one of the most common liver diseases. The main pathogenesis is necrosis of the liver cells, as well as the regeneration and hyperplasia of residual cells, which leads to the destruction of the liver structure and gradually develops into liver cirrhosis [1]. There are many causes of liver cirrhosis, among which the majority of them develop from hepatitis, and a few of them evolve from other diseases such as alcoholic liver disease and schistosomiasis liver disease [2]. In recent years, due to the changes in living habits, the number of patients with liver cirrhosis is on the rise. Liver cirrhosis causes great harm to the body, and it will also be complicated with various diseases in severe cases, among which, cirrhosis with hepatocel-

lular carcinoma is more common [3]. Liver cirrhosis is an important risk factor for hepatocellular carcinoma, and the occurrence of hepatocellular carcinoma in patients with liver cirrhosis is a complex multi-stage process, from the distortion of the liver solid structure to the formation of cirrhotic nodules, and from hyperplasia and dysplastic nodules to early hepatocellular carcinoma [4]. With the development of surgical intervention and radiofrequency ablation, the therapeutic effect of hepatocellular carcinoma has improved significantly, and its early diagnosis and treatment play an important role. Therefore, the early detection and diagnosis of hepatocellular carcinoma is extremely important. In liver imaging, it is important to improve the detection and diagnosis rates of early hepatocellular carcinoma, especially for small hepatocellular carcinoma in patients with liver cirrhosis [5]. Hepatic arteriography is used in the early diagnosis of liver cirrhosis combined with small hepatocellular carcinoma, and it has a significant diagnostic effect but is invasive. Gd-EOB-DTPA-enhanced MRI is used in the diagnosis of hepatocellular carcinoma and has the advantages of convenience and accuracy. The traditional detection method is MRI plain scan, but the specific diagnosis effect is not good. There have been few studies on the comparison of the diagnostic effects between Gd-EOB-DTPA-enhanced MRI and MRI plain scan. Therefore, this study compared the detection and final pathological results of MRI plain scan and Gd-EOB-DTPA-enhanced MRI, analyzed the incidence of breathing artifacts in the early and late arterial phases as well as the differences in diagnostic value after receiving an MRI plain scan or a Gd-EOB-DTPA-enhanced MRI to explore the diagnostic value of Gd-EOB-DTPA-enhanced MRI in small hepatocellular carcinoma in patients with liver cirrhosis. The report follows.

Materials and methods

General information

A retrospective analysis was performed on 120 patients with liver cirrhosis who were treated at the Affiliated Hospital of Youjiang Medical University for Nationalities from December 2018 to November 2019. They were divided into two groups according to different check-ups, with 60 cases in each group. The patients in the PS group underwent MRI plain scans, and the patients in the GE group underwent Gd-EOB-DTPA-enhanced MRI scans. The patients in the two groups underwent liver puncture or surgery, and specimens were taken for biopsy to determine the final pathological results. This clinical study was approved by the Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities.

Inclusion and exclusion criteria

Inclusion criteria: All the patients were diagnosed with liver cirrhosis [6]; the patients had complete medical data and were able to cooperate with the clinical diagnosis; the patients were informed of the study and signed informed consents; the patients were less than 70 years old.

Exclusion criteria: Patients with contraindications (metal objects in the body, pregnant women, critically ill patients, claustrophobic patients, epilepsy patients) in this study were excluded from the study; patients who suffered from hepatic metastatic tumors; patients who withdrew from study for no reason; patients who had liver surgery in the past.

Detection methods

PS group: The patients were examined with a GE3.0T MRI scanner (GE, American). All the patients underwent a routine axial MRI scan with a 3-dimensional volumetric interpolated breath-hold examination (3DVIBE) sequence (The layer thickness was 3 mm, the TE was 2.38 ms, and the TR was 4.89 ms) and axial fast spin echo (FSE) T2-weighted image (The layer thickness was 6 mm, the TE was 94 ms, and the TR was 5166 ms).

