Prevalence of Hepatic Hydrothorax in Patients with Chronic Liver Disease Presenting in Tertiary Center of Nepal

Shankhadev A, KC S, Karki N, Sharma D, Pradhan P

Department of Hepatology,

NAMS, Bir Hospital,

Kathmandu, Nepal.

Corresponding Author

Anil Shankhadev

DM Hepatology Resident,

NAMS, Bir Hospital,

Kathmandu, Nepal.

E-mail: shankhadev.anil@gmail.com

Citation

Shankhadev A, KC S, Karki N, Sharma D, Pradhan P. Prevalence of Hepatic Hydrothorax in Patients with Chronic Liver Disease Presenting in Tertiary Center of Nepal. *Kathmandu Univ Med J*. 2024;87(3):277-82.

ABSTRACT

Background

Hepatic hydrothorax is a common cause of pleural effusion in chronic liver disease. It is associated with poor outcome of the disease.

Objective

To study the prevalence of hepatic hydrothorax in patient with chronic liver disease.

Method

A hospital based prospective observational study conducted from July 15, 2022 to July 15, 2023. Diagnostic thoracentesis was performed to the patients presenting with pleural effusion at the time of admission. Chest x-ray was repeated at day 7 to assess the outcome of the appropriate treatment.

Result

Out of 752 enrolled participants, 105 were diagnosed with pleural effusion. The predominant cause was hepatic hydrothorax (80%), followed by tuberculosis (13.3%). 26.2% experienced spontaneous bacterial empyema. Most of the patients (74%) were classified as Child-Pugh C score. The prevalence of hepatic hydrothorax was 11.17%. Among 84 patients with hepatic hydrothorax, the mean age was 49.42±11.93 years, with a male predominance (male to female ratio, 68:32). Hepatic hydrothorax primarily occurred on the right side (78.6%), followed by left (15.5%) and bilaterally (6%). Mild hepatic hydrothorax was most common (48.8%), followed by moderate (31%) and massive (20.2%). About 65.5% were improved with treatment, while the mortality rate was 34.52%. Renal causes were the most common cause of death, accounting for 58.62% of mortalities.

Conclusion

Hepatic hydrothorax was prevalent in 11.17% of patients. It predominantly occurred on right side, with advanced Child Pugh score and often associated with spontaneous bacterial empyema (26.2%). The condition carried a mortality rate of 34.52%, with renal causes accounting for the majority of deaths (58.62%). All pleural effusions in chronic liver disease should undergo prompt evaluation because it is often associated with various complications and carries high mortality rate.

KEY WORDS

Ascites, Chronic liver disease, Hepatic hydrothorax, Prevalence, Spontaneous bacterial empyema, Tuberculosis

INTRODUCTION

Hepatic Hydrothorax (HH) is defined as abnormal accumulation of fluid in pleural space (usually > 500 mL) in a patient with cirrhosis after excluding other causes of pleural effusion (e.g. cardiac, pulmonary, or pleural disease).[1,2] Prevalence of HH is ranged between 4%-12% as reported in different studies.[2-4] Hepatic hydrothorax predominantly occurs on right side in approximately 85%, followed by left side in 13%, and bilaterally in 2%.[5] Right sided HH is more common because of the direct passage of peritoneal fluid into the pleural space via diaphragmatic defect and also the right hemi diaphragm is less muscular and less thicker than left hemidiaphragm.[6]

The common mechanisms are leakage of ascitic fluid via diaphragmatic defects, hypoalbuminemia, azygos veins hypertension, trans-diaphragmatic migration of fluid via lymphatic channels. Microscopic examination of the defect showed the discontinuities in the collagen bundles.[2,7] HH that accumulate slowly and in debilitated patients with chronic liver disease can be relatively asymptomatic even when large (up to 5 to 10 L) whereas the rapid accumulation with as little as 500 ml can manifest as severe dyspnoea and hypotension.[1]

The diagnosis of HH is clinically important because majority of cases have end stage liver disease and it has direct impact on outcome of the disease. The prevalence of hepatic hydrothorax has not been studied so far in Nepal. There is scarcity of studies on its impact on outcome of the disease. To my best knowledge, this is probably the first study on prevalence of hepatic hydrothorax in Nepal. So, this study is aimed to study its prevalence and their impact on outcome on the disease among patients with chronic liver disease.

