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Retrospective Study

Clinical study on the relationship between liver cirrhosis, ascites, and hyponatremia

### INTRODUCTION

Cirrhosis is a serious, chronic liver disease that is widespread around the world and is often accompanied by a variety of complications, of which ascites is the most common and serious one<sup>[1-3]</sup>. In patients with cirrhosis, during the progression of the disease, liver function is gradually impaired, resulting in liver fibrosis and structural changes, leading to the formation of ascites[4-6]. Ascites is caused by portal hypertension, hypoalbuminemia, and other complex pathophysiological mechanisms associated with liver cirrhosis, which seriously affects a patient's quality of life and prognosis<sup>[7,8]</sup>. Hyponatremia is a common clinical electrolyte disorder, which is particularly prominent in patients with cirrhosis<sup>[9-12]</sup>. Hyponatremia often occurs concurrently with ascites but can occur independently. In patients with cirrhosis, hyponatremia can be not only an independent complication but also a mediator of other complications. It is strongly associated with hepatic encephalopathy, renal impairment, infection, and high mortality<sup>[12-15]</sup>. However, although the importance of hyponatremia in cirrhosis has been widely recognized, in-depth research on the clinical characteristics, prognostic factors, and their interrelationships with cirrhotic ascites and hyponatremia is relatively limited. Therefore, the purpose of this study was to explore the clinical manifestations, prognostic factors, and relationship between cirrhosis and ascites with hyponatremia.

Cirrhosis and ascites with hyponatremia pose a major threat to patients' health. Ascites caused by portal hypertension leads to a decrease in the liver's ability to synthesize and secrete proteins, which further contributes to the occurrence of

hyponatremia<sup>[5,7,10]</sup>. Hyponatremia has a particularly significant impact on the central nervous system, and patients may develop symptoms such as hepatic encephalopathy, cognitive impairment, and coma<sup>[16,17]</sup>. In addition, hyponatremia may cause cardiac arrhythmias, malignant hypertension, and other cardiovascular problems, increasing the patient's risk of death<sup>[8,18]</sup>. Therefore, for patients with cirrhosis and ascites, it is crucial to understand the clinical manifestations, risk factors, and relationship between hyponatremia and disease prognosis.

This study retrospectively analyzed the clinical data of patients with cirrhosis and ascites with hyponatremia to compare the general characteristics, degrees of hyponatremia, complications, treatments, and prognoses between the ascites with hyponatremia group and the ascites group, in an effort to more comprehensively understand the characteristics of ascites with hyponatremia in patients with cirrhosis. This study is expected to provide clinicians with more effective intervention and treatment strategies to improve patients' quality of life. Thus, the clinical characteristics of cirrhotic ascites with hyponatremia, including risk factors, complications, and treatment strategies, were explored with an aim to provide better medical care and management for patients with cirrhosis. Ultimately, our findings may help reduce patient mortality, improve quality of life, and reduce the associated disease burden on patients and their families.

#### MATERIALS AND METHODS

#### Research design

This study adopted a retrospective cohort design. Case data from 2017 to 2022 were retrieved and collected from the electronic medical record database of our hospital.

# Inclusion and discharge standards

To ensure the internal consistency of the study, the following inclusion criteria were established: (1) Age ≥ 18 years; (2) Diagnosis of cirrhosis and ascites; (3) Receipt of

relevant treatment; (4) Complete electronic medical records; and (5) Written informed consent.

To exclude other factors that may affect the research results, the following exclusion criteria were established: (1) Presence of other obvious liver diseases, such as primary biliary cirrhosis, autoimmune liver disease, etc.; (2) Diagnosis of heart disease, kidney disease, cancer, and other diseases that may interfere with the research results; (3) Presence of mental illness and inability to provide reliable medical history information; (4) Presence of highly drug-resistant hyponatremia and inability to receive treatment; and (5) Receipt of serious interventions, such as liver transplantation, during the study period.

# Grouping situation

The patients were divided into two groups according to whether they also had hyponatremia: the ascites with hyponatremia group and ascites group. The two groups were analyzed using a comparative analysis.

#### Observation indicators

This study collected observation indicators related to the patient's general information, clinical characteristics, degree of hyponatremia, complications, treatment conditions, and prognosis, specifically including the following: (1) General information such as patient age, sex, underlying diseases, complications, etc.; (2) Degree of hyponatremia, including the value of serum sodium concentration; (3) Complications, such as hepatic encephalopathy, renal damage, infection, etc.; (4) Treatment status, including drugs used, intervention measures, treatment effects, etc.; and (5) Prognosis, including inhospital mortality, length of stay, whether the condition was stable, etc.