GE group: The patients underwent a Gd-EOB-DTPA-enhanced MRI scan with a GE3.0T MRI scanner (GE, American). A peripheral intravenous bolus injection of contrast agent was administered with a dosage of 0.025 mmpl/kg and an injection rate of 2 mL per second. After the injection, 20 mL of normal saline was given in time to flush the tube. A dynamic enhanced axial 3DVIBE full liver scan was performed 6 times with breath-holding, 8 seconds each time. 20 minutes after the contrast agent injection, a coronal and axial fat suppression 3DVIBE full liver scan was performed again.

Table 1. Comparison of the general information (n, $\bar{x}$ ± sd)

Group	PS group (n=60)	GE group (n=60)	χ^2/t	P
Gender			0.184	0.667
Male	23	26		
Female	37	34		
Types (cases)			0.027	0.869
Alcoholic cirrhosis	19	18		
Hepatitis hepatocirrhosis	22	19		
Others	19	23		
Age (year)	54.3±8.3	55.0±8.2	0.502	0.616
BMI (kg/m^2)	17.73±3.14	17.31±3.65	0.675	0.500
Course of disease	2.3±0.6	2.3±0.7	0.373	0.709

Note: PS: plain scan; GE: gadolinium-ethoxybenzyl-diethylenetriamine-enhanced; BMI: body mass index.

Outcome measures

After the examination, the diagnostic results were jointly determined by two or more doctors with three years of work experience. The comparisons between the diagnostic results and the final pathological results of the PS group and the GE group were made.

After the diagnoses, the incidences of breathing artifacts of small hepatocellular carcinoma in patients with liver cirrhosis in the early and late arterial phases were observed in the PS group and the GE group. The breathing artifacts in the arterial phase was graded as follows [7]: Severe: the diagnosis was seriously affected, or the breathing artifact couldn't be used for the diagnosis. The development time of the hepatic artery was 3-6 s, and the maximum development density time was 8-10 s. Moderate: The diagnosis was slightly affected. The development time of the hepatic artery was 2-4 s, and the maximum development density time was 7-9 s. Mild: the diagnosis wasn't affected. The development time of the hepatic artery was 0.5-6.5 s, and the maximum development density time was 3.5-6.5 s.

The diagnostic values of the ROC curves in the PS and GE groups were compared. The ROC curve was made by sensitivity as the ordinate and specificity as the abscissa. The more convex and the closer to the upper left corner the ROC curve was, the greater the diagnostic value was. The ROC curve was used to compare the different indicators and determine the critical value of the indicators. The ROC was only applicable to the continuous indicators.

Statistical analysis

All the obtained data were analyzed using SPSS 23.00 statistical software. The quantitative data conforming to a normal distribution were expressed as the mean ± standard deviation ($\bar{x}$ ± sd), and independent sample t-tests were used for the comparisons between groups. The count data was expressed as number of cases/percentage (n/%), and chi-square (X^2) tests were applied within the groups. The ROC curves were drawn for the analyses of the diagnostic value. P<0.05 was considered statistically significant.

Results

Comparison of the general information

There were no significant differences in the general information between the two groups (P>0.05). See **Table 1**.

Comparison of the detection and final diagnosis results in the PS group

According to the diagnosis results, in the PS group, there were 23 cases diagnosed with hyperplastic nodules, 25 with small hepatocellular carcinoma, and 12 with regenerative nodules. Compared with the final diagnosis of 16 cases with hyperplastic nodules, 39 with small hepatocellular carcinoma and 5 with regenerative nodules, there were significant differences within the group (P<0.05). The MRI plain scan results showed a big difference from the final diagnosis, and the accuracy of the MRI plain scan was lower. See **Table 2**.