METHODS

This was a hospital based prospective observational study conducted from July 15, 2022 to July 15, 2023, in the department of Hepatology, National Academy of Medical Sciences, Bir Hospital, Nepal.

Consecutive patients of chronic liver disease, aged 18 years or above presenting with pleural effusion were enrolled in this study. Detailed history, examination and laboratory investigation were performed. The pleural fluid analysis was done on bedside. Twenty milliliters of pleural fluid was sent for analysis including total count, differential count, sugar, protein, albumin, Adenosine Deaminase and Lactate dehydrogenase, culture and sensitivity. Other special tests in pleural fluid analysis were triglyceride, and polymerase chain reaction (PCR) for mycobacterium, amylase, and cytology when warranted. Similarly, all patients with ascites also underwent diagnostic paracentesis.

Liver cirrhosis/chronic liver disease was diagnosed on the basis of clinical evaluation, liver function tests, and abdominal imaging with or without a liver biopsy. Hepatic hydrothorax was diagnosed with high serum to pleural albumin gradient ≥ 1.2, pleural fluid cell count (Neutrophil < 250 cells/mm^3), pleural fluid protein < 2.5 g/dl and after ruling out other aetiologies.[1]

Prevalence of hepatic hydrothorax was calculated with the given formula. The total cases of hepatic hydrothorax were recorded after fulfilling the criteria and the total number of patients with chronic liver disease was collected from the registry department of Hepatology.

(Total number of hepatic hydrothorax / Total number of patient with chronic liver disease department of Hepatology) X 100

Hepatic hydrothorax with positive pleural fluid culture and polymorphonuclear leukocytes (PMN) count > 250 cells/mm^3 or negative pleural fluid culture and PMN count > 500 cells/mm^3, without evidence of pneumonia or para pneumonic effusion on imaging confirms the spontaneous bacterial empyema (SBE).[8] The severity of hepatic hydrothorax was graded as mild (pleural effusion did not exceed the 4^{th} rib), moderate (effusion located at the 2^{nd}-4^{th} rib); and severe (effusion exceeded the 2^{nd} rib) as per Hou et al.[9] Similarly, spontaneous bacterial peritonitis (SBP) was diagnosed by serum ascitic albumin gradient) ≥ 1.1, ascitic protein < 2.5 mg/dl, ascitic fluid neutrophils count ≥ 250 cells/mm^3, with or without positive ascitic fluid bacterial culture, and absence of secondary causes of peritonitis. Association between SBE and SBP, and their impact on outcome of disease were studied.

The approach to treatment of HH consisted of mobilising the ascitic fluid, limiting its access across the diaphragm, and emptying the pleural space. Salt and fluid restriction were advise d to all the patients diagnosed with ascites and hepatic hydrothorax. Conventional treatments were offered to all the patients with HH and ascites. Those who did not improve with conventional treatment, received a combination of infusion of albumin, diuretics, and octreotide as experimental regimen because there were few case reports with moderate benefits in treating HH with this regimen.[10] All the patients were given options for TIPS and liver transplantation once diagnosed with HH. All the patients were given options for TIPS and liver transplantation once diagnosed with HH.

Outcome of the treatment was measured by repeating the chest x-ray every 7^{th} day and at the time of discharge. The outcome was labelled “Improved” if there was complete absence or diminished pleural fluid on Chest x-ray view after treatment. It was labelled as “Not improved” if pleural fluid level did not improve or fluid level may increase from baseline Chest x-ray view despite treatment. “Recurrent” hepatic hydrothorax was labelled if there was reappearance of pleural fluid after its complete resolution.

Data was entered in Microsoft excel 2010 and was analyzed using international business machine (IBM) Statistical Package for Social Science version 26 (SPSS 26). Descriptive statistics was used to calculate prevalence. Comparisons was done using Student's t test or Chi square test as appropriate. Continuous variables with normal distribution were expressed as mean values ± standard deviation, and those with an unusual distribution were expressed as median values (range). P-values less than 0.05 were considered statistically significant. Informed consent was obtained before proceeding the study. Ethical clearance was taken from Institutional Review Board (IRB) of NAMS.