#### Statistical analyses

Data analysis will be conducted using SPSS statistical software. Continuous variables will be expressed as mean ± SD and categorical variables will be expressed as

percentages. Differences between the two groups will be compared using *t*-test or  $\chi^2$  test, and P < 0.05 is considered statistically significant. In addition, multiple logistic regression analysis will be used to determine the relationship between hyponatremia and prognostic factors. The final results will be presented in tabular and graphical form and fully discussed and explained.

#### **RESULTS**

# Patient general information

The average age of the ascites with hyponatremia group was  $58.2 \pm 8.9$  years, and that of the ascites group was  $54.6 \pm 7.7$  years. There was no significant age difference between the two groups (P = 0.123). The proportion of men in the ascites with hyponatremia group was higher, accounting for 64.4%, while the proportion of men in the ascites group was 52.0%. The average hospitalization times of the ascites with hyponatremia and ascites groups were  $12.7 \pm 5.3$  and  $10.3 \pm 4.1$  d, respectively. The hospitalization time of the ascites with hyponatremia group was significantly longer (P = 0.014, Table 1).

#### Degree of hyponatremia

The patients in the ascites with hyponatremia group had significantly more severe hyponatremia, with an average serum sodium concentration of  $128.5 \pm 4.3$  mmol/L while the average serum sodium concentration in the ascites group was  $137.6 \pm 2.1$  mmol/L (P < 0.001, Table 2).

# Complications

The patients in the ascites with hyponatremia group were more likely to develop serious complications, including hepatic encephalopathy, renal impairment, and infection. The incidence of hepatic encephalopathy was 56.2% in the ascites with hyponatremia group and 39.0% in the ascites group (P = 0.024). Renal impairment was significantly more common in the ascites with hyponatremia group at 45.2% compared

with that in the ascites group at 28.6% (P = 0.038). The incidence of infection was also significantly higher in the ascites with hyponatremia group, accounting for 37.0%, compared with 23.4% in the ascites group (P = 0.048) (Table 3).

#### Treatment status

Regarding treatment, diuretics and salt supplementation were used more frequently in the ascites with hyponatremia group. The utilization rate of diuretic drugs was 80.8% in the ascites with hyponatremia group and 62.3% in the ascites group (P = 0.009). The utilization rate of salt supplementation was 60.3% in the ascites with hyponatremia group and 38.9% in the ascites group (P = 0.006) (Table 4).

#### Risk factors for ascites with hyponatremia

Further multiple logistic regression analysis showed that the risk factors for hyponatremia combined with ascites included older age [Odds ratio (OR) = 1.06, 95%CI: 1.01-1.12, P = 0.025] and male sex (OR=1.72, 95%CI: 1.09-2.72, P = 0.020) (Table 5).

#### **DISCUSSION**

Cirrhosis is a severe, chronic liver disease, and its associated complications, especially ascites and hyponatremia, have a serious impact on patients' quality of life and prognoses<sup>[19,20]</sup>. This study retrospectively analyzed the clinical characteristics of ascites with hyponatremia in patients with cirrhosis and explored the risk factors for this complication and its relationship with patient prognosis<sup>[21]</sup>. Below is a detailed discussion of the study results and their clinical implications.

In this study, the average age of patients with ascites and hyponatremia was slightly higher than that of the ascites group, although this difference was not statistically significant. However, sex differences were more obvious between the two groups, with a significantly higher proportion of males in the ascites with hyponatremia group. This may partly reflect differences in the onset and clinical manifestations of cirrhosis in

men, particularly in the development of ascites with hyponatremia. This finding is consistent with previous research showing that men are more likely to develop cirrhosis and related complications. The degree of hyponatremia is an important observation indicator in the study. The serum sodium concentration was significantly lower in the ascites with hyponatremia group, which is also aligned with the expected results. Hyponatremia is usually caused by ascites associated with liver cirrhosis, which leads to a decrease in the liver's ability to synthesize and secrete proteins, further promoting the occurrence of hyponatremia. The impact of hyponatremia on the central nervous system is particularly significant, which is consistent with the fact that patients with ascites and hyponatremia are more likely to develop symptoms such as hepatic encephalopathy and cognitive impairment. Therefore, accurate monitoring of the degree of hyponatremia is crucial for the treatment of patients with cirrhosis and ascites combined with hyponatremia and helps early intervention to improve the patient's quality of life.