Comparison of the detection and final diagnosis results in the GE group

In the GE group, there were 6 cases diagnosed with hyperplastic nodules, 49 with small hepatocellular carcinoma, and 5 with regenerative nodules. Compared with the final diagnosis of 4 cases with hyperplastic nodules, 50 with small hepatocellular carcinoma, and 6 with regenerative nodules, there was little difference within the group (P>0.05). The results showed that

Table 2. Comparison of the detection and final diagnosis results in the PS group (n, %)

Group	Hyperplastic nodules	Regenerative nodules	Small hepatocellular carcinoma
PS group (n=60)	23 (38.33)	12 (20.00)	25 (41.67)
Histopathologic diagnosis (n=60)	16 (26.67)	5 (8.33)	39 (65.00)
χ^2	2.656	3.882	3.119
P	0.047	0.029	0.034

Note: PS: plain scan.

Table 3. Comparison of the detection and final diagnosis results in the GE group (n, %)

Group	Hyperplastic nodules	Regenerative nodules	Small hepatocellular carcinoma
GE group (n=60)	6 (10.00)	5 (8.33)	49 (81.67)
Histopathologic diagnosis (n=60)	4 (6.67)	6 (10.00)	50 (83.33)
χ^2	0.369	0.083	0.501
P	0.543	0.773	0.918

Note: GE: gadolinium-ethoxybenzyl-diethylenetriamine-enhanced.

Table 4. Comparison of the incidence of breathing artifacts in the early and late arterial phases (n, %)

Group	Severe	Moderate	Mild	Overall incidence
Early phase				
PS group (n=60)	3 (5.00)	1 (1.67)	2 (3.33)	6 (10.00)
GE group (n=60)	0 (0)	2 (3.33)	2 (3.33)	4 (6.67)
χ^2				0.369
P				0.543
Late phase				
PS group (n=60)	3 (5.00)	4 (6.67)	12 (20.00)	19 (31.67)
GE group (n=60)	1 (1.67)	3 (5.00)	4 (6.67)	8 (13.33)
χ^2				3.827
P				0.039

Note: PS: plain scan; GE: gadolinium-ethoxybenzyl-diethylenetriamine-enhanced.

the detection results of Gd-EOB-DTPA-enhanced MRI scan were similar to the final diagnostic results, and the detection results of the Gd-EOB-DTPA-enhanced MRI scan were more accurate. See **Table 3**.

Comparison of the incidence of breathing artifacts in the early and late arterial phases

The results showed that there were 6 cases in the PS group and 4 cases in the GE group who presented with breathing artifacts in the early arterial phase, with incidence rates of 10.00% and 6.67%, respectively (P>0.05). Meanwhile, in late arterial phase, there were 19 cases in the PS group and 8 cases in the GE group who presented with breathing artifacts, with incidence rates of 31.67% and 13.33%, respectively. The incidence of breathing artifacts in the late arterial phase in the PS group was significantly higher than it was in the GE group (P<0.05). See **Table 4**.

Analysis of the diagnostic value of MRI plain scans and Gd-EOB-DTPA-enhanced MRI scans in small hepatocellular carcinoma

The AUC of the Gd-EOB-DTPA-enhanced MRI scan was 0.806 in the patients with small hepatocellular carcinoma, and the diagnostic sensitivity and specificity were 76.64% and 88.32%, respectively. The AUC of the MRI plain scan was 0.791 in the patients with small hepatocellular carcinoma, and the diagnostic sensitivity and specificity were 77.74% and 75.35%, respectively (P=0.016). The ROC curve is shown in **Figure 1**.

Analysis of a typical case

A 48 year-old male patient was diagnosed with cavernous hemangioma with an MRI plain scan, but the same patient was diagnosed with small hepatocellular carcinoma with a Gd-EOB-DTPA-enhanced MRI scan. Hepatocellular carcinoma was confirmed by the postoperative pathology. See **Figure 2**.