RESULTS

Total number of patients with pleural effusion in patients with chronic liver disease were 105. The etiologies associated with appearance of pleural effusion in studied population is given in figure 1. Out of 105 participants, the predominant cause of pleural effusion was hepatic hydrothorax (80%), followed by tuberculosis (13.3%) and others (6.7%). Eighty-four patients with various degrees of hepatic hydrothorax were studied. The mean age of the study population was 49.52 ± 11.93 years with ages ranging from 24 to 71 years. Of them, 57 (67.9%) were male and 27 (32.1%) were female. The most common etiology was ethanol (95.24%). The majority of patient were categorised in CTP C (88.1%). Severity of the disease was calculated by CTP score and MELD-Na score. Mortality was associated with higher CTP C score (39.2%) and higher MELD-Na (Mean =27.03 ± 4.6).

Table 1. The demographic profile of the participants (n=84)

Variables	Frequency. (n)	Percentage (%)
Age (yr.), mean ± SD	84	49.52 ±11.93
Sex		
Male	57	67.9
Female	27	32.1
Etiology of CLD		
Ethanol	80	95.24
HBV infection	2	2.38
HCV infection	2	2.38
CTP		
A	0	0
B	10	11.9
C	74	88.1

Based on these findings, the hospital-based prevalence of pleural effusion was calculated as 13.96% whereas that of hepatic hydrothorax in cirrhotic was calculated as 11.17%.

Hepatic hydrothorax was predominant in the right side (78.6%), followed by left side (15.5%) and bilateral (6%). HH was mild in severity in 48.8%, followed by moderate (31%) and massive (20.2%).

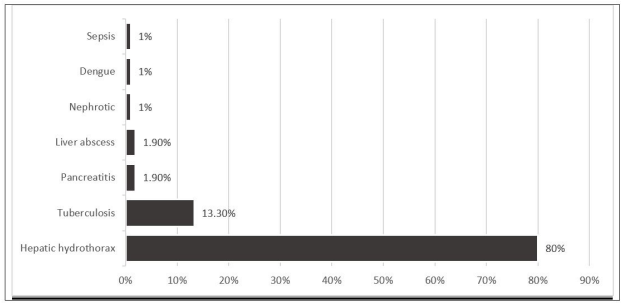

Figure 1. Etiology of pleural effusion in liver cirrhosis (n=105)

Spontaneous bacterial empyema (SBE) was detected in 26.2% whereas spontaneous bacterial peritonitis (SBP) was detected in 23.8 % among patients with HH. Both SBP and SBE were diagnosed at a same time in approximately 13.1%. In patient with SBP, 55% had SBE. Conversely, in patient without SBP, only 17.18 % had SBE (p-value = 0.02).

SBE was spotted larger in number with moderate hepatic hydrothorax (HH) (42.3%), followed by massive HH (29.4%) and mild HH (14.6%) (p-value =0.04). Additionally, SBE was observed in 28.4% of patients with CTP C score, and 10% with CTP B (p-value=0.2). Mean MELD-Na for detection of SBE was 24.1 ±6.35.

All patients with HH had varying degrees of ascites, with none presenting with HH without ascites. Out of 84 participants, the majority of HH cases were associated with moderate ascites (65.5%), followed by tense ascites (26.2%), and mild ascites (8.3%).

Mild HH was observed in 57.14% of patients with mild ascites, 60% of those with moderate ascites, and 18.18% of those with tense ascites. Moderate HH was found in 14.28% of patients with mild ascites, 27.27% with moderate ascites, and 45.45% with tense ascites. Massive HH occurred in 28.56% of patients with mild ascites, 12.72% with moderate ascites, and 36.36% with tense ascites (p-value =0.013).

The overall outcome with the given treatment was better in mild HH. Out of total 41 patients with mild HH, 78.04%, improved, while 21.95% expired. Among total of 26 patients with moderate HH, 57.7% improved, and 42.3% did not improve and expired. Among 17 patients with massive HH, 47.1% improved, and 52.9% expired (p-value =0.047).

In this study, majority of cases received only diuretics (55.95%). Most of these patients had mild HH (65.9%), followed by moderate HH (29.8%) and massive HH (4.3%) (p-value = < 0.001). Among these patients, 78.7% improved, while 21.3% expired with this regimen (p-value = 0.02).

Adding albumin to diuretics for treating HH (10.71%) resulted in 77.8 % improvement while 22.3 %) did not improve and expired (p-value =0.02). This regimen was administered to 55.6 %(n=5) of patients with mild HH and 44.4 %(n=4) with moderate HH (p-value= <0.001).