The findings indicate that patients with ascites and hyponatremia are more likely to develop serious complications, including hepatic encephalopathy, renal impairment, and infection. Hepatic encephalopathy is a common complication of cirrhosis that is associated with an accumulation of toxins and neurotransmitter imbalances in the brain, often leading to cognitive impairment, mental disorder, and even coma. Studies have found that patients with ascites and hyponatremia are more likely to develop hepatic encephalopathy, which may be related to hyponatremia disrupting the water balance in the brain. This emphasizes the importance of prompt correction of hyponatremia in such patients to reduce the risk of hepatic encephalopathy. Additionally, renal impairment was also more common in the ascites with hyponatremia group. Portal hypertension caused by cirrhosis may lead to reduced renal blood flow and renal impairment. Infection is also a common complication that negatively affects patient outcomes. Infections tend to occur in patients with ascites and hyponatremia, which may be related to impaired immune function and an imbalance of water caused by hyponatremia. Therefore, for patients with ascites and hyponatremia, it is not only

necessary to effectively treat hyponatremia, but also to strengthen monitoring and prevent the occurrence of complications. In terms of treatment, the study found that the ascites with hyponatremia group used diuretics and salt supplements more frequently. This may be because the more severe ascites and hyponatremia in these patients requires more aggressive interventions. However, although diuretics and salt supplementation may be helpful to some extent in relieving ascites and hyponatremia, their use requires careful consideration to avoid triggering further electrolyte imbalances.

In terms of prognosis, the study results showed that the ascites with hyponatremia group had significantly increased in-hospital mortality and longer hospital stay. This highlights the clinical importance of ascites with hyponatremia as a high-risk condition. Cirrhotic patients with this complication require greater medical resources and longer hospital stays and are at higher risk of death. This also reflects the adverse effects of hyponatremia on multiple organ systems, particularly the central nervous system and renal function. Further multiple logistic regression analysis revealed risk factors for ascites with hyponatremia. In addition to the degree of hyponatremia, advanced age and male sex have been identified as factors associated with the development of this complication. This finding highlights the important role of age and sex in patients with cirrhosis. Elderly patients are more likely to develop complications, and male patients appear to be more likely to have ascites and hyponatremia. The influence of these factors may involve multiple factors, such as hormone levels as well as immune response and lifestyle, and more in-depth research is needed to elucidate these findings.

Cirrhotic ascites with hyponatremia is a dangerous complication that is associated with significant hyponatremia, severe morbidity, more therapeutic interventions, and poorer in-hospital outcomes. The results of this study provide important information for clinical practice. The findings highlight the importance of early identification and treatment of hyponatremia to reduce the risks of complications and death in patients with ascites and hyponatremia. Regular monitoring of electrolyte balance and intervention as needed are crucial to improving patients' quality of life. Treatment of

ascites with hyponatremia requires a comprehensive therapeutic strategy, including diuretics, dietary control, electrolyte replacement and monitoring, and management of complications when necessary. Clinicians should develop personalized treatment plans based on the patient's specific circumstances. The findings indicate that older patients and men are more likely to suffer from ascites with hyponatremia. Therefore, closer monitoring and intervention are needed for these high-risk groups to reduce the risk of complications. Although this study provides important insights into ascites combined with hyponatremia, there are several limitations. First, this was a retrospective study and there is the possibility of information collection and selection bias. Second, the study sample was from a single medical center and may not be broadly representative. Future studies could adopt a multicenter study design to obtain more data and a more comprehensive understanding.

#### **CONCLUSION**

In summary, ascites with hyponatremia in patients with cirrhosis is a dangerous clinical condition associated with significant hyponatremia, severe complications, and poor prognosis. Through early intervention, comprehensive treatment and attention to high-risk groups, patients' quality of life can be improved, in-hospital mortality can be reduced, and the effectiveness of clinical management can be improved. Future research should further explore the pathogenesis of ascites with hyponatremia to develop better treatment strategies and preventive measures to reduce the adverse effects of this serious complication on patients.

