Analysis of clinical features and prognostic factors associated with Hepatic Hydrothorax: A single center study from China

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Abstract

Background: The clinical features and factors affecting prognostic survival of Hepatic Hydrothorax (HH) are currently unknown.

Aims: We aimed to analyze the clinical characteristics and prognostic factors associated with patients with HH.

Methods: We conducted a retrospective cohort study of 131 patients with HH, using the Kaplan-Meier method and Cox proportional risk regression analysis to assess factors influencing the prognosis of HH.

Results: A total of 131 patients were collected, male: female 80:51 (1.59:1), mean age 52.76±11.88 years, 30 survived and 101 died. Hepatitis B cirrhosis was the main cause of HH, accounting for 42% of cases. Abdominal distention and dyspnea were the most common clinical signs, present in 82.4% and 67.9% of patients, respectively. Ascites was present in varying amounts in all patients and was the most common decompensated complication, with pleural effusions mostly seen on the right side (107/131; 82%), followed by the left side (16/131; 12%) and bilateral effusions (8/131; 6%); 20 (15%) were treated with drug management alone, 111 (75%) patients were treated with drugs and thoracic intubation, with one patient treated with TIPS and three patients treated with liver transplantation at a later stage of treatment. Mortality rates were significantly higher in men than in women at all time points, with an overall 2-year mortality rate of 70.3% and a 5-year mortality rate of 100%. Univariate Cox proportional risk models indicating that gender, liver failure, hepatic encephalopathy, hyponatraemia, total bilirubin (TBIL), MELD score, and MELD-Na score were associated with survival ($P < 0.05$), and multifactorial Cox proportional risk models indicating that hepatic encephalopathy, hyponatraemia, and MELD score ($P < 0.05$) were independent risk factors for prognostic survival in patients with HH. Patients with HH had a worse prognosis with higher MELD scores and an even worse prognosis once combined with hyponatraemia, with a mean survival time difference of nearly two times.

Conclusion: HH patients have a high mortality rate, and liver encephalopathy, hyponatremia, and the MELD score are significantly associated with their condition and prognosis.

1. Introduction

Hepatic hydrothorax (HH) is a pleural effusion that is generally higher than 500 ml in size and is related with cirrhosis and portal hypertension in the absence of any cardiac, pulmonary, or pleural illness[1]. HH occurs in approximately 5%-15% of cases, is a rare complication of end-stage liver disease, can lead to hypoxia, respiratory distress, and infection, predicts a poor prognosis, and occurs independently of the specific cause of cirrhosis[2, 3]. HH is more prevalent on the right side of the chest (85%), although it can also occur on the left side (13%), and bilaterally (2%), even in the absence of clinical ascites[4]. Most studies suggest that the pathophysiological pathway through which HH occurs is through the formation of peritoneal-pleural defects through microscopic and macroscopic diaphragmatic defects. These diaphragmatic abnormalities are more prevalent in the right diaphragm, which is more fibrous and prone

to collagen fibre degradation, and contribute to the prevalence of right-sided pleural effusions in HH patients. Treatment of HH usually includes medical management with diuretics and sodium restriction and therapeutic thoracentesis as necessary. Dietary sodium restriction and diuretics are preferred for long-term management or mild pleural effusion, while therapeutic thoracentesis is usually used for acute relief of symptoms. However, transjugular intrahepatic portosystemic shunts (TIPS), liver transplantation (LT), and surgical repair of diaphragmatic defects are also advocated for some patients, particularly those with refractory HH.

In recent years, HH with hepatopulmonary syndrome and pulmonary hypertension have been recognized as the main pulmonary manifestations of chronic liver disease and cirrhosis[5]. Patients with HH are more likely to have acute kidney injury, hepatic encephalopathy, infectious shock and higher mortality[2]. A recent study has shown that HH is an independent decompensated event associated with long-term mortality in patients with cirrhosis[6]. Although HH usually occurs in end-stage liver disease, the prognostic impact on HH is currently unknown. In this study, we further explored the clinical characteristics and prognostic factors associated with the prognosis of the patients by retrospectively analyzing 131 patients with HH admitted to our hospital.

2. Materials And Methods

2.1 Study population

We conducted a retrospective cohort analysis of 5698 patients diagnosed with decompensated cirrhosis from January 2013 to June 2021 at the Department of Hepatology, First Hospital of Jilin University, China. Follow-up data was collected until December 30, 2021. All relevant clinical and laboratory data at the time of first diagnostic admission, including a complete medical history, were collected. Decompensated cirrhosis and decompensating events were defined according to the latest EASL Clinical Practice Guidelines on Decompensated Cirrhosis[7]. Inclusion criteria: 1) known diagnosis of cirrhosis, either biopsy confirmed or based on clinical complications present in the clinic consistent with cirrhosis; 2) known diagnosis of pleural effusion on chest radiograph or lung Computed tomography (CT); 3) pleural effusion consistent with known features of hepatic pleural fluid, but not considered consistent with the presence of infection, malignancy or other known chronic disease; 4) no history of primary cardiopulmonary dysfunction, including but not limited to congestive heart failure; 5) portal hypertension as determined by oesophageal varices, portal hypertensive gastropathy, ascites, portal vein thrombosis or elevated hepatic venous pressure gradient (HVPG). The criteria for exclusion of subjects were as follows: (i) combined malignancy or major organ failure, (ii) except for patients on hormonal or immunosuppressive agents, and (iii) patients with incomplete clinical data and information on additional tests. All patients were screened for ascites and pleural effusion using ultrasound on admission. In addition, all patients underwent standard chest radiographs or CT of the lungs to detect underlying lung disease (pneumonia, tumours, and other lesions). Patients with clinical, laboratory or electrocardiographic suspicion of heart failure underwent cardiac ultrasound to rule out decompensated heart disease. The

final 131 HH patients with ≥ 6 months of follow-up were included in this analysis (Fig. 1). The study protocol was approved by the Ethics Committee of the First Hospital of Jilin University and was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2 Study variables

