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Original Article

The Predictors of Survival in Cirrhotic Patients with Hepatic Hydrothorax

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SUMMARY

Objective: Hepatic hydrothorax is an uncommon complication of liver cirrhosis. The outcome of the patients is often poor. Multiple therapeutic options are available but there is no standard protocol of management. The predictors of survival are also indistinct.

Material and Methods: This single-center study retrospectively reviewed the medical records of cirrhotic patients with hepatic hydrothorax from August 2006 to August 2011. The characteristics of the patients, treatment methods, outcome of management, and survival were analyzed.

Results: Of the 48 patients, 26 (54.2%) were young age (< 65 years old) and 22 (45.8%) were elderly patients (≥ 65 years old). Among all, 32 (66.7%) patients received only conservative treatments, including sodium restricted diet, medications, peritoneal paracentesis, and thoracentesis. The other 16 (33.3%) patients had received additional aggressive treatment, such as video-assisted thoracic surgery, chest tube thoracostomy with or without pleurodesis, and liver transplantation. We defined the initial treatment success as the symptoms were relieved in the absence of thoracentesis for at least three months post-treatment. Multivariate analysis showed initial treatment success and a MELD score < 18 are independent predictors of survival.

Conclusions: For patients with liver cirrhosis and hepatic hydrothorax, despite their age and the methods for treatment, when resolution of the hydrothorax can be maintained for at least 3 months or when the patients have a MELD score < 18, the survival may improve.

1. Introduction

Hepatic hydrothorax is the excessive fluid accumulation in the pleural space in patients with liver cirrhosis, excluding other cardiac and pulmonary disease. It accounts for 2.7% of pleural effusion.[1] The estimated incidence of hepatic hydrothorax in cirrhotic patients is between 5–10%.[2] Most cases developed on the right side (85%), followed by 13% on the left and 2% on bilateral.[3] Passage of ascites from the peritoneal cavity to the pleural space through diaphragmatic defects is the most widely accepted cause of hepatic hydrothorax.[4,5] Unlike cirrhotic patients with massive ascites, which is more tolerable, only 500 mL of pleural effusion would cause symptoms, due to the low compliance of the thoracic cavity.[6] The diagnosis of hepatic hydrothorax depends on clinical information, image study such as chest X-ray, chest sonography, computed tomography (CT), magnetic resonance imaging (MRI), or peritoneal scintigraphy.[7] A vast of treatments had been applied include diet sodium restriction, administration of diuretics and/or colloid solution, peritoneocentesis, thoracentesis,[8,9] chest tube thoracostomy with or without pleurodesis,[10,11] surgery of video-assisted thoracoscopy[12] and liver transplantation, transjugular intrahepatic portosystemic shunt,[13–15] and indwelling tunneled pleural catheters.[16–18] However, the outcome of cirrhotic patients with hepatic hydrothorax is still dismal. The median survival time is only eight to twelve months.[19] Here we compared the survival of 48 cirrhotic patients with the diagnosis of hepatic hydrothorax, with respect of gender, age (young [< 65 y/o] or elderly [≥ 65 y/o]), conservative or aggressive treatment, initial treatment success, the history of hepatocellular carcinoma, the development of spontaneous bacterial empyema (SBEM), the Child-Pugh score, and the Model for End-Stage Liver Disease score. Our analysis showed that statistically initial treatment success and a MELD score < 18 are significant predictors with better survival.

2. Materials and methods

2.1. Patient enrollment

The adult patients with the diagnosis of liver cirrhosis and

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hepatic hydrothorax admitted to the Mackay Memorial Hospital from August 2006 to August 2011 were retrospectively reviewed. A total of 48 patients with complete medical records were selected for analysis. The diagnosis of hepatic hydrothorax was confirmed through clinical and laboratory findings, including at least one imaging study (chest x-ray, chest sonography, CT, MRI, or a peritoneal perfusion scan using 99mTc-sulfur colloid). If the cirrhotic patients with pleural effusion had other etiologies, including heart failure, pulmonary diseases, renal failure or neoplastic diseases (except hepatoma), the patients were excluded. The Internal Review Board of the Mackay Memorial Hospital approved this research.

