

Serum cystatin C and cystatin C/albumin ratio for the evaluation of liver function in patients with cirrhosis.

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Abstract

Purpose: The aim of this study is to analyze the serum cystatin C (Cys C) and cystatin C/albumin (Alb) ratio in patients with cirrhosis and evaluate the role of serum Cys C in the evaluation of liver function.

Methods: The liver function of patients was graded according to the Child-Pugh Score. According to the serum Cys C levels (determined with particle-enhanced immunonephelometric assay), the patients were divided into two groups: the high Cys C level group and normal Cys C level group. The correlation between the Child-Pugh grades/scores and the serum Cys C level, Cys C/Alb ratio were investigated.

Results: The Cys C values were not correlated to Child-Pugh grades and scores. Besides, the Cys C/Alb ratio of both groups had a linear regressive relationship with the Child-Pugh scores. Ninety-seven percentage sensitivity and 100% specificity were achieved for the evaluation of liver function in cirrhosis patients with high serum Cys C level.

Conclusion: Cys C value and Cys C/Alb ratio are accurate for liver function evaluation in the cirrhosis patients with high serum Cys C levels. Compared with the Cys C value, the Cys C/Alb ratio is more related to the liver function and can be used as an indicator in cirrhosis patients with normal serum Cys C level for the evaluation of liver function.

Keywords: Cystatin C, Cystatin C/albumin ratio, Cirrhosis, Child-pugh score.

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Introduction

Liver cirrhosis is a condition in which the normal liver tissue was replaced by scar tissue and formation of regenerative nodules. The gold standard for diagnosis of cirrhosis is a liver biopsy, but a biopsy is not necessary if the laboratory data suggests cirrhosis [1]. Recently, the evaluation of liver function in patients with cirrhosis has been widely studied. Compared with serum creatinine or creatinine clearance rate the serum Cys C reflects the glomerular filtration rate (GFR) more accurately [2,3]. The Cys C, a cysteine protease inhibitor which belongs to the super cystatin family, is a low molecular, basic and non-glycosylated protein that exists in body fluid and various cells and plays an important role in suppressing and regulating the activity of cathepsin. The serum Cys C can only be cleared through glomerular filtration which is independent of other influences such as gender, age and diet. Therefore, serum Cys C is treated as an optimal homologous marker to evaluate glomerular filtration rate. In addition, compared with serum creatinine, serum Cys C is a more sensitive indicator since earlier increase of serum Cys C can be detected along with the decrease of glomerular filtration rate. Furthermore, it is related to the hepatic failure mediated renal function changes [4] and thus a valid index for renal function evaluation and prognosis in patients with cirrhosis [5]. In this study, we analyzed the relationship between the Cys C/Alb ratio and the liver function

in patients with cirrhosis which provides a convenient and efficient way for the evaluation of liver function in patients with cirrhosis.

Methods

Materials

The clinical data involves 100 cases of patients with hepatic cirrhosis aged from 29 to 83 (60.96 ± 10.93) with 54 male cases and 46 female cases (sex ratio=1.17:1) which was collected between August 2015 and July 2016 from Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital. Among the 100 cases, 36 cases were hepatitis B cirrhosis, 25 cases were alcoholic cirrhosis, 6 cases were hepatitis B cirrhosis combined with alcoholic cirrhosis, 1 case was hepatitis C cirrhosis, 8 cases were primary biliary cirrhosis and 24 cases were occult cirrhosis. The following are the inclusion and exclusion criteria.

Inclusion criteria: 1. Patients with hypohepatia, portal hypertension like ascites, gastroscopically confirmed esophageal varix, underlying cause of cirrhosis such as viral hepatitis, long-term alcohol consumption and autoimmune liver disease, ultrasound or CT confirmed cirrhosis. 2. Patients with complete medical records.

Exclusion criteria: 1. Patients without cirrhosis; 2. Patients with both of liver cancer and cirrhosis; 3. Patients with cirrhosis and other cancers; 4. Patients had liver or renal surgical history; 5. Patients with primary renal diseases, hypertension or diabetes; 6. Patients without complete medical records.