All demographic and clinical information was confirmed directly from the electronic medical record, including demographic data (age and sex), demographic data and serum biochemical information (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total bilirubin (TBIL), albumin (ALB)), creatinine (Cr), serum sodium, international normalized ratio (INR), Lymphocyte absolute count (LY), Neutrophil absolute count (NE), Neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT), prothrombin time (PT), and imaging features. The diagnosis of cirrhosis is confirmed by liver biopsy or ultrasound without regard to the presence of portal hypertension. The Child-Pugh score was calculated from the original article published by Pugh et al. in 1973[8]. The MELD-Na score was calculated from Biggins et al.[9]. The ALBI scoring and grading system was implemented as described by Johnson et al.[10]. The Child-Pugh score is based on five indicators: serum ALB, TBIL, PT, ascites and hepatic encephalopathy, with a score of 5–6 for grade A, 7–9 for grade B and 10–15 for grade C. Criteria for judging the amount of pleural effusion: If the amount of pleural fluid is greater than 6 cm or greater than the 7th rib space by ultrasound or chest radiograph, it is a large amount; If the fluid level is 3–6 cm or greater than the 8th rib space, it is a medium amount; if the fluid level is less than 3 cm or the angle of the rib diaphragm is blunt, it is a small amount. Overt encephalopathy was defined as grade 2 to 4 liver encephalopathy according to the West Haven criteria[11]. Ascites was classified according to the most recent position paper published by the International Ascites Club[12].

All blood samples were tested in the Clinical Laboratory of Jilin University's First Hospital. An automated biochemical analyzer (7600–210, Hitachi, Japan) was used to detect blood biochemical indices. According to the manufacturer's instructions, the total blood count was determined using a SYSMEX XN-9000 hematological analyzer (Sysmex Corporation, Kobe, Japan). Clotting tests were carried out using the automated coagulometer "SYSMEX CS-5100" utilizing the clotting technique (Sysmex Corporation, Kobe, Japan).

2.3 Outcomes

We collected details of HH treatment, date of death, LT and final follow up. The outcome of cirrhosis loss was defined as the development of liver-related complications such as variceal bleeding, ascites, spontaneous bacterial peritonitis, hyponatraemia, liver failure, or liver encephalopathy. Outcomes were death or and loss to follow-up as endpoint events. Our primary time point analysis identified the correlation of various factors with death. This was calculated from the date the diagnosis of HH began to the date of death or the date of the last follow-up visit.

2.4 Statistical analysis

Parametric continuous variables are expressed as means (± standard deviation) and comparisons between groups were made using the independent student's t-test, while nonparametric continuous variables are shown as medians (Quartile 25- Quartile 75) and group comparisons were made using the Mann-Whitney U test. Categorical variables are shown as numbers (n) and proportions (%), and group comparisons were made using the chi-square test. Survival outcomes were compared between groups using the Kaplan-Meier method of log-rank tests, and hazard ratios were estimated using univariate Cox regression models (with the HH start date at time zero). After adjusting for other confounders, multivariate Cox regression models were used to determine the correlation between statistically significant factors and the prognostic impact of HH (univariate Cox regression analysis $p < 0.1$). All statistical analyses were performed using SPSS Statistics 26 (IBM, New York, NY, USA). A two-sided P value < 0.05 was considered statistically significant.

3. Results

3.1 Demographics

During the study period, 5698 patients with decompensated cirrhosis were screened, and according to the inclusion and exclusion criteria, follow-up data were obtained for 131 patients who met the diagnostic criteria for hepatic Hydrothorax. The prevalence of HH was 2.3%, of which 80 (61.1%) were men and 51 (38.9%) were women, HH was more common in men than in women, with a male-to-female ratio of 1.67:1. The minimum age was 25 years and the maximum age was 81 years, with a mean age of (52.76 ± 11.88) years and a median age of 58 years. At the time of primary treatment, post-hepatitis B cirrhosis was the most common cause in 55 cases (42%), followed by alcoholic cirrhosis in 29 cases (22.1%), post-hepatitis C cirrhosis and primary biliary cirrhosis in 15 cases (11.5%) and 10 cases (7.6%) respectively, and other etiologies in 22 cases (16.8%) **(see** Table 1**).**

Table 1
Demographics, Clinical manifestations, imaging findings and complications in the decompensated phase

	No. percent of patients (%) [n = 131]
Age (year), mean ± SD	52.76 ± 11.88
Sex Male	80(61.1%)
Female	51(38.9%)
Etiology	
Hepatitis B virus(HBV)	55(42%)
Hepatitis C virus(HCV)	15(11.5%)
Alcohol	29(22.1%)
Primary biliary cirrhosis(PBC)	10(7.6%)
Other	22(16.8%)
Respiratory difficulties	89(67.9%)
Cough	30(22.9%)
Payment	54(41.2%)
Bloating	108(82.4%)
Jaundice	54(42.2%)
Liver palm	34(26%)
Spider mole	25(19.1%)
Splenomegaly	110(84%)
Location of pleural effusion	
Right side	107(81.7%)
Left side	16(12.2%)
Bilateral	8(6.1%)
Volume of pleural effusion	
Small amount	4(3.1%)
Medium amount	19(14.5%)
large amount	108 (82.4%)

Data are expressed as mean (± standard deviation), number (proportion).