Similarly, patients who underwent pleurocentesis or paracentesis in addition to albumin and diuretics (28.6%), predominantly did not improve and expired (62.5%), while only 37.5% improved (p-value = 0.002). Most patients in this group had massive HH (50%), followed by moderate HH (33.3%). Therapeutic paracentesis was performed on patients with mild HH and tense ascites, along with diuretics and albumin in 16.7%, and all of these patients improved. (p-value = < 0.001).

Additionally, treatment with combination of diuretic, albumin, and octreotide showed improvement in 2.38%, though one experienced recurrent hepatic hydrothorax after three months of follow-up (p-value =0.002).

None of the patient underwent liver transplantation due to financial constraints and TIPS could not be offered because it is not readily availability in Nepal.

The outcome of the disease was also compared with detection of SBE in this study. Of total 22 cases of SBE, 59.1% improved, while 40.9% did not improve and expired (p-value = 0.4). All the patients who expired belonged to CTP C (39.2%), while patients with CTP B had no mortality (p-value = 0.014).

Mean MELD-Na score was 21.32 ± 6.8. The mortality rate was directly correlated to MELD-Na in our study. Mean MELD-Na was 27.03 ± 4.6 in the mortality category, while that in improved category was 18.30 ± 5.7 (p-value = < 0.001).

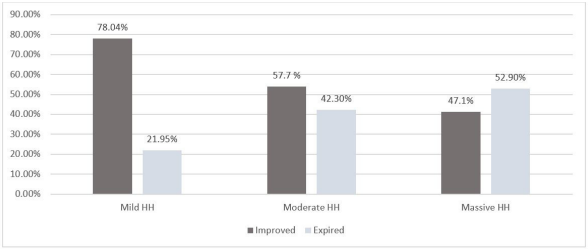

Figure 2. **Outcome of hepatic hydrothorax (n=84)**

Mortality was recorded in 34.52% of cirrhotic patients with HH. The majority of deaths were contributed by renal impairment (58.62%), followed by sepsis (27.58%), others (13.8%). The causes of deaths are mentioned in figure 3. The mortality rate increased to 40.9% in presence of SBE.

DISCUSSION

Pleural effusion is a common disorder in patients with chronic liver disease. The hospital-based prevalence of pleural effusion was calculated as 13.96% in our study. This figure appeared little lower than the study by Hou et al. which showed incidence of 20.8%.[9] Approximately 80% of those were contributed to hepatic hydrothorax. Overall, the prevalence of hepatic hydrothorax was 11.17% in our study, which was within the range of 4%-12% as shown in

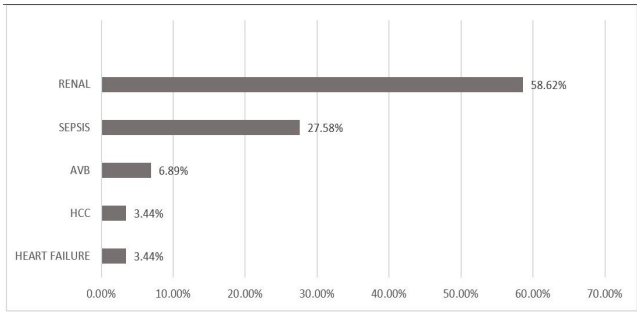

Figure 3. **Cause of death (n=29)**

previous studies.[2-4] This figure was lower than the study by Badillo et al., in which 16% of hospitalized cirrhotic patients had hepatic hydrothorax.[4] Additionally, we found that hepatic hydrothorax was common on right side (78.6%) followed by left side (15.5%) and bilateral (6%). The result n our study was comparable to a study by Xiol et al. who claimed that it developed on the right side in approximately 85%, on the left side in approximately 13%, and bilaterally in approximately 2%.[5] Similarly, a recent study by Ma et al. also approved that it was mostly seen on the right side (82%), followed by the left side (12%) and bilateral effusions (6%).[12]

Identification of spontaneous bacterial empyema had a direct impact on outcome of the disease. It was detected in 26.2% of the patients. Similar findings were observed in a study by Xiol et al., which reported that 30% of patients had complicated hepatic hydrothorax involving infection, blood, or pus.[11] However, this percentage was higher than the 15.6% incidence of spontaneous bacterial empyema (SBE) reported in a study by Reiche et al.[12]

Our study observed no significant correlation between occurrence of SBE with severity of hepatic hydrothorax but liver dysfunction was directly related to the development of SBE. In this study, we found that SBE was predominantly observed with CTP C score (28.4%) and mean MELD-Na score of 24.1 ± 6.35. Similar outcomes were observed in study conducted by Chen et al. and Mohamed et al.[13,14] In this study, we found that SBE was predominantly observed with moderate hepatic hydrothorax (42.3%) and lesser in massive hepatic hydrothorax (29.4%) and mild hepatic hydrothorax (14.6%). There was scarcity of similar type of studies comparing severity of hepatic hydrothorax and SBE.