Discussion

Hepatocellular carcinoma is one of the most common primary cancers in the human body,

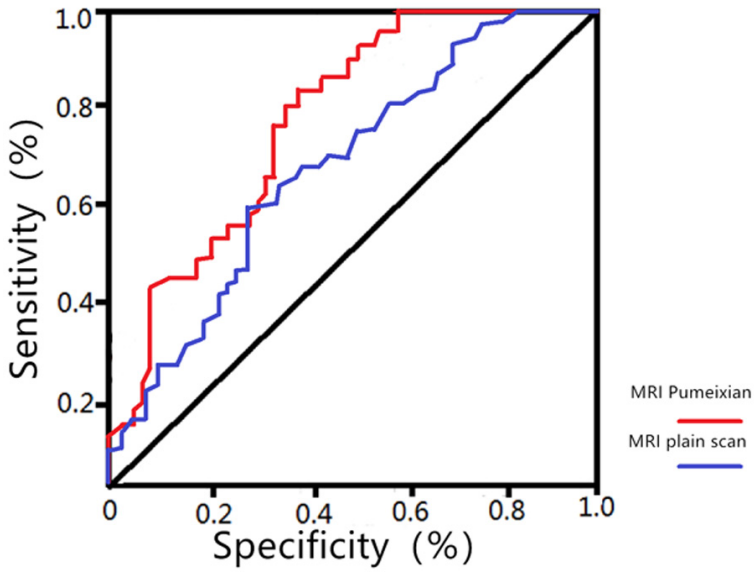

Figure 1. Analysis of the diagnostic value of MRI plain scanning and Gd-EOB-DTPA-enhanced MRI scanning in small hepatocellular carcinoma. Gd-EOB-DTPA-enhanced MRI: gadolinium-ethoxybenzyl-diethylenetriamine-enhanced magnetic resonance imaging.

and it is also the third most common cause of death among cancer-causing lesions, after lung cancer and gastric cancer. In clinical practice, liver damage in patients with liver cirrhosis combined with hepatocellular carcinoma is aggravated, and the disease is difficult to control, which eventually leads to liver failure and even metastasis to the whole body. The overall treatment effect for the disease is poor. Therefore, early examinations of patients with liver cirrhosis can significantly improve the clinical response rate [8, 9]. In China, hepatitis cirrhosis is the most important cause of hepatocellular carcinoma. Currently, the main clinical applications of imaging include ultrasound contrast imaging, MRI, etc. Non-invasive examinations play an important role in the screening of small hepatocellular carcinoma in patients with liver cirrhosis. Different imaging examinations have their own advantages. Therefore, in this study, Gd-EOB-DTPA-enhanced MRI scanning was applied in the diagnosis of small hepatocellular carcinoma in patients with liver cirrhosis.

Early diagnosis and treatment can effectively improve the survival rate of patients with cirrhosis. However, the specificity of the manifestations of this type of liver cirrhosis disease in the early stage is not high, only the changes in the patients' body temperature and the decline in immunity, etc. can be found. It will only be detected at a later stage by routine examinations. Although early diagnosis has a certain significance in prevention and treatment, it is difficult to promptly diagnose and treat [10, 11]. Studies have shown that liver cirrhosis is an important risk factor of hepatocellular carcinoma, and the occurrence of hepatocellular carcinoma in patients with liver cirrhosis is a complex multi-stage process, from the distortion of the liver's solid structure to the formation of cirrhotic nodules, and from hyperplasia and dysplastic nodules to early hepatocellular carcinoma. The examination results showed that Gd-EOB-DTPA is a new type of MRI contrast agent that can clearly distinguish the boundary between hepatoma carcinoma cells and normal hepatocytes. Therefore, the uptake of Gd-EOB-DTPA in the lesion areas was significantly reduced, and it was also very obvious compared with the uptake in the liver parenchyma peripherally. At the same time, the images in the lesion area showed no signal or a low signal. The main reason for this change was that benign cirrhotic nodules can devour healthy cells, so there is a significant difference between benign and normal cells. For the cancerous nodules of liver cirrhosis, due to the significant number of lesions in the hepatocytes, the accuracy and sensitivity of the lesion diagnosis can be improved by a Gd-EOB-DTPA-enhanced MRI scan [12, 13]. This study indicated that the accuracy of MRI plain scanning is lower, and the detection results of Gd-EOB-DTPA-enhanced MRI scanning is more accurate. There was no significant difference in the incidence of breathing artifacts in the early arterial phase in the PS group and the GE group. The incidence of breathing artifacts in the late arterial phase in the PS group was significantly higher than it was in the GE group. The diagnostic specificity and accuracy in the GE group were higher than they were in the PS group, and there was no significant difference in the sensitivity in the diagnosis of small hepatocellular carcinoma in patients with liver cirrhosis [14, 15]. Clinical trials have shown

