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The Serum Magnesium Level of Different Etiologies of Liver Cirrhosis: A Retrospective Study

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Abstract

Liver cirrhosis remains a major health issue globally. Serum magnesium deficiency is common among liver cirrhosis patients, but there are very limited large-scale studies on it. Our study aimed to investigate the serum magnesium level of cirrhotic patients and determine the distribution of serum magnesium deficiency in different etiologies among liver cirrhosis patients, in Hangzhou, China. We collected clinical data of cirrhotic patients admitted in our hospital from 1st January to 31st December 2022. A total of 1128 individuals were enrolled in the research, including 756 male and 372 female. Viral hepatitis, alcohol liver disease (ALD), autoimmune hepatitis (AIH) were main etiologies, accounting for 55.05%, 13,92%, 10.46%, respectively. Among the patients with viral hepatitis, HBV remains the predominant cause of liver cirrhosis. Serum magnesium levels were variable within different etiologies of cirrhotic patients, while that of ALD group was 0.72, significantly lower than normal range and that of other main etiologies. Taking 0.75 mmol/L as the lower cut-off limit, the overall prevalence of serum magnesium deficiency among cirrhotic patients was 33.2%, and that was 60.5%, 39.8%, 24.0% for ALD, cryptogenic cirrhosis, and HBV, respectively. The prevalence of magnesium deficiency in ALD group was considered higher than the other two groups HBV and cryptogenic cirrhosis (^{2}=78.072, P<0.001). In summary, HBV remains a common cause for liver cirrhosis and patients with ALD were more likely to occur serum magnesium deficiency than other etiologies of liver cirrhosis.

Keywords: Liver Cirrhosis; Magnesium; Serum Magnesium Deficiency; Etiology; Prevalence

List of Abbreviations: HBV: hepatitis B virus; ALD: alcoholic liver disease; PBC: primary biliary cirrhosis; AIH: autoimmune hepatitis; HCV: hepatitis C virus; SL=schistosomiasis cirrhosis; CLD: cholestatic liver disease; HAV: hepatitis A virus; CC: cryptogenic cirrhosis; LC: liver cirrhosis.

Introduction

Magnesium is the most abundant divalent cation in the cell and the fourth most abundant element in the human body. It is an essential element for the correct activity of many enzymes related to energy, such as ATP-involving reactions and the metabolism of nucleic acids. Magnesium level in the body is determined by the ratio between its excretion and intake or reabsorption [1]. The kidney regulates its secretion, the gut adjusts its uptake, and bones act as warehouse. Magnesium status is closely associated with liver function and may be linked to the etiology of chronic liver disease. It's reported that in vivo, extracellular magnesium deficiency modulates the expression levels of molecules related to oxidative stress/antioxidant response in HepG2 human hepatoma cells [2]. Animal studies have shown that magnesium deficiency could induce the emergence of mast cells in the liver of rats. In liver, mast cells contribute to liver fibrosis [3].

Liver cirrhosis develops after a long period of chronic liver inflammation that results in the disruption of healthy liver parenchyma, irreversible diffuse hepatic fibrosis, and the formation of regenerative nodules [4]. Cirrhosis is a consequence of different causes, such as obesity, non-alcoholic fatty liver disease, alcohol consumption, viral hepatitis, autoimmune liver disease, cholestatic disease [5]. During the progression of liver cirrhosis, hypomagnesemia often emerges. Conversely, magnesium deficiency can act as a stimulatory factor to exacerbate liver cirrhosis, thereby establishing a vicious cycle. Previous studies have reported serum magnesium deficiency among cirrhotic patients [6-9]. Lim *et al* reported magnesium deficiency in cirrhotic patients as early as 1972 [10]. However, most studies on magnesium level of cirrhotic patients were small-size, the statistical power limited, large-scale epidemiological studies are needed. In addition, serum magnesium level of different etiologies of liver cirrhosis patients were rarely reported, and remains poorly described.

Based on the background, we designed this retrospective study to investigate serum magnesium level among patients with liver cirrhosis, assess the prevalence of serum magnesium deficiency within cirrhotic patients, explore whether magnesium deficiency is associated with the etiology of liver cirrhosis.