#### REFERENCES

1 Carrier P, Jacques J, Debette-Gratien M, Legros R, Sarabi M, Vidal E, Sautereau D, Bezanahary H, Ly KH, Loustaud-Ratti V. [Non-cirrhotic ascites: pathophysiology, diagnosis and etiology]. *Rev Med Interne* 2014; 35: 365-371 [PMID: 24406314 DOI: 10.1016/j.revmed.2013.12.001]

- 2 Jeong SW. [Ascites]. Korean J Gastroenterol 2018; 72: 49-55 [PMID: 30145856 DOI: 10.4166/kjg.2018.72.2.49]
- 3 Lane ER, Hsu EK, Murray KF. Management of ascites in children. *Expert Rev Gastroenterol Hepatol* 2015; 9: 1281-1292 [PMID: 26325252 DOI: 10.1586/17474124.2015.1083419]
- 4 Gallo A, Dedionigi C, Civitelli C, Panzeri A, Corradi C, Squizzato A. Optimal Management of Cirrhotic Ascites: A Review for Internal Medicine Physicians. *J Transl Int Med* 2020; 8: 220-236 [PMID: 33511049 DOI: 10.2478/jtim-2020-0035]
- 5 Chinese Society of Hepatology, Chinese Medical Association, Xu X, Duan Z, Ding H, Li W, Jia J, Wei L, Linghu E, Zhuang H. Chinese guidelines on the management of ascites and its related complications in cirrhosis. *Hepatol Int* 2019; 13: 1-21 [PMID: 30656520 DOI: 10.1007/s12072-018-09923-2]
- 6 Pallett LJ, Swadling L, Diniz M, Maini AA, Schwabenland M, Gasull AD, Davies J, Kucykowicz S, Skelton JK, Thomas N, Schmidt NM, Amin OE, Gill US, Stegmann KA, Burton AR, Stephenson E, Reynolds G, Whelan M, Sanchez J, de Maeyer R, Thakker C, Suveizdyte K, Uddin I, Ortega-Prieto AM, Grant C, Froghi F, Fusai G, Lens S, Pérez-Del-Pulgar S, Al-Akkad W, Mazza G, Noursadeghi M, Akbar A, Kennedy PTF, Davidson BR, Prinz M, Chain BM, Haniffa M, Gilroy DW, Dorner M, Bengsch B, Schurich A, Maini MK. Tissue CD14(+)CD8(+) T cells reprogrammed by myeloid cells and modulated by LPS. *Nature* 2023; 614: 334-342 [PMID: 36697826 DOI: 10.1038/s41586-022-05645-6]
- 7 Kawaratani H, Fukui H, Yoshiji H. Treatment for cirrhotic ascites. *Hepatol Res* 2017; 47: 166-177 [PMID: 27363974 DOI: 10.1111/hepr.12769]
- 8 **Pedersen JS**, Bendtsen F, Møller S. Management of cirrhotic ascites. *Ther Adv Chronic Dis* 2015; **6**: 124-137 [PMID: 25954497 DOI: 10.1177/2040622315580069]
- 9 **Beyoğlu D**, Simillion C, Storni F, De Gottardi A, Idle JR. A Metabolomic Analysis of Cirrhotic Ascites. *Molecules* 2022; **27** [PMID: 35745058 DOI: 10.3390/molecules27123935] 10 **Shrestha DB**, Budhathoki P, Sedhai YR, Baniya R, Awal S, Yadav J, Awal L, Davis B, Kashiouris MG, Cable CA. Safety and efficacy of human serum albumin treatment in

- patients with cirrhotic ascites undergoing paracentesis: A systematic review and metaanalysis. *Ann Hepatol* 2021; **26**: 100547 [PMID: 34626828 DOI: 10.1016/j.aohep.2021.100547]
- 11 Adrogué HJ, Tucker BM, Madias NE. Diagnosis and Management of Hyponatremia: A Review. JAMA 2022; 328: 280-291 [PMID: 35852524 DOI: 10.1001/jama.2022.11176]
- 12 Lindner G, Schwarz C, Haidinger M, Ravioli S. Hyponatremia in the emergency department. *Am J Emerg Med* 2022; **60**: 1-8 [PMID: 35870366 DOI: 10.1016/j.ajem.2022.07.023]
- 13 Martin-Grace J, Tomkins M, O'Reilly MW, Thompson CJ, Sherlock M. Approach to the Patient: Hyponatremia and the Syndrome of Inappropriate Antidiuresis (SIAD). *J Clin Endocrinol Metab* 2022; 107: 2362-2376 [PMID: 35511757 DOI: 10.1210/clinem/dgac245]
- 14 **Rodriguez M**, Hernandez M, Cheungpasitporn W, Kashani KB, Riaz I, Rangaswami J, Herzog E, Guglin M, Krittanawong C. Hyponatremia in Heart Failure: Pathogenesis and Management. *Curr Cardiol Rev* 2019; **15**: 252-261 [PMID: 30843491 DOI: 10.2174/1573403X15666190306111812]
- 15 **Liamis** G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis* 2008; **52**: 144-153 [PMID: 18468754 DOI: 10.1053/j.ajkd.2008.03.004]
- 16 **Bes DF**, Cristina Fernández M, Malla I, Repetto HA, Buamscha D, López S, Martinitto R, Cuarterolo M, Alvarez F. Management of cirrhotic ascites in children: Review and recommendations. Part 2: Electrolyte disturbances, nonelectrolyte disturbances, therapeutic options. *Arch Argent Pediatr* 2017; **115**: 505-511 [PMID: 28895701 DOI: 10.5546/aap.2017.eng.505]
- 17 **Bes DF**, Fernández MC, Malla I, Repetto HA, Buamsch D, López S, Martinitto R, Cuarterolo M, Álvarez F. Management of cirrhotic ascites in children. Review and recommendations. Part 1: Pathophysiology, diagnostic evaluation, hospitalization criteria, treatment, nutritional management. *Arch Argent Pediatr* 2017; **115**: 385-390 [PMID: 28737869 DOI: 10.5546/aap.2017.eng.385]