The coexistence of SBE and SBP was observed in 13.1%. SBE was found in 17.18% patient who did not have SBP. In contrast, this figure was reported significantly low as compared to a study by Allam et al. where approximately 40% of SBE were not associated with SBP.[8] However, we found that the presence of SBP increased the incidence of SBE increased to 55%.

Detection of ascites was usually the first decompensating event in cirrhotic patients. However, there are few case reports where hepatic hydrothorax was reported as the first decompensating event. Similarly, Badillo et al., Lazaridis et

al. and Krok et al. reported that hepatic hydrothorax could occur in absence of ascites.[4,15,16] In contrast, we found that all patients with hepatic hydrothorax had ascites. None of the cirrhotic patients presented with hepatic hydrothorax in absence of ascites. Similarly, as per Islam et al. all cirrhotic patients with hepatic hydrothorax presented with appreciable amount of ascites.[17]

Severity of hepatic hydrothorax was not correlated with severity of ascites and liver dysfunction. The majority of the cases with tense ascites had moderate hepatic hydrothorax. Similarly, most of the cases with moderate ascites had mild hepatic hydrothorax. Additionally, the majority of the cases with advanced Child Pugh score had mild hepatic hydrothorax. To our best knowledge, this was the first study comparing severity of hepatic hydrothorax with severity of ascites and liver dysfunction.

Hepatic hydrothorax plays important role in mortality of the disease. The mortality rate in patient with hepatic hydrothorax was 34.52%, whereas the figure increased to 40.9% in presence of SBE. Renal causes were the predominant cause of death, accounting for 58.62% of mortalities. The independent factors related to poor outcome were renal impairment, bacterial infections, and high MELD-Na score and advanced Child Pugh score. Similar results were observed in a study conducted by Badillo R et al4 and Chen et al.[13]

In this study, patients with mild hepatic hydrothorax were benefitted by diuretics irrespective of severity of ascites. Similar response was seen in the study performed by Al-sharif et al.[18] In those patients with mild hepatic hydrothorax, additional treatment with albumin infusion and paracentesis was offered for those with moderate to tense ascites when warranted. In patients with moderate hepatic hydrothorax, most benefit was seen with diuretics and albumin infusion. In those patients, pleurocentesis and paracentesis were performed when indicated. However, requirement of therapeutic pleurocentesis or paracentesis did not improve the outcome but only relieved patient's discomfort. Moreover, it was found that those who had frequent pleurocentesis or paracentesis had higher mortality rate (62.5%). The increased mortality in this group of population was contributed by the development of infection, pulmonary edema or post procedural circulatory dysfunction. These results were comparable to other studies performed by Garbuzenko et al. and Chaaban et al.[19,20] In patients with massive hepatic hydrothorax, most of the patients received diuretics, albumin and pleurocentesis and/or paracentesis were also performed when indicated. Benefit of pleurocentesis was described by Porcel et al., however, most of the patients required TIPS or liver transplantation in their study.[21]

Patient who received combination of albumin, diuretics and octreotide improved but the number of sample size was limited. The benefit of this new investigational regimen in treating hepatic hydrothorax was observed in few case reports.[10,22] Further study is recommended to establish its potential role in treating moderate to massive hepatic hydrothorax.

CONCLUSION

Hepatic hydrothorax was prevalent in approximately 11.17% of patients. It predominantly occurred in males (68%), on right side (78.6%) and CTP C (88.1%). It was often complicated by spontaneous bacterial empyema (26.2%) and its association was directly correlated with poor outcome of the disease. All the patients had various degrees of ascites. The condition carried a mortality rate of 34.52% with renal causes accounting for the majority of deaths (58.62%). The independent factors for poor outcome of the disease were determined by advanced CTP score and higher MELD-Na score, bacterial infection and renal impairment. The combination of diuretic, albumin and octreotide exhibited promising outcomes however, the sample was very small and further studies will clarify its benefit in future.