Serum Cys C level detection

The serum Cys C level was detected by particle-enhanced immunonephelometric assay (Roche Diagnostic, Barcelona, Spain) (Normal serum Cys C \leq 1.15 mg/L).

Liver function evaluation

The liver function was evaluated according to the Child-Pugh scores [6], as shown in Table 1. In patients with primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC), according to the bilirubin level, the corresponding score is 1 (17-68 μ mol/L), 2 (68-170 μ mol/L), 3 (>170 μ mol/L) respectively.

Table 1. Child-Pugh scoring.

Items	Score		
	1	2	3
Hepatic encephalopathy	None	I-II	III-IV
Ascites	None	Mild	Moderate, severe
Bilirubin (μ mol/L)	<34	34-51	>51
Albumin (g/L)	\geq 35	28-35	\geq 28
Prothrombin time (s)	\leq 14	14-18	\leq 18

Note: The grading is according to the total scores of the 5 items. Grade A: 5-6, Grade B: 7-9, Grade C: 10-15.

Grouping and relationship analysis

According to the serum Cys C level, the patients were divided into two groups: the high Cys C level group and the normal

Table 2. The relationship between the Child-Pugh grades/scores and Cys C value, or Cys C/Alb ratio.

Items	Child A	Child B	Child C	Rg	Rs	P value
High Cys C level group						
(Cys C)/(mg/L)	1.25 \pm 0.11	1.39 \pm 0.17	1.59 \pm 0.26	0.497	0.546	0.001
(Cys C/Alb)/($\times 10^{-5}$)	3.59 \pm 0.33	4.82 \pm 0.62	6.50 \pm 0.59	0.868	0.932	0
Normal Cys C level group						
(Cys C)/(mg/L)	0.94 \pm 0.11	0.95 \pm 0.14	0.98 \pm 0.16	0.087	0.091	0.521
(Cys C/Alb)/($\times 10^{-5}$)	2.85 \pm 0.39	3.04 \pm 0.55	3.76 \pm 0.60	0.486	0.548	0.501

Note: Rg is the coefficient between the Child grades and Rs is the coefficient between the Child scores.

Cys C level group. The relationship between the Child-Pugh grades/scores and the Cys C value or Cys C/Alb ratio were investigated. Analyze the the Cys C/Alb ratio and the Child-Pugh scores though linear regression.

Statistical analysis

SPSS19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The relationship between the Cys C value, Cys C/Alb ratio and the Child-Pugh scores was analyzed by Person correlation. The correlation between the Cys C/Alb ratio and the Child-Pugh scores was determined through linear regression. Receiver operating characteristic (ROC) curve was used to evaluate the accuracy of diagnosis and the significance level was set at $p < 0.05$.

Results

Child-pugh grading

Among the 100 cases, 43 cases with increased serum Cys C level (high Cys C level group) and 57 cases with normal serum Cys C level (normal Cys C level group). According to the Child-Pugh grading, there were 4 Child A cases, 19 Child B cases and 20 Child C cases in the high Cys C level group. In the normal Cys C level group, there were 8 Child A cases, 35 Child B cases and 14 Child C cases.

The relationship between the liver function and the Cys C value, Cys C/Alb ratio

The Cys C value, Cys C/Alb ratio and the related Child-Pugh grades/scores for patients with cirrhosis in two groups are shown in Table 2.

The linear regression relationship between the Cys C/Alb ratio and the child scores

There is a linear regression relationship between the Cys C/Alb ratio and the Child scores in two groups. Compared with the normal Cys C level group, the Cys C/Alb ratio in the high Cys C level group is more closely related to the Child grading (Figure 1).

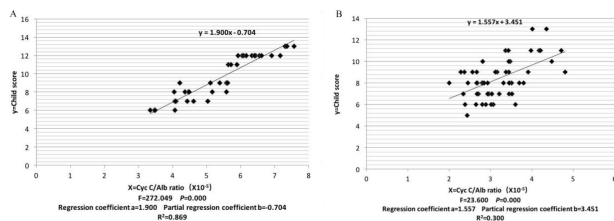


Figure 1. The linear regression relationship between the Cys C/Alb ratio and the Child scores A. The linear regression relationship between the Cys C/Alb ratio and Child scores in high Cys C level group. B. The linear regression relationship between the Cys C/Alb ratio and the Child scores in the normal Cys C level group.