	No. percent of patients (%) [n = 131]
Combined with massive ascites	87 (66.4%)
Compression dysplasia	96 (73.3%)
Liver Failure	21 (16%)
Hepatic encephalopathy	16 (12.2%)
Gastrointestinal bleeding	16 (12.2%)
Pleural fluid infection	30 (22.9%)
Spontaneous peritonitis	18 (13.7%)
Hyponatremia	52 (39.7%)
Renal insufficiency	24 (18.3%)
Hepatorenal syndrome	9 (6.9%)
Data are expressed as mean (± standard deviation), number (proportion).	

3.2 Clinical manifestations, imaging findings, and combined decompensated complication events

At the time of first diagnosis, most patients usually had multiple complaints, with the most common symptoms being abdominal distention (82.4%), dyspnoea (67.9%), poor appetite (41.2%), and cough (22.9%). Splenomegaly (84%) was the most common sign. Only pleural effusion on the right side was found in more than three quarters of the patients (107 out of 131; 81.7%). Left-sided effusion alone was found in 16 cases (12.2%) and bilateral effusion in 8 cases (6.1%). According to radiological criteria, massive pleural fluid predominated in 108 cases (82.4%), followed by moderate amounts in 19 cases (14.5%) and small amounts in 4 cases (3.1%). All patients had pleural fluid combined with ascites, including 87 cases (66.4%) with massive pleural fluid combined with massive ascites and 96 cases (73.3%) with compressive pulmonary atelectasis. Ascites was present in varying amounts in all patients and was the most common complication of the decompensated phase. This was followed by hyponatraemia in 52 cases (39.7%), infection of the pleural fluid in 30 cases (22.9%), renal insufficiency in 24 cases (18.3%), liver failure in 21 cases (16%), peritonitis in 18 cases (13.7%), hepatic encephalopathy and gastrointestinal bleeding both in 16 cases (12.2%) and hepatorenal syndrome in 9 cases (6.9%) **(see** Table 1**).**

3.3 Laboratory Features and Scoring Prognostic System

Routine blood collection and prognostic score data **(see** Tables 2**)**. Laboratory data are noteworthy in that most patients do not show neutrophilia and thrombocytopenia is typical. Serum cholinesterase and serum albumin levels are usually low. Almost all patients had significant liver dysfunction, including elevated bilirubin levels, prothrombin time (PT), thromboplastin time (TT), activated partial

thromboplastin time (APTT), international normalized ratio (INR), and significantly lower than normal prothrombinactivity (PTA) [58.86 (55.06–62.65)%]. Child-Pugh classification of A in 3 cases (9%), B in 42 cases (32%) and C in 86 cases (65%) reflecting underlying liver dysfunction in the majority of patients in this study. MELD score ≤ 15 in 107 cases (81%) and MELD score > 15 in 24 cases (19%), with a mean score of 10.20 ± 6.78. MELD-Na score 16 in 101 cases (77%), MELD-Na score > 16 in 30 cases (22%), mean score 10.53 ± 13.09. There were 2 cases (1.5%) with an ALBI classification of 1, 37 cases (28%) with a classification of 2 and 92 cases (70.5%) with a classification of 3, with a mean score of -1.16 ± 0.54.

Table 2
Laboratory Features and Scoring Prognostic System

	At first diagnosis	Range of reference values	No.(%)[n = 131]
AST (U/L)	60.68 (50.69, 70.67)	15–40.0	
ALT (U/L)	42.42 (33.89, 50.96)	9–50.0	
GGT (U/L)	77.71 (62.02, 93.40)	10–60.0	
ALP (U/L)	121.18 (107.48, 134.88)	45–125.0	
CHE (U/L)	2288.09 (2097.47, 2478.42)	4620–11500	
ALB (g/L)	26.49 (25.62, 27.37)	40–55.0	
TBIL (umol/L)	65.68 (53.68, 77.67)	0.0–26.0	
DBIL (umol/L)	30.81 (24.15, 37.46)	0.0-6.8	
IBIL (umol/L)	34.82 (28.94, 40.70)	5.0–20.0	
Cr (umol/L)	78.72 (71.97, 85.46)	57–97	
BUN (mmol/L)	7.80 (6.82, 8.77)	3.1-8.0	
FBG (mmol/L)	7.22 (6.61, 7.83)	3.1–6.1	
NE(10ˆ9/L)	3.77 (3.22, 4.32)	1.80–6.30	
LY(10ˆ9/L)	1.00 (0.85, 1.14)	1.10–3.20	
NLR	3.30 (2.17, 5.91)	0.56–5.73	
PLT(10ˆ9/L)	85.49 (75.72, 95.26)	125–350	
TT (s)	18.20 (17.65, 18.76)	11.0–21.0	
APTT (s)	37.88 (36.30, 39.47)	21–33	
PT (s)	17.22 (16.34, 18.10)	9.0–13.0	
INR	1.45 (1.38, 1.52)	0.8–1.2	
PTA(%)	58.86 (55.08, 62.65)	80–120	

Data are expressed as mean (± standard deviation), number (proportion) and median (quartile 25, quartile 75).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; CHE, cholinesterase; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; Cr, Creatinine; BUN, blood urea nitrogen; FBG, fasting blood glucose; NE, Neutrophil absolute count; LY, Lymphocyte absolute count; NLR, Neutrophil-to-lymphocyte ratio; PLT, platelet; TT, Thrombin time; APTT, Activated partial thromboplastin time; INR, International normalized ratio; PT, prothrombin time; PTA, Prothrombinactivity; MELD, model for end-stage liver disease; ALBI, Albumin-bilirubin.