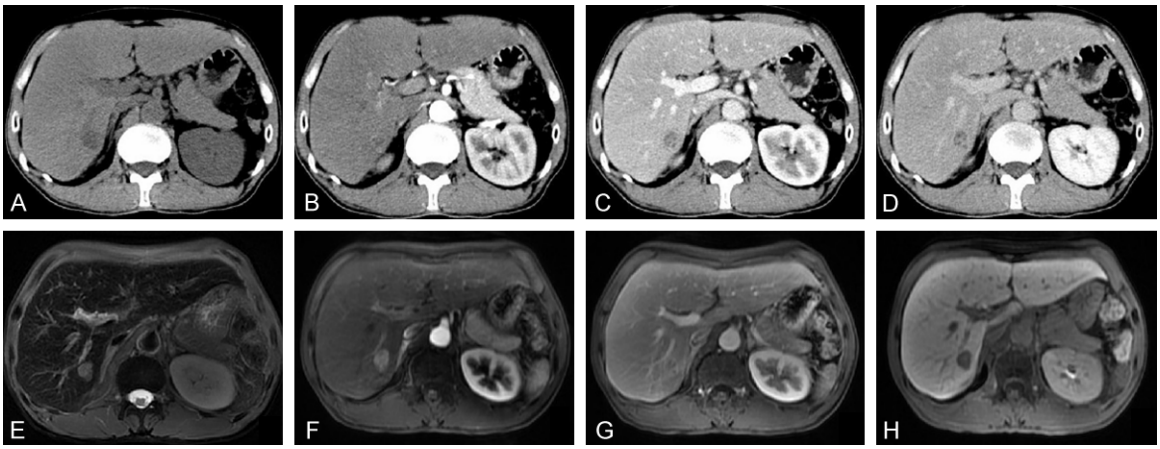

Figure 2. Analysis of a typical case. A: A type of circular low density was noted in the inferior segment of the right posterior lobe of the liver; B: The edge of the lesion was strengthened, the contrast agent gradually increased; C: The contrast agent in the lesion in the portal venous phase gradually increased; D: The contrast agent in the lesion at the equilibrium stage gradually increased; E: The nodules on the T2-weighted image (T2WI) showed hyperintensities compared with the liver parenchyma; F: The nodules in the inferior segment of the right posterior lobe of the liver in the enhancement arterial phase were significantly strengthened; G: The enhancement degree of the nodule in the portal venous phase decreased and showed hypo intensity; H: The nodules in the hepatobiliary specific phase showed no uptake of the contrast agent and hypo intensity.