Material and methods

Study Population

Patients were retrospectively collected from Xixi hospital of Hangzhou city between January 1, 2022 and December 31, 2022. Inclusion criteria: patients were of 18 years old or older with liver cirrhosis. Exclusive criteria: patients of pregnancy and hepatocellular carcinoma were excluded.

Data Collection

Laboratory parameters, complications and demographic characteristics were collected. We used automatic biochemical analyzer (Beckman coulter, America) to measure magnesium (Mg), calcium (Ca), albumin (ALB), alanine transaminase, aspartate aminotransferase (AST), glutamyl transpeptidase (GGT), total bilirubin (TB); an automatic analyzer (Roche Cobas e601, Switzerland) to detect interleukin-6 (IL-6), and an automatic analyzer (Ortho VITROS 4600, China) to test Ammonia (AMMON) in the clinical laboratory of our hospital. Etiology was multiple as hepatitis B, hepatitis C, hepatitis A, alcoholic liver disease, cholestatic liver disease, primary biliary cirrhosis, autoimmune hepatitis, schistosomiasis cirrhosis and Wilson's disease. The normal reference range of serum magnesium was 0.75-1.02 mmol/L. Magnesium deficiency was defined as serum magnesium level less than 0.75mmol/L.

Statistical Analysis

IBM SPSS Statistics version 25.0 was used for all statistical data processing and analysis. All continuous variables were performed normality first and the results were expressed as mean ± standard deviation (SD) if following normally distribution and median (P25, P75) for abnormal distribution. Categorical variables were presented as n (%) and compared by *chi*-square test. Student's *t*-test was used to compare the difference between the two normally distributed groups and Kruskal-Wallis Test was used to detect the difference between more than two groups that were not all normally distributed. Pearson correlation and Spearman rank correlation test were applied to test the correlation between magnesium levels and laboratory parameters. In order to determine factors independently related to magnesium levels, multivariate linear regression was performed. All *P*-values were bilateral and p-value <0.05 was considered as statistically significant.

Results

Demographical Characteristics of All Enrolled Patients

Of 1128 patients with liver cirrhosis enrolled in this research, 756 (67%) were male, 372(33%) were female, and the ratio of male to female was 2.03:1. The average age of all individuals was 58.10±10.38, ranged from 27 to 86 years. The mean serum magnesium level of all enrolled patients was 0.78±0.10 mmol/L, within the normal reference range (0.75-1.02 mmol/L). The average level of Alb was 32.10±6.89 g/L, lower than the normal serum Alb level (40-55 g/L). The median level of AST, TB, IL-6, and Ammon was 39U/L, 24.75μmol/L, 19.80pg/mL and 39μmol/L respectively, all higher than the normal serum level. Meanwhile, the average level of Ca was 2.22±0.15 mmol/L, and the median level of ALT and GGT were 26U/L and 36U/L respectively, all in the normal reference range (Table 1).

Table 1: Lab parameters of cirrhotic patients

Parameters	Mean ± SD / Median (P25,P75)	95%CI	Reference range
Age (years)	58.10±10.38	57.50-58.71	
Gender (n, %)			
Male (756, 67.0)	0.78±0.10	0.77-0.79	0.75-1.02
Female (372, 33.0)	0.78±0.10	0.77-0.79	0.75-1.02
Mg (mmol/L)	0.78±0.10	0.78-0.79	0.75-1.02
Alb (g/L)	32.10±6.89	31.69-32.50	40-55
Ca (mmol/L)	2.22±0.15	2.21-2.23	2.20-2.65
ALT (U/L)	26 (18, 39)	/	14793
AST (U/L)	39 (29, 60)	/	13-35
GGT (U/L)	36 (22, 72)	/	16619
TB (U/L)	24.75 (15.46, 44.17)	/	0-23
IL-6 (U/L)	19.8 (5.9, 67.7)	/	0-7
Ammon (μmol/L)	39 (24, 66)	/	45930

Mg: magnesium; Alb: albumin; Ca: calcium; ALT: alanine transaminase; AST: aspartate aminotransferase; GGT： glutamyl transpeptidase; TB: total bilirubin; IL-6: interleukin-6; CI: confidence interval; SD: standard deviation

Etiology Distribution

The etiology distribution of all enrolled patients is presented in Table 2. The top five LC causes were viral hepatitis (55.05%), alcohol liver disease (13.92%), autoimmune hepatitis (10.46%), and mixed etiology (9.57%), cryptogenic cirrhosis (9.13%). Among the remaining patients, schistosomiasis cirrhosis, cholestatic liver disease and Wilson's disease were identified in 1.33%, 0.44% and 0.09%, respectively.