	At first diagnosis	Range of reference values	No.(%)[n = 131]
MELD Score	10.20 ± 6.78		131
≤ 15	7.74 ± 4.43		107 (81%)
>15	21.19 ± 3.93		24 (19%)
MELD-Na Score	10.53 ± 13.09		131
≤ 16	4.08 ± 7.08		101 (77%)
>16	29.86 ± 9.75		30 (22%)
ALBI Score	-1.16 ± 0.54		131
ALBI grade 1	-2.95 ± 0.01		2 (1.5%)
ALBI grade 2	-1.72 ± 0.26		37 (28%)
ALBI grade 3	-0.90 ± 0.35		92 (70.5%)
Child-Pugh Score	10.43 ± 2.00		131
Class grade A	6.00 ± 0.00		3 (2%)
Class grade B	8.40 ± 0.76		42 (33%)
Class grade C	11.57 ± 1.34		86 (65%)
Data are expressed as mean (± standard deviation), number (proportion) and median (quartile 25, quartile 75).			
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; CHE, cholinesterase; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; Cr, Creatinine; BUN, blood urea nitrogen; FBG, fasting blood glucose; NE, Neutrophil absolute count; LY, Lymphocyte absolute count; NLR, Neutrophil-to-lymphocyte ratio; PLT, platelet; TT, Thrombin time; APTT, Activated partial thromboplastin time; INR, International normalized ratio; PT, prothrombin time; PTA, Prothrombinactivity; MELD, model for end-stage liver disease; ALBI, Albumin-bilirubin.			

3.4 Treatment and mortality

131 patients at first diagnosis, of whom 20 (15%) were treated with drug management alone, mean age 53.35 ± 11.91 years, median MELD score 10.14 (0.47–24.76) and mean survival time 21.10 ± 10.56 months. 111 (75%) patients were treated with medication and thoracic intubation, mean age 57.32 ± 11.83 years, median MELD score 10.22 (0.0-30.50), mean survival time 19.28 ± 14.19 months. During the later stages of treatment, one patient was treated with TIPS, with a MELD score of 16 and a survival time of 32 months, and three patients were treated with liver transplantation, with a mean MELD score of 18, all of whom are currently alive **(see** Table 3**).** A total of 101 patients experienced death and lost to follow-up endpoints during the 131 patient telephone and medical record follow-ups; 9 (8.9%) deaths at 30 days, 8 (7.9%) in males and 1 (0.9%) in females. 12 (11.9%) deaths at 60 days, 11 (10.8%) in men and 1 (0.9%)

in females; 16 (15.8%) deaths at 90 days, 14 (13.8%) in men and 2 (1.9%) in females; 23 (22.8%) deaths at 6 months, 17 (16.8%) in men and 6 (5.9%) in females; 38 (37.6%) deaths at 1 year, 29 (28.7%) in men and 9 (8.9%) in females; 71 (70.3%) deaths in 2 years, 52 (51.5%) in men and 19 (18.9%) in females; 95 (94.1%) deaths in 3 years, 62 (61.3%) in men and 33 (32.7%) in females; 99 (98.1%) deaths at 4 years, 65 (64.3%) males and 34 (33.6%) females; 101 (100%) deaths at 5 years, 66 (65.3%) in males and 35 (34.6%) in females. Based on the above data, it is clear that the mortality rate for males is significantly higher than that for females at all time periods, with an overall 2-year mortality rate already exceeding two-thirds and a 5-year mortality rate of 100%.

Table 3
Comparison of treatment modalities

Treatment modalities	No.(%)	Age (year)	MELD Score	Survival time (months)
Drugs (At first diagnosis)	20/131(15%)	53.35 ± 11.91	10.14(0.47–24.7)	21.10 ± 10.56
Thoracic intubation (At first diagnosis)	111/131(75%)	57.32 ± 11.83	10.22(0.00-30.50)	19.28 ± 14.19
TIPS (At post-treatment)	1/131(0.7%)	45	16	32
LT (At post-treatment)	3/131(2.2%)	52	18	-
Data are expressed as mean (± standard deviation), median (quartile 25, quartile 75) or number (proportion).				
Abbreviations: TIPS, Transjugular intrahepatic portosystemic shunt; LT, Liver transplantation; MELD, model for end-stage liver disease.				