that there is a close relationship between the pathological grading and postoperative recurrence of hepatocellular carcinoma. Gd-EOB-DTPA is a hepatocyte-specific contrast agent, and it has a potential correlation with the pathological grading of hepatocellular carcinoma, but its molecular mechanism needs to be further explored [16, 17]. At present, the internationally recognized diagnostic criteria for hepatocellular carcinoma in patients with liver cirrhosis have a higher diagnostic accuracy for larger tumors, but a lower diagnostic efficacy for small hepatocellular carcinoma. For some hepatocellular carcinoma, especially those lesions with a diameter of less than 2-3 cm, the arterial tumor blood vessels in the early stage are not fully formed, the typical enhancement and recession characteristics are lacking, and the imaging features of some cirrhotic hyperplastic nodules and small hepatocellular carcinoma are overlapping, so it is difficult to diagnose small hepatocellular carcinoma in patients with liver cirrhosis. However, Gd-EOB-DTPA-enhanced MRI scanning can respond significantly to these small lesions [18, 19]. A large number of studies have shown that there is no significant difference in the diagnostic sensitivity of small hepatocellular carcinoma between the MRI plain scan and the Gd-EOB-DTPA-enhanced MRI scan. But the definitive diagnosis of small hepatocellular carcinoma by MRI plain scan is difficult, so it is easy to miss smaller tumors [20-22].

This study has some shortcomings in the process of the research. Due to cost and other issues, all the patients were not given a comprehensive physical examination, so the influence of other factors couldn't be excluded. Also, due to the insufficient time frame, the number of selected patients was small, so the results might be somewhat biased. This study only adopted one detection method for the diagnoses, which was limited. More experimental methods should be added in future studies to provide more favorable experimental evidence for the diagnosis of small hepatocellular carcinoma in patients with liver cirrhosis.

To sum up, compared with MRI plain scanning, Gd-EOB-DTPA-enhanced MRI scanning has a higher diagnostic rate and a better diagnostic value in the diagnosis of small hepatocellular carcinoma in patients with liver cirrhosis.

Acknowledgements

This work was supported by the 2016 Self-financing Research Project of the Health & Family Planning Commission of Guangxi Zhuang Autonomous Region (Z2016415).

Disclosure of conflict of interest

None.

Address correspondence to: Hengguo Li, Medical Imaging Center, The First Affiliated Hospital of Ji'nan

University, No. 613 West Huangpu Avenue, Tianhe District, Guangzhou 510630, Guangdong Province, China. Tel: +86-18928903895; E-mail: lihengguo56uy@163.com

References

[1] Cao YL and Li W. Current status of ALPPS in the treatment of advanced liver cancer with insufficient future liver remnant. Zhonghua Wai Ke Za Zhi 2018; 56: 307-311.

[2] Scherber PR, Gabelein G, Eisele RM, Igna D and Glanemann M. Early stage liver cancer: hepatocellular carcinoma. Chirurg 2018; 89: 281-288.

[3] Kondo R, Kage M, Iijima H, Fujimoto J, Nishimura T, Aizawa N, Akiba J, Naito Y, Kusano H, Nakayama M, Mihara Y, Tanigawa M and Yano H. Pathological findings that contribute to tissue stiffness in the spleen of liver cirrhosis patients. Hepatol Res 2018; 48: 1000-1007.

[4] Deng HY, Zheng X, Zha P, Liang H, Huang KL and Peng L. Can we perform esophagectomy for esophageal cancer patients with concomitant liver cirrhosis? A comprehensive systematic review and meta-analysis. Dis Esophagus 2019; 32: doz003.

[5] Lou WY, Liu JX, Gao YJ, Zhong GS, Ding BS, Xu L and Fan WM. MicroRNA regulation of liver cancer stem cells. Am J Cancer Res 2018; 8: 1126-1141.

[6] Yasutake K, Koga S, Hokko Y, Ikemoto M, Yaguchi Y, Sakai H, Murata Y, Ohe K, Kohjima M, Nakamuta M and Enjoji M. Relevance of the mini nutritional assessment in cirrhotic liver disease patients. Asia Pac J Clin Nutr 2018; 27: 300-305.

[7] He YL, Yan LIU, Chao Y and Mu CL. Effect of CEUS examination on early diagnosis accuracy of patients with liver cirrhosis complicated with small liver cancer. Chin J Control Endemic Dis 2019; 34: 98-107.