Among the 621 LC patients with viral hepatitis, HBV was the predominant cause; HBV accounted for about 97% of all viral hepatitis cases and 53.1% of the study population. HCV was the second major cause of viral hepatitis liver cirrhosis, but the proportion was only 1.6%. Meanwhile, the overlapping viral hepatitis involved in 3 cases of HBV plus HCV. Only one case was HAV infection caused liver cirrhosis. The proportion were both less than 1.0% of all cases.

118 (10.46%) cases of autoimmune cirrhosis were composed of 63 (5.59%) cases of primary biliary cirrhosis, 43 (3.81%) cases of autoimmune hepatitis, and 12 (1.06%) cases of AIH plus PBC. In the 108 (9.57%) cases of mixed etiology liver cirrhosis, we observed 71 (6.29%) cases of HBV plus ALD, 13 (1.15%) cases of ALD plus SL, 5 (0.44%) cases of ALD plus AIH, 4 (0.35%) cases of ALD plus CLD, 4 (0.35%) cases of HBV plus CLD, 3 (0.27%) cases of HCV plus ALD, 2 (0.18%) cases of HBV plus AIH, 1 (0.09%) case of AIH+PBC+ALD, 1 (0.09%) case of AIH+SL+CLD, 1 (0.09%) case of HAV+ALD, 1 (0.09%) case of HBV+PBC, 1(0.09%) case of HBV+SL, 1(0.09%) case of HCV+SL.

Etiology Distribution in Different Genders

The etiology distribution among different genders is listed in Table 2. With respect to the etiology in different genders, we observed that the main etiology was viral hepatitis in both genders. However, the prevalence of viral hepatitis, alcoholic liver disease, mixed etiology was higher among men, whereas that of autoimmune cirrhosis, cryptogenic cirrhosis, and cholestatic liver disease (CLD)was higher among women (P<0.001).

Table 2: Etiology composition of liver cirrhosis

Etiology	Total (n, %)	Male (n, %)	Female (n, %)	P-Value
Viral hepatitis	621 (55.05)	451 (59.66)	170 (45.70)	<0.001
HBV	599 (53.10)	445 (58.86)	154 (41.40)	
HCV	18 (1.60)	5 (0.66)	13 (3.49)	
HBV+HCV	3 (0.27)	1 (0.13)	2 (0.54)	
HAV	1 (0.09)	0	1 (0.27)	
ALD	157 (13.92)	145 (19.18)	12 (3.23)	<0.001
Autoimmune	118 (10.46)	14 (3.07)	104 (27.96)	<0.001
PBC	63 (5.59)	10 (1.32)	53 (14.25)	
AIH	43 (3.81)	4 (0.53)	39 (10.48)	
AIH+PBC	12 (1.06)	0	12 (3.23)	
CC	103 (9.13)	38 (5.03)	65 (17.47)	<0.001
Mixed etiology	108 (9.57)	100 (13.23)	8 (2.15)	<0.001
HBV+ALD	71 (6.29)	71 (9.39)	0	
ALD+SL	13 (1.15)	10 (1.32)	3 (0.81)	