2.2. Data collection

All the patients' data were collected, including: age, gender, complete blood count, blood biochemistry, pleural analysis (transudate or exudate, according to the Light's criteria;[20] spontaneous bacterial empyema (SBEM), by the definition of (i) positive pleural fluid culture and a polymorphonuclear neutrophils (PMN) count > 250 cell/mm^3 or, if a negative culture, pleural fluid PMN count > 500 cells/mm^3, (ii) No evidence of pneumonia on a chest radiography or CT, (iii) Presence of pleural effusion before the infection or transudate pleural fluid during infection[21]), the predominant side of pleural effusion, the etiologies of liver cirrhosis, and whether the patient had hepatoma. The Child-Pugh classification and the model for end-stage liver disease (MELD) score were calculated for each of the patients. The MELD score is calculated using the United Network for Organ Sharing modification of the original formula.

2.3. Treatment groups

All the patients were put on a sodium-restricted diet, and received intermittent administration of diuretics and/or colloid solution. Peritoneocentesis and thoracentesis were conducted according to the clinical condition. We defined the sodium restricted diet, diuretics, the colloid solution, peritoneocentesis, and thoracentesis as the conservative treatments. If the conservative treatments were ineffective, the aggressive treatments such as surgery of video-assisted thoracic surgery (VATS) and chest tube thoracostomy with or without pleurodesis would be carried out. The survival time of the patients were collected.

2.4. Statistical analysis

For the analysis, values are expressed as mean ± standard deviation (SD) (continuous variables) or as number (percentage) (categorical variables). Kaplan-Meier survival curves were constructed, and the log-rank test was used to compare the management outcomes. We analyzed the data using the Cox regression model. For the outcome analysis, we examined the association between management outcome and survival, which was adjusted by potential confounders that included gender, age, the history of hepatoma, development of SBEM, Child Pugh score, MELD score, method of treatment, and treatment outcome. The effects on survival of the clinical variables are presented as relative risks with 95% CIs. All tests were two-sided and used a significance level of p = 0.05. All statistical analyses were performed using the SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Demographic characteristics of the study population

The characteristics of the study population are shown in Table 1. The mean age of the patients at time of diagnosis was 60.6 ± 11.4 years (ranging 35–83 years). The patients were divided into two

Table 1
Demographic data of patients with hepatic hydrothorax.

Characteristics	All patients (n = 48)	Age < 65 y/o (54.2%; n = 26)	Age ≥ 65 y/o(45.8%; n = 22)	p value
Age (years)	60.6 ± 11.4	52.2 ± 7.8	70.6 ± 5.1	< 0.001
Gender				0.011
Male	64.6% (N = 31)	80.8% (N = 21)	45.5% (N = 10)	
Female	35.4% (N = 17)	19.2% (N = 5)	54.5% (N = 12)	
Laboratory data				
Creatinine	1.7 ± 1.5	1.7 ± 1.5	1.6 ± 1.6	0.726
Albumin	2.6 ± 0.5	2.6 ± 0.6	2.5 ± 0.4	0.510
Bilirubin	5.3 ± 5.9	5.9 ± 6.7	4.5 ± 4.9	0.422
SAAG	1.0 ± 0.8	0.9 ± 0.8	1.2 ± 0.6	0.486
SPAG	0.8 ± 1.2	0.9 ± 1.2	0.8 ± 1.2	0.727
Child-Turcotte-Pugh classification				0.782
A	8.3% (N = 4)	11.5% (N = 3)	4.5% (N = 1)	
B	16.7% (N = 8)	15.4% (N = 4)	18.2% (N = 4)	
C	75.0% (N = 36)	73.1% (N = 19)	77.3% (N = 17)	
Total scores	10.4 ± 2.1	10.2 ± 2.4	10.6 ± 1.8	0.614
MELD score	17.9 ± 7.3	18.7 ± 8.4	16.9 ± 5.8	0.413
Etiology of cirrhosis*				
Alcohol	35.4% (N = 17)	50.0% (N = 13)	18.2% (N = 4)	0.022
Hepatitis B	52.1% (N = 25)	42.3% (N = 11)	63.6% (N = 14)	0.141
Hepatitis C	22.9% (N = 11)	19.2% (N = 5)	27.3% (N = 6)	0.509
PBC	2.1% (N = 1)	3.8% (N = 1)	0%	> 0.999
Location of pleural effusion				0.854
Right side	83.3% (N = 40)	80.8% (N = 21)	86.4% (N = 19)	
Left side	8.3% (N = 4)	7.7% (N = 2)	9.1% (N = 2)	
Bilateral	8.3% (N = 4)	11.5% (N = 3)	4.5% (N = 1)	
Pleural effusion analysis**				> 0.999
Transudate	85.4% (N = 41)	84.6% (N = 22)	86.4% (N = 19)	
Exudate	14.6% (N = 7)	15.4% (N = 4)	13.6% (N = 3)	
SBEM	6.3% (N = 3)	7.7% (N = 2)	4.5% (N = 1)	
History of hepatocellular carcinoma	43.8% (N = 21)	19.2% (N = 5)	72.7% (N = 16)	< 0.001
Follow-up time (months)	18.6 ± 26.0	22.2 ± 26.6	14.3 ± 25.3	