3.5 Analysis of factors associated with the prognostic impact of HH

Three of the 131 study subjects are currently alive by liver transplantation and a total of 128 patients were followed up with a normal natural survival history of HH. 128 patients were analysed for prognostic-related factors. We used univariate and multivariate Cox regression analyzes to identify indicators related to the prognostic impact of HH. In the univariate Cox regression analysis, the factors associated with prognostic impact of HH were male (hazard ratio [HR]: 0.564, 95% confidence interval [CI]: 0.373–0.854, P<0.01), liver failure (hazard ratio [HR]: 1.820, 95% confidence interval [CI]: 1.040–3.185, P = 0.036), hepatic encephalopathy (hazard ratio [HR]: 2.361, 95% confidence interval [CI]: 1.354–4.116, P<0.01), hyponatremia (hazard ratio [HR]: 1.721, 95% confidence interval [CI]: 1.156–2.562, P<0.01), high TBIL

level (hazard ratio [HR]: 1.004, 95% confidence interval [CI]: 1.000–1.007, $P = 0.045$), high MELD Score (hazard ratio [HR]: 1.061, 95% confidence interval [CI]: 1.026–1.098, $P<0.01$), and high MELD-Na Score (hazard ratio [HR]: 1.020, 95% confidence interval [CI]: 1.005–1.036, $P = 0.01$) at baseline. After adjusting for potential confounders using a multivariate Cox regression model, liver encephalopathy (hazard ratio [HR]: 2.172, 95% confidence interval [CI]: 1.118–4.219, $P = 0.022$), hyponatremia (hazard ratio [HR]: 1.636, 95% confidence interval [CI]: 1.044–2.564, $P = 0.032$), and high MELD score (hazard ratio [HR]: 1.063, 95% confidence interval [CI]: 1.009–1.121, $P = 0.023$) were found to be independently associated with the prognostic survival impact of HH (Table 4).

Table 4
Univariate and multivariate analysis for the risk of HH

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age (years)	0.993 (0.977, 1.009)	0.400		
Gender (M/F)	0.564 (0.373, 0.854)	<0.01*	0.657 (0.413, 1.045)	0.076
Liver failure	1.820 (1.040, 3.185)	0.036*	1.488 (0.783, 2.829)	0.225
Hepatic encephalopathy	2.361 (1.354, 4.116)	<0.01*	2.172 (1.118, 4.219)	0.022*
Digestive bleeding	1.320 (0.758, 2.298)	0.327		
Pleural fluid infection	0.832 (0.513, 1.349)	0.455		
Spontaneous peritonitis	0.909 (0.523, 1.580)	0.736		
Hypokalemia	0.852 (0.565, 1.283)	0.443		
Hyponatremia	1.721 (1.156, 2.562)	<0.01*	1.636 (1.044, 2.564)	0.032*
Hepatorenal syndrome	1.569 (0.724, 3.399)	0.253		
Grade III ascites	1.336 (0.831, 2.146)	0.232		
AST (U/L)	0.998 (0.993, 1.002)	0.301		
ALT (U/L)	0.998 (0.993–1.003)	0.445		
GGT (U/L)	0.999 (0.996, 1.001)	0.265		
ALP (U/L)	0.998 (0.995, 1.001)	0.143		
ALB (g/L)	0.971 (0.933, 1.011)	0.159		
TBIL (umol/L)	1.004 (1.000, 1.007)	0.045*	1.000 (0.995, 1.006)	0.911
TT (s)	1.014 (0.947, 1.087)	0.684		
PT (s)	1.035 (0.995, 1.077)	0.083	0.982 (0.918, 1.050)	0.593
Portal vein width (mm)	0.956 (0.884, 1.035)	0.265		
Child–Pugh Class C	1.246 (0.816, 1.903)	0.308		
Child–Pugh Score	1.096 (0.984, 1.220)	0.097	0.868 (0.716, 1.052)	0.148

Abbreviations: M, male; F, female; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; TBIL, total bilirubin; ALB, albumin; PLT, platelet; TT, Thrombin time; PT, prothrombin time; MELD, model for end-stage liver disease; ALBI, Albumin-bilirubin; HH, Hepatic Hydrothorax; HR, hazard ratio; CI, confidence interval.

Variables	Univariate analysis		Multivariate analysis	
MELD Score	1.061 (1.026, 1.098)	<0.01*	1.063 (1.009, 1.121)	0.023*
MELD-Na Score	1.020 (1.005, 1.036)	0.010*	1.003 (0.980, 1.028)	0.777
ALBI Score	1.420 (0.964, 2.093)	0.076	1.274 (0.716, 2.266)	0.410
ALBI Grade 3	1.362 (0.870, 2.132)	0.177		

Abbreviations: M, male; F, female; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; TBIL, total bilirubin; ALB, albumin; PLT, platelet; TT, Thrombin time; PT, prothrombin time; MELD, model for end-stage liver disease; ALBI, Albumin-bilirubin; HH, Hepatic Hydrothorax; HR, hazard ratio; CI, confidence interval.