ALD+AIH	5 (0.44)	4 (0.53)	1 (0.27)	
ALD+CLD	4 (0.35)	4 (0.53)	0	
HBV+CLD	4 (0.35)	3 (0.40)	1 (0.27)	
HCV+ALD	3 (0.27)	3 (0.40)	0	
HBV+AIH	2 (0.18)	2 (0.26)	0	
AIH+PBC+ALD	1 (0.9)	1 (0.13)	0	
AIH+SL+CLD	1 (0.9)	0	1 (0.27)	
HAV+ALD	1 (0.9)	1 (0.13)	0	
HBV+PBC	1 (0.9)	0	1 (0.27)	
HBV+SL	1 (0.9)	1 (0.13)	0	
HCV+SL	1 (0.9)	0	1 (0.27)	
SL	15 (1.33)	7 (0.93)	8 (2.15)	0.102
CLD	5 (0.44)	1 (0.13)	4 (1.08)	0.043
Wilson's disease	1 (0.99)	0	1 (0.27)	0.33
Total	1128 (100.0)	756 (67.0)	372 (33.0)	

HBV=hepatitis B virus; ALD=alcoholic liver disease; PBC=primary biliary cirrhosis; AIH=autoimmune hepatitis; HCV=hepatitis C virus; SL=schistosomiasis cirrhosis; CLD=cholestatic liver disease; HAV=hepatitis A virus; CC= cryptogenic cirrhosis.

Serum Magnesium Levels and the Incidence of Magnesium Deficiency among Different Etiologies of Liver Cirrhosis

Serum magnesium levels and the incidence of magnesium deficiency among different etiologies of liver cirrhosis are listed in Table 3 and Table 4. The serum magnesium level of patients with ALD was 0.72 (0.66,0.81), which was lower than the patients with HBV 0.81 (0.75,0.87), cryptogenic cirrhosis 0.76 (0.72, 0.84), primary biliary cirrhosis 0.79 (0.74,0.82), autoimmune hepatitis 0.80 (0.75,0.85) and hepatitis C 0.81 (0.76,0.85) (H=89.466, **P*<0.05). Although the serum magnesium level in ALD+AIH and CLD groups were lower than normal range, we didn't discuss it for the little sample size.

A total of 374 patients had magnesium deficiency, the overall incidence was 33.2%. As shown in table 4, magnesium deficiency occurred in 144 (24.0%) cases with HBV, 95 (60.5%) cases with ALD, 41 (39.8%) cases with cryptogenic cirrhosis, 33 (46.5%) cases with HBV plus ALD. The incidence of magnesium deficiency was higher among patients with ALD than patients with HBV and cryptogenic cirrhosis (^{2}=78.072, *P*<0.01).

Table 3: Serum magnesium levels of different etiologies of liver cirrhosis

			Mg (mmol/L)	
Etiology	**Case (n)**	**median**	**P_{25}**	**P_{75}**
HBV	599	0.81	0.75	0.87
ALD	157	0.72	0.66	0.81
CC	103	0.76	0.72	0.84
PBC	63	0.79	0.74	0.82

AIH	43	0.8	0.75	0.85
HCV	18	0.81	0.76	0.85
SL	15	0.81	0.7	0.84
HBV+ALD	71	0.75	0.71	0.84
ALD+SL	13	0.83	0.72	0.86
AIH+PBC	12	0.76	0.71	0.77
ALD+AIH	5	0.7	0.68	0.72
CLD	5	0.71	0.66	0.8

HBV=hepatitis B virus; ALD=alcoholic liver disease; PBC=primary biliary cirrhosis； AIH=autoimmune hepatitis； HCV=hepatitis C virus； SL=schistosomiasis cirrhosis； ; CC： Cryptogenic cirrhosis; CLD=cholestatic liver disease.

Table 4: The prevalence of magnesium deficiency among different etiologies of liver cirrhosis

Etiology	N	Total	Mg deficiency (%)
Viral hepatitis	149	620	24
HBV	144	599	24
HCV	3	18	16.7
HBV+HCV	2	3	66.7
ALD	95	157	60.5
CC	41	103	39.8
Autoimmune	31	118	26.3
PBC	18	63	28.6
AIH	8	43	18.6
AIH+PBC	5	12	41.7
Mixed etiology	51	115	44.3
HBV+ALD	33	71	46.5
ALD+AIH	4	5	80
ALD+CLD	4	4	100
ALD+SL	3	13	23.1
HBV+CLD	3	4	75
ALD+HCV	1	3	33.3
ALD+SL	1	13	7.7
ALD+HAV	1	1	100
AIH+CLD+SL	1	1	100
SL	4	15	26.7
CLD	3	5	60
Total	374	1128	33.2