* One patient has alcohol, HBV, & HCV as the etiologies. Three had both alcohol and HBV. One has both HBV & HCV.
** The exudate is defined by the Light's criteria: (i) a pleural fluid-to-serum protein ratio > 0.5; (ii) a pleural fluid-to-serum LDH ratio > 0.6; and (iii) a pleural fluid LDH > 200 IU or > 2/3 upper limit of normal serum LDH.[20,22]

groups: the young (age < 65 years old) and the elderly group (age ≥ 65 years old). In the young group, 26 patients had an average age of 52.2 ± 7.8 years old. In the elderly group, the average age of 22 patients was 70.6 ± 5.1 years old. The male-to-female ratio was 1.8:1 in the whole study group. Overall, 75.0% of patients were at Child-Pugh stage C, 16.7% at Child-Pugh stage B, and 8.3% at Child-Pugh stage A. The etiologies of liver cirrhosis were hepatitis B (52.1%), hepatitis C (22.9%), alcohol use (35.4%), and primary biliary cirrhosis (2.1%). The average MELD score was 17.9 points. The hepatic hydrothorax was right-side in 83.3%, left-side in 8.3%, and both sides in 8.3%. The pleural analysis revealed transudate in 85.4% and exudate in 14.6% of the patients. Among all the patients, 6.3% had SBEM. There was a statistic significance in gender between two groups (male prevalence in young group; p = 0.011). It was also more prevalent in the young group to have alcoholic liver cirrhosis (p = 0.022). The elderly group patient had more hepatoma (p < 0.001). The other parameters showed no statistical significance between the young and elderly groups.

3.2. Therapeutic management and initial treatment success rate of the patients

The therapeutic management and outcome of the patients were showed in Table 2. We defined the initial treatment success as the symptoms were relieved in the absence of thoracentesis for at least three months post-treatment. Overall, aggressive treatment was conducted in 33.3% of patients; whereas 66.7% of patients received conservative treatments only. In the aggressive treatment group, all the patients received chest tube thoracostomy. The initial treatment success rates of VATS with thoracostomy and chemical pleurodesis, VATS with thoracostomy, thoracostomy with chemical pleurodesis, thoracostomy only, and liver transplantation were 44.4%, 0%, 50.0%, 66.7%, 100%, respectively, with an overall success rate of 50.0%. Among the eight patients with aggressive treatment failure, two died within three months due to other cirrhosis-related complications, and six suffered a recurrence of hepatic hydrothorax within three months after intervention. The chance of success of medicatios only and medications with thoracentesis/peritoneocentesis were 44.4% and 30.4%, respectively, with an overall success rate of 34.4%.

3.3. Comparison between the young group and the elderly group

In the young group, 42.3% of patients received aggressive treatment and the initial treatment successful rate was 45.5%. The successful rate was 40% in the remaining 57.5% young patients receiving conservative treatment. In the elderly group, 22.7% of patients received aggressive treatment and the successful rate was 60%. On the other hand, the successful rate was 29.4% in the 77.3% of elderly patients receiving conservative treatment. The overall successful rate was 39.6% in the whole study group, 42.3% in the young group, and 36.4% in the elderly group, respectively.

3.4. Survival of management

The median survival of all 48 patients was 4.73 months (ranging 0.03–60 months). The mortality rate of the young and the elder groups were 88.5% and 86.4%, respectively, during a five-year observation period. No statistically significant difference was observed (p = 0.207, Figure 1A). The mortality rate of the conservative and aggressive treatment groups were 81.8% and 100%, respectively. There was also no significant difference (p = 0.312, Figure 1B). However, the survival of patients who had the initial treatment success was significantly longer than those with treatment failure (p = 0.008, Figure 1C). By using univariate analysis, initial treatment