[8] Pang Y, Kartsonaki C, Turnbull I, Guo Y, Clarke R, Chen Y, Bragg F, Yang L, Bian Z, Millwood IY, Hao J, Han X, Zang Y, Chen J, Li L, Holmes MV and Chen Z. Diabetes, plasma glucose, and incidence of fatty liver, cirrhosis, and liver cancer: a prospective study of 0.5 million people. Hepatology 2018; 68: 1308-1318.

[9] Fukui N, Golabi P, Otgonsuren M, de Avila L, Bush H and Younossi ZM. Hospice care in Medicare patients with primary liver cancer: the impact on resource utilisation and mortality. Aliment Pharmacol Ther 2018; 47: 680-688.

[10] Nault JC, Ningarhari M, Rebouissou S and Zucman-Rossi J. The role of telomeres and telomerase in cirrhosis and liver cancer. Nat Rev Gastroenterol Hepatol 2019; 16: 544-558.

[11] Chung W, Jo C, Chung WJ and Kim DJ. Liver cirrhosis and cancer: comparison of mortality. Hepatol Int 2018; 12: 269-276.

[12] Tsuchida T, Lee YA, Fujiwara N, Ybanez M, Allen B, Martins S, Fiel MI, Goossens N, Chou HI, Hoshida Y and Friedman SL. A simple diet- and chemical-induced murine NASH model with rapid progression of steatohepatitis, fibrosis and liver cancer. J Hepatol 2018; 69: 385-395.

[13] Aoyagi T, Takabe K, Tamanuki T, Matsubara H and Matsuzaki H. Pseudocirrhosis after chemotherapy in breast cancer, case reports. Breast Cancer 2018; 25: 614-618.

[14] Murugesan V, Huang J and Cho W. Mo1204 - trend of mortality in non-variceal upper gastrointestinal bleeding in patients with liver cirrhosis and chronic liver disease. Gastroenterology 2018; 154: S-706.

[15] Dong W, Wen Z, Shuqin LV and Ward VIP. Effect of Shugan Yipi decoction on the immune level of patients with HBeAg-positive liver cancer complicated with cirrhosis. J Xinjiang Med Univ 2019.

[16] Yi SW, Choi JS, Yi JJ, Lee YH and Han KJ. Risk factors for hepatocellular carcinoma by age, sex, and liver disorder status: a prospective cohort study in Korea. Cancer 2018; 124: 2748-2757.

[17] Lodes U, Jacob D and Meyer F. Acute liver failure, acute-on-chronic liver failure, hepatorenal syndrome, hepatopulmonary syndrome and portopulmonary hypertension, artificial liver support on the ICU. Zentralbl Chir 2017; 142: 275-286.

[18] Golob-Schwarzl N, Krassnig S, Toeglhofer AM, Park YN, Gogg-Kamerer M, Vierlinger K, Schroder F, Rhee H, Schicho R, Fickert P and Haybaeck J. New liver cancer biomarkers: PI3K/AKT/mTOR pathway members and eukaryotic translation initiation factors. Eur J Cancer 2017; 83: 56-70.

[19] Rudnick DA. Antifibrotic therapies in liver disease: ready for primetime? Clin Liver Dis (Hoboken) 2017; 9: 138-140.

[20] Wu DB and Tang H. Advances in the study of cirrhosis and precancerous lesions of liver cancer. Chin J of Hepatol 2019; 27: 483-486.

[21] Veith NT, Histing T, Menger MD, Pohlemann T and Tschernig T. Helping prometheus: liver protection in acute hemorrhagic shock. Ann Transl Med 2017; 5: 206.

[22] Chen R, Zhu S, Fan XG, Wang H, Lotze MT, Zeh HJ 3rd, Billiar TR, Kang R and Tang D. High mobility group protein B1 controls liver cancer initiation through yes-associated protein-dependent aerobic glycolysis. Hepatology 2018; 67: 1823-1841.