Based on these data, another subgroup analysis was performed on 128 patients without transplant HH. As depicted in Fig. 2A, we compared graft-free survival rates by gender using the Kaplan-Meier method. We found that male patients had a significantly lower probability of graft-free survival than female patients (log-rank $P = 0.005$). Among the 101 patients with known endpoint events, the mean survival time was 16.21 ± 12.09 months for men and 21.00 ± 11.40 months for women. As depicted in Fig. 2B, we compared graft-free survival with and without hyponatraemia using the Kaplan-Meier method. We found that patients with hyponatraemia had a significantly lower probability of graft-free survival than those without hyponatraemia (log-rank $P = 0.005$). Among the 101 patients with known endpoint events, mean survival was 13.09 ± 11.09 months and 21.41 ± 11.52 months for patients with combined hyponatraemia and normal blood sodium levels, respectively. As depicted in Fig. 2C, we compared graft-free survival with and without hepatic encephalopathy using the Kaplan-Meier method. We found that patients with liver encephalopathy had a significantly lower probability of graft-free survival than those without liver encephalopathy (log-rank $P = 0.001$). Among the 101 patients with known endpoint events, the mean survival time was 10.47 ± 10.30 months for patients with liver encephalopathy and 19.16 ± 11.88 months for patients without liver encephalopathy. As shown in Fig. 2D, when stratifying HH patients according to a MELD score of 15, significantly different graft-free survival curves emerged. We found that the probability of graft-free survival was significantly lower for MELD scores above 15 than for patients with MELD scores below or equal to 15 (log-rank $P < 0.001$). Among the 101 patients with known endpoint events, those with scores above this threshold had a mean survival of 11.62 ± 8.56 months, while those with scores below 15 had a mean survival of 19.51 ± 12.29 months. The survival gap increased with increasing MELD score, with a mean survival time of 8.27 ± 8.29 months in 101 patients with known endpoint events when the threshold of 20 points was exceeded and 19.04 ± 11.91 months in patients with scores below or equal to 20 points, compared to a mean survival time gap of nearly two times, as depicted in Fig. 2E (log-rank $P < 0.001$). When stratified according to a MELD score greater than 15 and combined with hyponatraemia, the survival gap was significantly greater than for hyponatraemia and the MELD score alone, with a mean survival of 9.83 ± 9.94 months for patients with MELD combined with hyponatraemia, compared to 18.96 ± 11.91 months for control patients, out of 101 patients with known endpoint events months (log-rank $P < 0.01$), compared to a mean survival time difference of nearly twofold, as shown in Fig. 2F (log-rank $P = 0.001$).

4. Discussion

HH is a serious and difficult to manage complication of cirrhosis and portal hypertension that can progress to end-stage liver disease. However, the specific prognostic survival impact of HH patients, and the interrelationship between its long-term impact on mortality and on cirrhosis-related decompensated events are currently unknown. Here, we aim to examine the clinical characteristics, natural history and factors associated with long-term prognostic survival. More complete clinical data from hospital records of patients with decompensated cirrhosis and ascites admitted to the First Hospital of Jilin University from January 2013 to June 2021 were extracted for retrospective analysis, and risk factors affecting prognostic survival were further analysed based on follow-up survival time. The diagnosis of hepatic pleural fluid was based on currently accepted clinical features of the disease, including a known diagnosis of cirrhosis, the presence of portal hypertension, the analysis of pleural effusion, and the absence of primary cardiopulmonary disease. It is intended to further guide clinicians to clarify the clinical features of HH and the natural history of long-term survival and to seek more appropriate diagnosis and treatment.

In this study, we selected a large number of patients with decompensated cirrhosis in combination with one or both pleural effusions, for a total of 131 patients with HH according to the inclusion criteria. The current study compares with the previous literature on HH and our data represent one of the largest study cohorts[6,13–15] with a comprehensive analysis of demographic, clinical presentation, laboratory test and examination findings data in this unique patient population.

In this study, the ratio of men to women with HH was 1.67:1, the youngest age was 25 years, the oldest was 81 years, the mean age was (52.76 ± 11.88) years and the median age was 58 years. Hepatitis B virus was the most common cause of HH, which is more consistent with most studies[6,13–15], and HH was more common in men than in women. The most common symptoms of HH are dyspnoea and abdominal distention, which may be associated with massive pleural effusion compressing the lung tissue and massive accumulation of abdominal fluid resulting in. Splenomegaly and jaundice are the most common signs in patients with HH and are also common signs of decompensated cirrhosis and are not clearly specific. In the thoracoabdominal imaging of HH patients a large amount of ascites combined with a large amount of pleural fluid can be observed commonly, and pleural effusion is commonly found on the right side in about 87 cases (66.4%), with only a few located on the left side and bilaterally. The pathophysiology of HH is not yet fully understood[3], and the most prominent view is that pleural effusion is aided by the negative intrathoracic pressure generated during inspiration, with ascites entering the thoracic cavity directly through diaphragmatic defects of various sizes and is produced[16, 17], as the liver is anatomically similar to the diaphragm and the right diaphragm is less muscular than the left. Most patients with HH have compressive atelectasis on CT of the lungs (73.3%), which is closely related to compression of lung tissue by a large pleural effusion.

HH as a complication in patients with decompensated cirrhosis can often be combined with other complications, with peritoneal effusion being the most common, followed by electrolyte disturbances, but with hepatic encephalopathy and liver failure being the most severe and with a poor prognosis, in general agreement with the data reported in the literature[6]. Based on our data, the prognosis of patients with HH may be comparable to that predicted based on the MELD model, with a mean MELD score of 10.20 for the entire cohort at first diagnosis and a MELD score > 15 in 19% of the population, indicating a relatively short survival time and a significantly higher risk of death. Our MELD score data were somewhat lower than in a previous study in the literature[13], where the mean MELD score was 16, possibly due to the larger cohort of our data and the early diagnosis of patients. When using the MELD-Na score for prediction, the mean score was 10.53 and the number of people with > 16 was 22%, which is generally consistent with the MELD score. We also performed Child-Pugh grading and ALBI grading, where Child-Pugh grade C and ALBI grade 3 were 65% and 70.5%, respectively, both higher than 54% and 60% in a recent retrospective study in 2021[6], also indicating that most patients had poor liver function. Although our follow-up data suggest that most patients with HH eventually die from severe liver failure, some patients instead die from complications related to their lung disease, as we were unable to determine the specific cause of death for all patients who died. Therefore, based on our data, caution is needed in identifying the most likely cause of death in patients with HH.