HBV=hepatitis B virus; ALD=alcoholic liver disease; PBC=primary biliary cirrhosis; AIH=autoimmune hepatitis； HCV=hepatitis C virus； SL=schistosomiasis cirrhosis； CLD=cholestatic liver disease； HAV=hepatitis A virus

LC Complication Distribution

221 (19.6%) cirrhotic patients were complicated with hepatitis encephalopathy (HE). 116 (10.3%) patients were complicated with gastrointestinal (GI) bleeding. 256 (22.7%) patients had ascites. 556 (49.3%) patients had esophageal and gastric varices (EGV). 367 (32.5%) patients were complicated with inflammation. Magnesium levels in cirrhotic patients with hepatic encephalopathy (HE), GI bleeding, and ascites were 0.73±0.10, 0.72±0.12, and 0.74±0.11, respectively, lower than normal range and that of the patients without corresponding complication (P<0.001). Serum magnesium levels of patients with esophageal and gastric varices (EGV) and inflammation were 0.77±0.10, 0.76±0.10, respectively, within normal range, but lower than that of patients with no corresponding syndrome (P<0.05 and P<0.001, respectively). Hepatic renal syndrome (HRS) was a rare complication (only 30 cases, 2.7%); serum magnesium level of patients with HRS was 0.73±0.14, lower than normal range, but there was no significant correlation between HRS and serum magnesium level (P>0.05) (Table 5).

Table 5: Correlation between serum magnesium and complications of cirrhosis

Complication	N (%)	Mean ± SD	95%CI (D)	t-Value	p-Value
HE					
No	907 (80.4)	0.79±0.10	0.06	9.17	<0.001
Yes	221 (19.6)	0.73±0.10	0.05-0.08		
GI bleeding					
No	1012 (89.7)	0.79±0.09	0.07	5.58	<0.001
Yes	116 (10.3)	0.72±0.12	0.04-0.09		
Ascites					
No	872 (77.3)	0.79±0.09	0.05	6.7	<0.001
Yes	256 (22.7)	0.74±0.11	0.03-0.06		
EGV					
No	572 (50.7)	0.79±0.10	0.02	2.59	0.01
Yes	556 (49.3)	0.77±0.10	0.00-0.03		
HRS					
No	1098 (97.3)	0.78±0.10	0.05	2.03	0.052
Yes	30 (2.7)	0.73±0.14	0.00-0.10		
Inflammation					
No	761 (67.5)	0.79±0.10	0.03	5.14	<0.001
Yes	367 (32.5)	0.76±0.10	0.02-0.04		

HE: hepatic encephalopathy; GI: gastrointestinal; EGV: esophageal and gastric varices; HRS： hepatorenal syndrome; SD： standard deviation; D: difference; CI: confidence interval.

Correlation between Serum Magnesium Levels and Laboratory Parameters

Univariate analysis on age presented association with magnesium level (r=0.059, p=0.049). However, when examining sex, no

significant association was observed (r_s=0.014, p=0.646). Laboratory tests showed that serum magnesium level was correlated with the level of albumin (r=0.516, p<0.001), IL-6 (r_s=0.438, p<0.01), ALT (r_s=0.157, p<0.01), AST (r_s=0.380, p<0.01), GGT (r_s=0.135, p<0.01), TB (r_s=0.474, p<0.01), Ca (r_s=0.463, p<0.01) and ammonia (r_s=0.487, p<0.01). Multivariate linear regression analysis on laboratory parameters and complications of cirrhosis showed that age, Alb, Ca, HE, and GI bleeding were independent predictors of serum magnesium level (P<0.001, P<0.001, P<0.05, P<0.05, and P<0.001 respectively), simultaneously, ascites, EGV and inflammation were not associated with serum magnesium level (P>0.05) (Table 6).

Table 6: Multivariate linear regression analysis of magnesium levels on laboratory parameters and complications of cirrhosis.