REFERENCES

1. Cárdenas A, Kelleher T, Chopra S. Hepatic hydrothorax. *Aliment Pharmacol Ther*. 2004;20(3):271-9.
2. Siddappa PK, Kar P. Hepatic hydrothorax. *Trop Gastroenterol.* 2010;30(3):135-41.
3. Gines P, Wong F, Kim W. Diagnosis, evaluation, and management of ascites and hepatorenal syndrome. *Hepatology.* 2021;74(2):1014-48.
4. Badillo R, Rockey DC. Hepatic hydrothorax: clinical features, management, and outcomes in 77 patients and review of the literature. *Medicine.* 2014;93(3):135-42.
5. Xiol X, Castellvi JM, Guardiola J, Sese E, Castellote J, Perelló A, et al. Spontaneous bacterial empyema in cirrhotic patients: a prospective study. *Hepatology.* 1996;23(4):719-23.
6. Sadler T. Langman's medical embryology. 7th ed. Baltimore. MD: Williams and Wilkins. 1995:221-3.
7. Lieberman FL, Hidemura R, Peters RL, Reynolds TB. Pathogenesis and treatment of hydrothorax complicating cirrhosis with ascites. *Ann Intern Med*. 1966;64(2):341-51.
8. Allam NA. Spontaneous bacterial empyema in liver cirrhosis: an underdiagnosed pleural complication. *Saudi J Gastroenterol*. 2008;14(1):43-5.
9. Hou F, Qi X, Ning Z, Zhao J, Zhang X, Deng H, et al. Prevalence, risk factors, and in-hospital outcome of pleural effusion in liver cirrhosis: a retrospective observational study. *Int J Clin Exp Med*. 2016;9(2):3265-79.
10. Kiafar C, Gilani N. Hepatic hydrothorax: current concepts of pathophysiology and treatment options. *Ann Hepatol.* 2008;7(4):313-20.
11. Hein YP, Ekladious A. Hepatic hydrothorax as the first sign of decompensated cirrhosis of liver in the absence of clinical ascites. *Intern Med J*. 2020;50(5):639-40.

12. Ma B, Shang T, Huang J, Tu Z, Wang Y, Han Y, et al. Analysis of clinical features and prognostic factors in patients with hepatic hydrothorax: a single-center study from China. *BMC Gastroenterol*. 2022;22(1):333.
13. Chen CH, Shih CM, Chou JW, Liu YH, Hang LW, Hsia TC, et al. Outcome predictors of cirrhotic patients with spontaneous bacterial empyema. *Liver Int.* 2011;31(3):417-24.
14. Mohamed A, Atef M, Alsebaey A, Elhabshy MM, Salama M. Combined spontaneous bacterial empyema and peritonitis in cirrhotic patients with ascites and hepatic hydrothorax. *Arab J Gastroenterol.* 2017;18(2):104-7.
15. Lazaridis KN, Frank JW, Krowka MJ, Kamath PS. Hepatic hydrothorax: pathogenesis, diagnosis, and management. *Am J Med.* 1999;107(3):262-7.
16. Krok KL. Hepatic hydrothorax: Current concepts. *Clin Liver Dis*. 2014;4(2):35-7.
17. Islam N, Ali S, Kabir H. Hepatic hydrothorax. *Br J Dis Chest.* 1965;59(4):222-7.
18. Al-sharif H, Sharma S. Hepatic hydrothorax: How would you manage it? *Can Respir J*. 2005;12(8):440-2.
19. Garbuzenko DV, Arefyev NO. Hepatic hydrothorax: an update and review of the literature. *World J Hepatol*. 2017;9(31):1197.
20. Chaaban T, Kanj N, Bou Akl I. Hepatic hydrothorax: an updated review on a challenging disease. *Lung*. 2019;197:399-405.
21. Porcel JM. Management of refractory hepatic hydrothorax. C*urr Opin Pulm Med*. 2014;20(4):352-7.
22. Barreales M, Sáenz-López S, Igarzabal A, Muñoz-Yagüe T, Casis B, Alonso-Navas F, et al. Refractory hepatic hydrothorax: successful treatment with octreotide. *Rev Esp Enferm Dig*. 2005 Nov;97(11):830-5.