We performed a statistical analysis of treatment modalities at the time of first diagnosis in 131 patients with HH and found that HH management was similar to portal hypertensive ascites, with restriction of sodium intake and the use of diuretics, drainage of puncture placement, and TIPS and liver transplantation as options for later treatment[3,18–21]. Pleural catheter drainage has been previously reported[22] and no significant efficacy has been observed, but it is notable that all our patients did not receive this treatment. Successful treatment of patients with refractory hepatic pleural fluid who did not meet the criteria for TIPS by repairing the diaphragmatic defect with televised thoracoscopic surgery (VATS) has also been reported in the literature[23], but none of our patients attempted this treatment. All our patients received diuretics at first diagnosis and their combination ratio of furosemide and spironolactone was individualized, commonly furosemide 60 mg combined with spironolactone 100 mg in a single dose, with the addition of tolvaptan, a selective vasopressin V2 receptor antagonist with an affinity for vasopressin V2 receptors that is 1.8 times higher than that of natural arginine vasopressin (AVP), when diuresis was not effective. 1.8 times the affinity of natural arginine vasopressin (AVP). Of these, 20 (15%) were treated with drugs alone and 111 (75%) were treated with drugs combined with thoracic intubation, which also suggests that most pleural effusions were massive and required puncture and drainage to relieve the compression of lung tissue and thereby relieve the symptoms of dyspnoea. There was no statistically significant difference in MELD scores or survival time between patients first diagnosed with drugs alone and those with drugs combined with thoracic intubation. Only one patient in our study was found to have undergone TIPS at a later stage of treatment, three then underwent liver transplantation and the three patients who underwent liver transplantation are still alive today.

By following the survival time of patients, we found that the overall prognosis of HH patients was poor, with approximately more than half dying within one year of the onset of symptoms and only 34 cases (33.7%) surviving after a year. However, patients survived significantly longer after receiving liver transplantation, considering that liver transplantation may be a better treatment option than drugs and chest tube drainage, but caution is needed in interpreting these data as only a very small number of patients, 2.2% of the entire study population, received liver transplantation, and it is also possible that patients with a better prognosis were more likely to opt for liver transplantation treatment. In addition, the selection of liver transplant recipients is extremely complex and although patients with advanced liver failure are selected based on screening criteria, transplant candidates are usually rarely comorbid with other diseases. Therefore, retrospective conclusions based on a very small amount of data may be inaccurate.

The long-term natural history of this complication of HH in patients with decompensated cirrhosis described in this study excludes the radical treatment of portal hypertension with liver transplantation, and there are not many studies in this direction. There are few studies on long-term mortality in patients with HH. In this study 101 patients with known clinical endpoint events had mortality rates of 70.3%, 94.1%, 98.1% and 100% at 2, 3, 4 and 5 years respectively, with close to more than two thirds of patients dying within 2 years and almost all facing death within 3 years, with one patient surviving for up to 5 years. Three patients underwent liver transplantation late in their treatment and are currently alive, with survival times of 33, 35, and 38 months after their first diagnosis of HH, respectively, with more follow-up still needed to clarify the ultimate survival time. Therefore, based on the data available to us, it is not possible to determine exactly to what extent liver transplantation has an impact on the survival time of patients with HH and there is a lack of reference in the previous literature.

Gender, liver encephalopathy, hyponatremia, and MELD score had a significant effect on mortality when assessing the prognosis of patients with HH. After multifactorial analysis, the findings indicated that liver encephalopathy, hyponatraemia, and MELD score were independent risk factors for prognostic survival in HH, and the MELD score appeared to be a good predictor of mortality in patients with HH. On the contrary, the Child-Pugh score and the ALBI score were not as good as the MELD score in predicting survival outcomes in this subgroup, possibly because the MELD takes more factors into account. Additionally, the presence of a MELD score above the threshold of 15, liver encephalopathy or hyponatraemia in patients with HH was more likely to result in a poorer prognosis, and the survival gap increased further with increasing MELD scores. In this context, early identification of patients with HH in patients with decompensated cirrhosis and timely diagnosis and consequently timely management of patients with a combination of other decompensated events, HH can be a marker presentation of poor prognosis. In patients with HH, early identification of patients with a poor prognosis based on factors affecting the prognosis, together with targeted treatment, is particularly important.

In conclusion, to our knowledge, we have the largest volume of data on patients with HH of any published study to date, and typically the majority of patients usually have predominantly liver and lung symptoms. We believe that an early and accurate diagnosis is the key to guiding personalized treatment. Patients

with HH generally have a poor prognosis, and those who receive liver transplants generally have a relatively good prognosis. Future studies may require multiple centre, prospective studies that critically evaluate the different diagnostic criteria and treatment modalities typically used in these patients.

Limitations in this study: (1) This study is a single-centre retrospective analysis and does not exclude the influence of subjective factors by patients and medical record keepers; Additionally, not all patients were followed up in our department and therefore detailed information on the cause of death or other relevant clinical events is lacking. (2) Data collection throughout follow-up taking into account changes in compliance with sodium restriction and diuretic dose was relatively difficult, therefore throughout the natural history of HH we did not specify the impact of various treatment modalities on their prognosis, which can certainly be an important prognostic modifier, nor the impact of clinical presentations related to HH on their prognosis, but this may help better understand the impact of decompensated events on the prognosis of patients with HH. (3) The small number of patients undergoing TIPS and liver transplantation did not allow inclusion in the Cox proportional risk model survival analysis.