Variables	Regression coefficient	Standard coefficient	t-Value	p-Value
Age	0.001	0.098	3.932	<0.001
Albumin	0.005	0.344	8.312	<0.001
Ca	0.062	0.093	2.526	0.012
HE	-0.021	-0.083	-3.143	0.002
GI bleeding	-0.038	-0.115	-4.461	<0.001
Ascites	0.001	0.004	0.137	0.891
EGV	-0.007	-0.033	-1.289	0.198
Inflammation	-0.004	-0.019	-0.764	0.445

HE=hepatic encephalopathy; GI= gastrointestinal; EGV=esophageal and gastric varices.

Discussion

In this study, we found that viral hepatitis was the most prevalent etiology of LC (short for liver cirrhosis), accounting for more than half percentage of the study population. In addition, most of the viral hepatitis LC was caused by HBV (nearly 97% of all viral hepatitis LC patients), which was consistent with previous studies of Wang X et al. [11] and Li M et al. [12]. Although the infection rate of HBV has decreased significantly due to the popularization of vaccination, China is still a highly endemic area of HBV [13]. Alcoholic liver disease, used to be the main cause of cirrhosis of western countries as the United States and European countries [14], was the second predominant etiology of cirrhosis in this research, owing to the changes of lifestyle and dietary habits in Chinese people. Autoimmune-related cirrhosis including AIH, PBC and AIH mixed PBC was another critical etiology of cirrhosis. As a relatively rare disease, the proportion of autoimmune liver disease cases has been showing an upward trend in recent years [11], due to the spring up of detection methods for autoantibodies, immunoglobulin and other hepatitis biomarkers. It was noted that cryptogenic cirrhosis was the fifth leading etiology in our study and the cases were more common in females (17.5% vs 5.0%, P<0.001), a similar trend in gender observed within autoimmune liver disease. It was reported that cryptogenic cirrhosis cases were mostly older female with Type 2 diabetes, hyperlipidemia, and obesity [15]. Therefore, they supposed that some cases may have undetected autoimmune liver disease or may have developed from nonalcoholic steatohepatitis to LC. Similarly, we presumed that some cases with cryptogenic cirrhosis in our study may bear occult autoimmune related liver disease or non-alcoholic fatty liver disease due to the absence of liver biopsy and adequate laboratory evidence. Further studies are warranted to confirm the hypothesis.

In our observation, the overall prevalence of serum magnesium deficiency among the study population was 33.2% (374/1128), which was lower than 60.5% (92/152) that the finding of Peng X et al. [8]. On the other hand, the overall serum magnesium level among cirrhotic patients were within normal range, which was in accordance with the finding of K. Kar et al in India [16], whereas different from the research of Peng X et al in China [8] and Nangliya. V et al in India [7]. However, all the studies

aforementioned were small size, maybe the statistical power was not enough to illustrate the real level of serum magnesium of cirrhotic patients. Our finding may reflect a relatively true condition of serum magnesium concentration. From the point of our research, disparities in serum magnesium level among different etiologies of liver cirrhosis do exist, with that of ALD was significantly lower than normal range, while that of other major etiologies as HBV, CC, autoimmune related cirrhosis and HCV were all within normal range. For limited reports on serum magnesium level of HBV, CC, autoimmune related cirrhosis and HCV, further large-scale studies were needed to confirm our observation. It's interesting to find that serum magnesium levels of HBV LC, HBV plus ALD LC, and ALD LC showed a decreasing trend (0.81 vs 0.75 vs 0.72), whereas the prevalence of magnesium deficiency for that displayed an increasing trend (24.0% vs 46.5% vs 60.5%). The finding suggested that alcohol consumption was associated with serum magnesium deficiency. Several studies have reported hypomagnesemia in patients with ALD [17-19], which was in accordance with our observation. In addition, the prevalence of serum magnesium deficiency in alcoholic cirrhotic patients was highest among the major etiologies of cirrhosis, followed by mixed etiology, cryptogenic cirrhosis, and HBV, which may suppose that patients with alcoholic cirrhosis were more likely to be serum magnesium deficiency than other etiologies of cirrhosis. The mechanism underlying alcohol related magnesium deficit is complicated and the process is clearly multifactorial as diet, ethanol-dependent malnutrition and/or increased diuresis, far from being clarified, hence, more mechanistic studies are needed to be conducted.