The accuracy of liver function evaluation in patients with cirrhosis by serum Cys C/Alb ratio

As the result shown in Table 3, the sensitivity and specificity of liver function evaluation in patients with cirrhosis by serum Cys C/Alb ratio. According to the maximum Youden's index, the optimal critical value of serum Cys C/Alb ratio is 4.072×10^{-5} for the evaluation of liver function in patients with moderate or severe cirrhosis which exhibits higher sensitivity, specificity and accuracy in the high Cys C level group. However, ROC analysis doesn't find the critical value of serum

Table 3. The sensitivity and specificity of liver function evaluation in patients with cirrhosis by serum Cys C/Alb ratio.

Cirrhosis type and optimal critical value	Sensitivity (%)	Specificity (%)	AUC	95% confidence interval	Youden's index
Patients with moderate or severe cirrhosis (including normal Cys C and increased Cys C levels)					
Cys C/Alb $\geq 4.072 \times 10^{-5}$	50	100	0.748	0.638~0.858	0.5
Patients with severe cirrhosis in the high Cys C level group					
Cys C/Alb $\geq 4.072 \times 10^{-5}$	97.4	100	0.994	0.974~1.000	0.974

The serum Cys C not only reflects the renal function changes in patients with cirrhosis [16,17], but also displays the variation degree of portal hypertension and renal/systemic hemodynamics [18,19]. Besides, studies have shown that serum Cys C level is positively direct to the cirrhosis-mediated inflammation and macrophage hypersecretion [20] and increases significantly along with the increase of cathepsin level in chronic liver disease [21]. Therefore, serum Cys C increases with the development of chronic liver disease and is a potential indicator for liver fibrosis [22]. Study has demonstrated that serum Cys C level could even reflect the degree of liver fibrosis and inflammation in animal chronic liver disease models with normal renal function [23]. In addition, serum Cys C level is related to prognosis such as the

Cys C/Alb ratio in the normal Cys C level group to distinguish patients with moderate or severe cirrhosis (Figure 2).

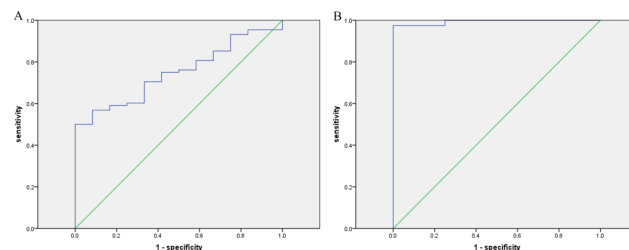


Figure 2. A) The characteristic curve for the evaluation of liver function in patients with moderate or severe cirrhosis (Grade \geq B) by serum Cys C/Alb ratio. B) The characteristic curve for liver function evaluation in patients with moderate or severe cirrhosis (Grade \geq B) in the high Cys C level group by serum Cys C/Alb ratio.

Discussion

The renal function in patients with cirrhosis plays an important role in disease prognosis. However, serum creatinine cannot accurately reflect the glomerular filtration rate due to the cirrhosis-mediated malnutrition and decreased muscle mass [7,8]. Instead of serum creatinine, serum Cys C is universally recognized as the indicator for the evaluation of glomerular filtration rate in patients with cirrhosis [9]. Furthermore, serum Cys C can also reflect the renal function in cirrhosis patients with ascites and normal serum creatinine [10]. Since the content of serum Cys C is stable and independent of other influences, such as gender, age, muscle mass, drugs and inflammation [11], it reflects the glomerular filtration rate more precisely than serum creatinine [12-15].

survival rate, mortality rate [24-28]. Child-Pugh score is a standard method for the evaluation of liver function in patients with hepatic cirrhosis and mainly includes the index of liver function [6]. With the development of cirrhosis, changes have been occurred in the renal function, liver inflammation and the degree of liver fibrosis. Serum Cys C level is closely related to these changes and thus reflects the degree of hepatic cirrhosis.