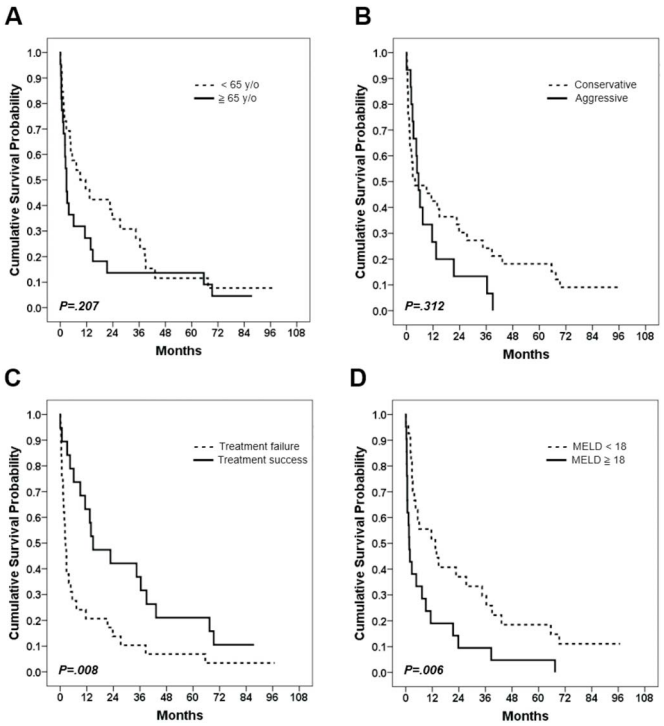

Figure 1. The survival of patients. A: young (< 65 y/o) and elderly (≥ 65 y/o). B: Conservative and aggressive treatment. C: Initial treatment success and failure. D: MELD < 18 and MELD ≥ 18.

Table 2
Therapeutic management and initial treatment success rate of patients.

	All patients (n = 48)		Age < 65 y/o (n = 26)		Age ≥ 65 y/o (n = 22)		p value
	No. of patients	Success, % (n)	No. of patients	Success, % (n)	No. of patients	Success, % (n)	
Aggressive treatment	16	50% (8)	11	45.5% (5)	5	60% (3)	0.152
Liver transplant	1	100% (1)	1	100% (1)	0	N/A	> 0.999
VATs + tube + pleurodesis	9	44.4% (4)	5	40% (2)	4	50% (2)	> 0.999
VATs + tube	1	0% (0)	1	0% (0)	0	N/A	> 0.999
Tube + pleurodesis	2	50% (1)	1	0% (0)	1	100% (1)	> 0.999
Tube thoracostomy only	3	66.7% (2)	3	66.7% (2)	0	N/A	0.239
Conservative treatment	32	34.4% (11)	15	40.0% (6)	17	29.4% (5)	0.152
Thoracentesis and/or peritoneocentesis	23	30.4% (7)	10	40.0% (4)	13	23.1% (3)	0.154
Medical treatment only	9	44.4% (4)	5	40.0% (2)	4	50.0% (2)	> 0.999
Overall	48	39.6% (19)	26	42.3% (11)	22	36.4% (8)	0.675

* The initial treatment success was defined as the symptoms were relieved in the absence of thoracentesis for at least three months post-treatment.

success (p = 0.008) and MELD score < 18 (p = 0.006, Figure 1D) were significant predictors that affected survival. Gender, age, conservative or aggressive treatment, the history of hepatoma, the Child-Pugh score, and whether the patients had SBEM, were all insignificant predictors. The multivariate analysis showed that MELD score < 18 (p = 0.033) and treatment success (p = 0.041) were independent predictors of survival (Table 3).

4. Discussion

Our study reviewed the patients with hepatic hydrothorax and tried to establish the predictors of survival. Our analysis, after controlling potential confounding variables, suggests that patients achieving an initial treatment success (defined as the symptoms were relieved in the absence of thoracentesis for at least three months post-treatment) and a MELD score < 18 can have a better outcome. These two factors are both the independent predictors of survival, either by univariate or multivariate analysis.

At present time, there is no standard treatment for cirrhotic patients with hepatic hydrothorax. In conservative managements, sodium-restricted diet, diuretics, and colloid solution are the main managements. Thoracentesis is an effective way to remove pleural effusion. Simultaneously, peritoneocentesis should be carried out to reduce intra-abdominal pressure.[23] In our study, all the sixteen patients in the aggressive treatment group received tube thoracostomy. Eleven of them had chest tube insertion following the operation. The other five patient received chest tube insertion with or without pleurodesis. Although chest tube insertion along for the patients with hepatic hydrothorax was discouraged in some literature because of its high morbidity and mortality,[5,6,24,25] the procedure is still carried out in the clinical setting. Among the ten patients receiving video-assisted thoracoscopy (VATS), all had chest tube insertion, and 90% also had pleurodesis. In the nine patients having VATS with pleurodesis, the successful rate was 44.4%. In one previous series, success was defined as symptomatic hydrothorax under control in the first 30 days after the procedure. In this report, 53% of patients with a single VATS with pleurodesis and 73% of patients with two sessions of VATS, can have a symptomatic control without procedure-related mortaliy.[12]