From correlation analysis, we found that serum magnesium level of LC patients with complication was significantly lower than that of patients without corresponding complication (Table 5). The possible mechanisms underlying magnesium deficiency in LC patients with complications are listed as follows. First, LC patients progressing to the stage of complications usually have severe impaired liver function, metabolic capacity and detoxification of the liver decrease, therefore, the body have to increase the urinary secretion to lighten the burden of the body, which cause magnesium loss. Second, Patients with cirrhosis are usually accompanied by portal hypertension which may further develop into gastrointestinal edema and EGV [5]. Thus, magnesium-rich food such as whole cereals and legumes, nuts are not fit for cirrhotic patients, resulting in the insufficient intake of dietary magnesium. Third, for LC patients with complications, the intake of drugs is increased, although the ability of the liver to metabolize them decreases, enhancing their renal excretion and contributing to hypomagnesemia[20]. In addition, serum magnesium decline among LC patients with GI bleeding can be attributed to reduced blood flow and volume with a decreased albumin content. Hepatic encephalopathy (HE) is an important complication of LC and its spectrum ranges from mini hepatic encephalopathy (MHE), without apparent clinical symptoms, to signs of overt encephalopathy with risk of cerebral edema and death. Keren MD found that magnesium participated in the pathophysiology of MHE [21], confirming our observation that there is an association between magnesium level and HE. There are only 30 cirrhotic patients combined with HRS, whose average level of serum magnesium was lower than normal range, but it turns out to be no statistically significance in comparison with that of LC patients without HRS, perhaps due to the small sample size. Thus, large scale epidemiological studies are needed to confirm our observation.

Last but not least, age, albumin and calcium were also the independent predictors for serum magnesium level besides HE and GI bleeding (Table 6). Magnesium deficiency is very common in old age and a growing body of evidence showed the relation of magnesium and aging. Aging is a risk factor for magnesium deficiency [22] and there is an age-related reduction in intracellular magnesium levels [23]. According to the NHANES Ⅲ survey, the intake of magnesium is insufficient by the elderly [24]. Furthermore, in old age, the occurrence of related primary disease such as diabetes, IR (insulin resistance) also decreases magnesium reabsorption [25].

For cirrhotic patients, the synthetic function of damaged liver has been severely impaired, resulting in the decline of albumin content, which directly influence the transport of magnesium, contributing to hypomagnesemia.

Calcium is another important element in human body that is mainly deposited in bone. Calcium and magnesium could be re-

gard as antagonist to each other in variable biological processes and metabolic pathways [26]. Former studies on human individuals illustrate that a high intake of calcium may affect the absorption rate of magnesium, which in turn can be linked to a high risk of several disease [27-29]. Hadi et al found that higher dietary Ca to Mg intake ratio is associated with a greater development of non-alcoholic fatty liver disease (NAFLD) [30]. Similar findings were observed, only in subjects who had daily calcium intake <1200 mg, that the magnesium intake was related to an approximately 30% reduced risk of NAFLD and prediabetes [31] and there was an inverse association between total magnesium intake and significant fibrosis [32]. Both findings displayed that the advantage of magnesium intake might reduce when calcium intake is higher than recommend amount by Dietary Reference Intakes.

However, our research has several limitations. First, as this is a retrospective, cross-sectional study, it is difficult to avoid possible bias in the selection of cirrhotic patients. Second, the sample size of LC patients with HCV, schistosomiasis, cholestatic, Wilson's disease and some mixed etiologies was relatively small. Third, the epidemiologic conclusion based on a single center clinical practice is limited. Future prospective, randomized controlled studies, are needed to explore whether magnesium supplementation could do cirrhotic patients some favor.

Conclusion

In summary, this study demonstrated serum magnesium levels across different etiologies of LC. Notably, the serum magnesium level of ALD group was significantly lower than normal range different from other etiologies. In addition, we found that serum magnesium levels were lower in LC patients with complications than that without corresponding complications.

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Conflicts of Interest

The authors declare no conflict of interest

Author Contributions

Yan-ju Zhu: Study design, statistical analysis, and drafting of the manuscript. Juan Chen: Critical revision of the manuscript for important intellectual content. The final version of the manuscript was approved by all authors.

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