The results in this study proved that serum Cys C value and Cys C/Alb ratio are positively related to the Child grades and scores in cirrhosis patients with high serum Cys C levels. On the contrary, in cirrhosis patients with normal serum Cys C levels, the serum Cys C value had no relationship with the Child grade and scores, however, the Cys C/Alb ratio is

positively related to the Child grades and scores. Compared with the serum Cys C value, the Cys C/Alb ratio is better related to the liver function. Besides, there is a linear regression relationship between the Cys C/Alb ratio and the Child scores in both groups. According to the linear regression curve, a closer linear relationship is found between the Cys C/Alb ratio and the Child scores in cirrhosis patients with high Cys C level which reflects the degree of cirrhosis more precisely. The Cys C value and Cys C/Alb ratio in cirrhosis patients with increased serum Cys C level can better reflect the degree of cirrhosis and the Cys C/Alb ratio is more closely related to the liver function. In addition, it is more precise to evaluate the liver function in patients with moderate or severe cirrhosis (Grade \geq B) with the critical value of serum Cys C/Alb ratio $\geq 4.072 \times 10^{-5}$, however, this critical value still plays a certain role in the evaluation of liver function in cirrhosis patients with normal serum Cys C level.

References

- Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet* 2008; 371: 838-851.
- Arias IM, Pobes A, Baños M. [Cystatin C. New marker of renal function]. *Nefrologia* 2005; 25: 217-220.
- Cholongitas E, Shusang V, Marelli L, Nair D, Thomas M, Patch D, Burns A, Sweny P, Burroughs AK. Renal function assessment in cirrhosis-difficulties and alternative measurements. *Aliment Pharmacol Ther* 2007; 26: 969-978.
- Ustundag Y, Samsar U, Acikgoz S, Cabuk M, Kiran S, Kulah E, Aydemir S. Analysis of glomerular filtration rate, serum cystatin C levels, and renal resistive index values in cirrhosis patients. *Clin Chem Lab Med* 2007; 45: 890-894.
- Adachi M, Tanaka A, Aiso M, Takamori Y, Takikawa H. Benefit of cystatin C in evaluation of renal function and prediction of survival in patients with cirrhosis. *Hepato Res* 2015; 45: 1299-1306.
- Cholongitas E, Papatheodoridis G V, Vangeli M, Terreni N, Patch D, Burroughs AK. Systematic review: the model for end-stage liver disease-should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? *Aliment Pharmacol Ther* 2005; 22: 1079-1089.
- Demirtas S, Bozbas A, Akbay A, Yavuz Y, Karaca L. Diagnostic value of serum cystatin C for evaluation of hepatorenal syndrome. *Clin Chim Acta* 2001; 311: 81-89.
- Teneva BH. Pathogenesis and assessment of renal function in patients with liver cirrhosis. *Folia Med (Plovdiv)* 2012; 54: 5-13.
- Pöge U, Gerhardt T, Stoffel-Wagner B, Klehr HU, Sauerbruch T, Woitas RP. Calculation of glomerular filtration rate based on cystatin C in cirrhotic patients. *Nephrol Dial Transplant* 2005; 21: 660-664.
- Kim DJ, Kang HS, Choi HS, Cho HJ, Kim ES, Keum B, An H, Kim JH, Seo YS, Kim YS. Serum cystatin C level is a useful marker for the evaluation of renal function in patients with cirrhotic ascites and normal serum creatinine levels. *Korean J Hepatol* 2011; 17: 130.
- Weinert LS, Camargo EG, Soares AA, Silveiro SP. Glomerular filtration rate estimation: performance of serum cystatin C-based prediction equations. *Clin Chem Lab Med* 2011; 49: 1761-1771.
- Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. *J Hepatol* 2010; 52: 605-613.
- Torre A, Aguirre-Valadez JM, Arreola-Guerra JM, García-Flores OR, García-Juárez I, Cruz-Rivera C, Correa-Rotter R, Niño-Cruz JA. Creatinine versus cystatin c for estimating GFR in patients with liver cirrhosis. *Am J Kidney Dis* 2016; 67: 342-344.
- Beben T, Rifkin DE. GFR estimating equations and liver disease. *Adv Chronic Kidney Dis* 2015; 22: 337-342.
- Wang D, Feng J-F, Wang A-Q, Yang Y-W, Liu Y-S. Role of Cystatin C and glomerular filtration rate in diagnosis of kidney impairment in hepatic cirrhosis patients. *Medicine (Baltimore)* 2017.
- Gerbes AL, Gülberg V, Bilzer M, Vogeser M. Evaluation of serum cystatin C concentration as a marker of renal function in patients with cirrhosis of the liver. *Gut BMJ* 2002; 50: 106-110.
- Omar M, Abdel-Razek W, Abo-Raia G, Assem M, El-Azab G. Evaluation of serum cystatin C as a marker of early renal impairment in patients with liver cirrhosis. *Int J Hepatol* 2015.
- Mindikoglu AL, Dowling TC, Wong-You-Cheong JJ, Christenson RH, Magder LS, Hutson WR, Seliger SL, Weir MR. A pilot study to evaluate renal hemodynamics in cirrhosis by simultaneous glomerular filtration rate, renal plasma flow, renal resistive indices and biomarkers measurements. *Am J Nephrol* 2014; 39: 543-552.
- Hurry PK, Poulsen JH, Bendtsen F, Møller S. Neutrophil gelatinase-associated lipocalin and cystatin C in cirrhosis and portal hypertension: Relations to organ extraction and dysfunction. *J Gastroenterol Hepatol* 2017; 32: 473-481.
- Korolenko TA, Filatova TG, Iuz'ko I, Savchenko NG, Voloshina NB, Goncharova NV. [Cystatin C: a biological role and impaired secretion in viral hepatitis c and hepatic cirrhosis]. *Klin Lab Diagn* 2007; 12: 18-20.
- Chu SC, Wang CP, Chang YH, Hsieh YS, Yang SF, Su JM, Yang CC, Chiou HL. Increased cystatin C serum concentrations in patients with hepatic diseases of various severities. *Clin Chim Acta* 2004; 341: 133-138.
- Takeuchi M, Fukuda Y, Nakano I, Katano Y, Hayakawa T. Elevation of serum cystatin C concentrations in patients with chronic liver disease. *Eur J Gastroenterol Hepatol* 2001; 13: 951-955.
- Ladero JM, Cárdenas MC, Ortega L, González-Pino A, Cuenca F, Morales C, Lee-Brunner A. Serum cystatin C: a non-invasive marker of liver fibrosis or of current liver fibrogenesis in chronic hepatitis C? *Ann Hepatol* 2012; 11: 648-651.
- Seo YS, Jung ES, An H, Kim JH, Jung YK, Kim JH, Yim HJ, Yeon JE, Byun KS, Kim CD. Serum cystatin C level is a good prognostic marker in patients with cirrhotic ascites

- and normal serum creatinine levels. *Liver Int* 2009; 29: 1521-1527.
25. Chung MY, Jun DW, Sung SA. Diagnostic value of cystatin C for predicting acute kidney injury in patients with liver cirrhosis. *Korean J Hepatol* 2010; 16: 301.
26. Sharawey MA, Shawky EM, Ali LH, Mohammed AA, Hassan HA, Fouad YM. Cystatin C: a predictor of hepatorenal syndrome in patients with liver cirrhosis. *Hepatol Int* 2011; 5: 927-933.
27. Ahn HS, Kim YS, Kim SG, Kim HK, Min SK, Jeong SW, Jang JY, Lee SH, Kim HS, Kim BS. Cystatin C is a good predictor of hepatorenal syndrome and survival in patients with cirrhosis who have normal serum creatinine levels. *Hepatogastroenterology* 2012; 59: 1168-1173.
28. Belcher JM, Sanyal AJ, Garcia-Tsao G, Ansari N, Coca SG, Shlipak MG, Parikh CR. Early trends in cystatin C and outcomes in patients with cirrhosis and acute kidney injury. *Int J Nephrol* 2014.

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