Transjugular intrahepatic portosystemic shunting (TIPS) had been used in cirrhotic patients.[26] TIPS can also improve the chance of survival without liver transplantation in cirrhotic patients with refractory or recurrent ascites, compared to paracentesis.[27] In our hospital, TIPS are not available. Indwelling tunneled pleural catheters (ITPCs) had been used in patients with malignant pleural effusion[28,29] and in hepatic hydrothorax.[16–18] In a meta-analysis, the rate for spontaneous pleurodesis could be 51.3% in non-malignant pleural effusion with a low complication rate of 17.2%.[30] Although ITPCs is promising,[18] some authors consider series of thoracentesis as the first line drainage method because catheter drainage being an independent risk factor of the 30-day mortality had been reported.[31]

There were discussions about the outcomes of different treatments in cirrhotic patients with hepatic hydrothorax. The Model for End Stage Liver Disease (MELD) score was developed to predict survival in patients with complications of portal hypertension but its advantage over Child Pugh classification is still debatable.[32] Another article, though focused on patients receiving TIPS, suggested event-free survival is similar between young (< 65 y/o) and elderly (≥ 65 y/o) patients, but there is a trend toward greater mortality and hospitalization in the elderly, although it is statistically insignificant.[33] An analysis by Hung, suggested that the presence of pleural effusion is an indicator of poor outcome in patients with liver cirrhosis.[34]

The study by Liu divided 52 patients into two groups: 28 receiving supportive care with thoracentesis and the other 24 patients receiving chemical pleurodesis, surgical intervention, or both. They defined intervention success as resolution of hydrothorax for at least 3 months following the procedure and the successful rate could achieve 50%. The median survival of intervention success (22.5 months) was significantly longer than those with intervention failure (5.4 months) and supportive care (6.3 months). They concluded that patients may have a better survival rate when resolution of hydrothorax can be maintained for at least 3 months after interventional procedure.[35] In our study, we defined the treatment as successful if the symptoms are relieved in the absence of thoracentesis for at least three months after treatment. This is similar to their definition except we didn't emphasize the interventional procedure. The median survival of 48 patients was 4.73 months in our study. The survival of patients had the initial treatment success (18.4 months), whether they received conservative or aggressive treatment, was significantly longer than those with initial treatment failure (2.4 months). In addition, the survival of patients with MELD < 18 (13.3 months) was also significantly longer than MELD ≥ 18 (1.5 months). Although the median survival in the young patients (9.1 months) seemed to be longer than the elderly patients (2.8 months), it was statistical insignificance (p = 0.207). The survival between patients with supportive (3.8 months) and aggressive treatment (5.4%) had no significant difference (p = 0.312).

Our study has several limitations. First of all, it was a retrospective study. Despite we had reviewed and collected the data for more than five years in our institution, most of the patients couldn't live more than five years. Secondly, the sample size is small. Cirrhotic patients with hepatic hydrothorax are a small group of patients and the cumulative data are sometimes missing because of their high mortality rate. Third, our intervention group was not homogeneous because of different clinical conditions. Our institution didn't have the capability to carry out transjugular intrahepatic portosystemic shunt, which is a main treatment method in other studies. We excluded other neoplasm except hepatoma in our study because patients with liver cirrhosis and hepatic hydrothorax have a high probability to have hepatoma (in our study, 43.8%). The study by

Table 3
Prediction factors for survival for hepatic hydrothorax (Cox regression).

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Gender (male)	0.82	0.44~1.51	0.517			
Age (elderly, ≥ 65 y/o)	1.46	0.81~2.65	0.207			
History of HCC	1.22	0.67~2.21	0.511			
Child Pugh Score	1.01	0.88~1.17	0.844			
MELD Score ≥ 18	2.35	1.29~4.29	0.006	1.97	1.06~3.69	0.033
Treatment method	1.40	0.73~2.68	0.312			
Treatment success	0.43	0.23~0.81	0.008	0.51	0.27~0.97	0.041
SBEM	0.97	0.30~3.17	0.961			

Hung also revealed cirrhotic patients with pleural effusion had a high chance (29.1% of all) to have hepatoma.[34]

In conclusion, initial treatment success, so defined if the symptoms are relieved in the absence of thoracentesis for at least three months post-treatment, and a MELD score < 18 may have a better survival in cirrhotic patients with hepatic hydrothorax. Gender, age, conservative or aggressive treatment, the history with or without hepatoma, the Child-Pugh score, and whether the patients had SBEM, were insignificant predictors.

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