Declarations

Ethics approval and consent to participate

This study protocol was approved by the First Hospital of Jilin University and conducted according to the principles of the Declaration of Helsinki. All methods were performed in accordance with the relevant guidelines and regulations. We obtained written informed consent from all patients.

Consent for publication

Not Applicable.

Availability of Data and Material (ADM)

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflicts of interest with respect to this manuscript.

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Authors' contributions

BM analyzed the literature and wrote the manuscript. TS studied concept and design. JH and ZT helped in collecting the data and edited the manuscript. YW and YH collected the data and interpreted the diagnosis. XW and QJ provided the framework for the study, reviewed, and edited the manuscript. All authors read and approved the final manuscript.

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Figures

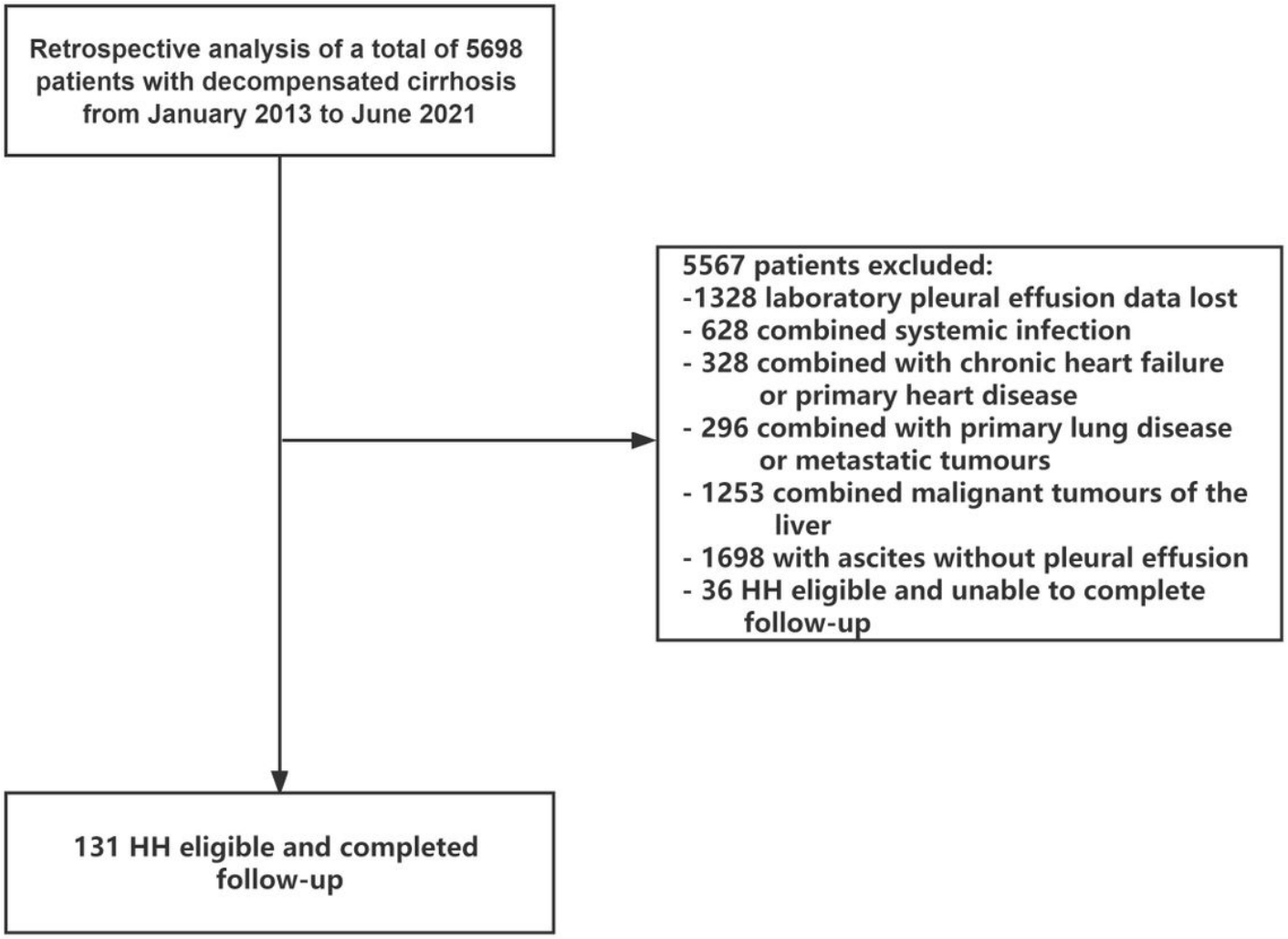

Figure 1

Study the flow diagram

Abbreviations: HH, Hepatic hydrothorax.

Figure 2

Subgroup survival analysis for patients with liver hydrothorax, based on the presence of sex (male / female) (A), hyponatremia (B), liver encephalopathy (C), a MELD score greater than 15 (D), a MELD score greater than 20 (E), a MELD score greater than 15 combined with hyponatremia (F).

Abbreviations: MELD, model for end-stage liver disease.