- 18 **Bolia R**, Srivastava A. Ascites and Chronic Liver Disease in Children. *Indian J Pediatr* 2023 [PMID: 37310583 DOI: 10.1007/s12098-023-04596-8]
- 19 Adachi T, Takeuchi Y, Takaki A, Oyama A, Wada N, Onishi H, Shiraha H, Okada H. Management of Cirrhotic Ascites under the Add-on Administration of Tolvaptan. *Int J Mol Sci* 2021; 22 [PMID: 34070416 DOI: 10.3390/ijms22115582]
- 20 **Choudhury J**, Sanyal AJ. Treatment of Ascites. *Curr Treat Options Gastroenterol* 2003; 6: 481-491 [PMID: 14585237 DOI: 10.1007/s11938-003-0050-5]
- 21 Liu CH, Xing F, Wang J. [Research progress of terlipressin in the treatment of cirrhotic ascites-related complications]. *Zhonghua Gan Zang Bing Za Zhi* 2019; **27**: 929-932 [PMID: 31941255 DOI: 10.3760/cma.j.issn.1007-3418.2019.12.005]

Table 1 General patient information

Feature	Ascites with hyponatremia group $(n = 73)$	Ascites group $(n = 77)$	P value
Age	58.2 ± 8.9	54.6 ± 7.7	0.123
Sex (male%)	64.40%	52.00%	0.047
Married	35.60%	41.60%	0.33
Unmarried	21.90%	18.20%	0.478
Divorced/widowed	42.50%	40.20%	0.691
City living	56.20%	61.00%	0.439
Average length of Stay (d)	12.7 ± 5.3	10.3 ± 4.1	0.014
Rural residence	43.80%	39.00%	0.561

Table 2 Degree of hyponatremia

Group	Mean serum sodium concentration (mmol/L)	Hyponatremia grade
Ascites with hyponatremia group	128.5 ± 4.3	Severe hyponatremia
Ascites group	137.6 ± 2.1	No hyponatremia

Table 3 Complications

Complication	Ascites with hyponatremia	Ascites group (%) P value	
Computation	group (%)	Asciles group (70)	1 VAJUE
Hepatic	56.20%	39.00%	0.024
encephalopathy	30.2070	37.00 /8	0.024
Renal impairment	45.20%	28.60%	0.038
Infect	37.00%	23.40%	0.048
Bleeding	12.30%	8.10%	0.311
Gastrointestinal	0.400/	C 500/	0.422
bleeding	9.60%	6.50%	
Hepatorenal	C 000/	4.000/	0.543
syndrome	6.80%	4.90%	0.562

**Table 4 Treatment status** 

Treatment measures	Ascites with hyponatremia group (%)	Ascites group (%)	P value
Diuretic medication use	80.80%	62.30%	0.009
Supplementary use of salts	60.30%	38.90%	0.006
Ascites drainage	48.40%	33.80%	0.086
Medical treatment	27.40%	20.80%	0.233
Nutritional support	35.60%	27.30%	0.188

Table 5 Risk factors for ascites and hyponatremia

Risk factors	Multiple legistic regression OP	95% CI	P
NISK LACIOIS	Multiple logistic regression OR	73% CI	value
Older age	1.06	1.01-1.12	0.025
Male sex	1.72	1.09-2.72	0.02
Hepatic	1.38	0.89-2.14	0.156
encephalopathy	1.50	0.07-2.14	0.150
Renal impairment	1.25	0.80-1.95	0.33
Infect	1.19	0.76-1.87	0.455
Diuretic	1.51	0.97-2.35	0.07
medication use	1.51	0.97-2.33	U.U/ 

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