

Repeat thoracentesis in hepatic hydrothorax and non-hepatic hydrothorax effusions: a case control study

Samira Shojaee¹, MD, MPH, FCCP, Marwah Khalid¹, MD, George Kallingal¹, DO, Le Kang², PhD, Najib Rahman³, MD, D. Phil, MSc, FRCP

¹Virginia Commonwealth University Medical Center, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Richmond, VA

²Virginia Commonwealth University Medical Center, Department of Statistics, Richmond, VA

³University of Oxford, Nuffield Department of Medicine, Oxford Center for Respiratory Medicine, Oxford, England. Oxford National Institute of Health Research Biomedical Centre.

Corresponding Author
Samira Shojaee, MD, MPH, FCCP
Assistant Professor of Medicine
Pulmonary Disease and Critical Care Medicine
Virginia Commonwealth University
PO Box 980050
Richmond, VA 23298
Email: sas3867@mail.harvard.edu
Phone: 804 828-9071
Fax: 804 828-2578

Running Title – Complications of repeat thoracentesis

Keywords: complications, repeated thoracentesis, pleural effusion, hepatic hydrothorax, liver disease, cirrhosis

IRB Number:

Virginia Commonwealth University Medical Center – HM20002940

There was no funding available for the performance of this study. All work and data analysis was performed and confirmed by each author. All authors had access to the final data and manuscript submission.

Author Contributions:

Dr. Shojaee participated in study design, data collection, data analyses, manuscript writing, and manuscript review.

Dr. Khalid participated in data collection and manuscript review.

Dr. Kallingal participated in data collection and manuscript review.

Dr. Kang participated in data analyses and manuscript review.

Dr. Rahman participated in study design, data analyses, manuscript writing, and manuscript review.

Declaration of Interest:

Dr. Shojaee has no conflicts of interest to declare.

Dr. Khalid has no conflicts of interest to declare.

Dr. Kallingal has no conflicts of interest to declare.

Dr. Kang has no conflicts of interest to declare.

Dr. Rahman has received an unrestricted educational grant from rocket medical and provides clinical advice to them and reports no other potential conflicts related to this manuscript.

Abstract:**Background:**

Repeat thoracentesis for symptom control is offered to patients with refractory hepatic hydrothorax (HH) but the risk profile for this management strategy remains unclear.

Objectives:

This study aimed to compare complication frequency and nature during repeat thoracentesis in patients with and without HH.

Methods:

Complication rates in patients undergoing repeat thoracentesis for symptom relief was compared between patients with HH, and a control group (non-HH group) at a single center from 2010-2015. Records were reviewed for demographics, laboratory values, number of thoracentesis and associated complications with each procedure.

Results:

82 patients with HH (274 thoracenteses) and 100 control patients (188 thoracenteses) were included. A complication was noted in 17/462 (0.03%) procedures in the entire cohort. There was a higher overall complication rate with repeat thoracentesis in the HH group (8% vs 0%, $p=0.016$, 95% CI: 1.5%, 14.6%). In the HH group; cumulative risk of complications increased with sequential thoracenteses; a complication occurring in the preceding intervention was the strongest predictor for subsequent complication (OR=17.1, $p=0.0013$) and more than 1 previous complication was associated with a 15 fold increased risk of subsequent complication ($p<0.001$). In multivariate analysis within the HH group, MELD score was an independent predictor of hemothorax (OR: 1.19, 95% CI: 1.03, 1.36, $p=0.012$).

Conclusions:

Repeat thoracentesis is an overall low-risk procedure although it carries a higher complication rate in HH compared with non-HH patients. The presence of a previous complication significantly increases the risk of future complications in the HH population.

Introduction:

Hepatic hydrothorax (HH) is a transudative pleural effusion that develops in cirrhotic patients with portal hypertension and in the absence of cardiopulmonary disease. ¹ HH accounts for 2-3% of all pleural effusions. ^{2,3} The incidence of HH in cirrhotic patients is reported in varying range (4-15%) in the literature depending on the chest imaging modality.^{4,5}

The goal of treatment in hepatic hydrothorax is to reduce symptomatic pleural fluid caused by ascitic fluid in the pleural cavity. The first step in management is sodium restriction and diuretic therapy. ⁶ Approximately 21-26% of these patients suffer from refractory HH and repeated thoracentesis is required for symptom control particularly when patients are not proper candidates for transjugular intrahepatic portosystemic shunt (TIPS), liver transplant, or are awaiting transplant. ⁷ Depending on the rate of fluid re-accumulation and symptoms, patients are required to undergo thoracentesis from every few days to every 2-3 weeks. This treatment plan towards alleviating dyspnea is standard practice in the management of HH. ^{6,8}

Safety profile and complications of thoracentesis as a procedure in general are studied and reported in the literature with pneumothorax rate of 0.6-6% and hemothorax rate of 0-2% among major complications. ⁹⁻¹¹ However, despite routine implementation of repeat thoracentesis as a therapeutic and palliative regimen in HH, the risk profile is not clear. We hypothesize that repeat thoracentesis in patients with HH carries a higher risk secondary to their immunocompromised state with abnormal coagulation factor synthesis and function, bone marrow suppression and thrombocytopenia to name a few. Complication rate of repeat thoracentesis and its safety profile comparing patients with and without HH has not been examined in the literature.

This study was designed to assess complication rate of repeat thoracentesis in patients with HH and control group, and explore potential predictive factors for complications in this vulnerable population.

Study Population and Method:

This is a comparative retrospective case-control study of repeat thoracentesis in patients aged ≥ 18 with and without HH who underwent thoracentesis at Virginia Commonwealth University (VCU) from January 2010 to September 2015. Charts were reviewed of all cirrhotic patients (identified based on chart reported coding as well as detailed review of medical history, hepatology consultation review and implemented treatment strategies) with pleural effusion who underwent thoracenteses.

In parallel, charts of non-cirrhotic patients (non-HH group) were reviewed, with pleural effusion due to etiologies other than HH (malignancy, parapneumonic effusion/empyema, heart or renal failure induced, other) who required thoracentesis within the same time period. It was anticipated

that a total of 100 patients with HH would be collected within 5 years' time period based on which, *a priori* decision was made to include 100 patients in the control group. The cases were not matched between two groups. Due to a much larger population of non-HH pleural effusion per year, control group selection was performed from year 2013 (halfway between 2010-2015). This timeline was selected to reflect ongoing expertise and complications rates similar to the HH population. Procedural technique, method of supervision and the supervising team were the same within the five-year time period. Etiology of pleural effusions are provided in table 1. For both groups, all thoracentesis recorded in the patients' medical record were included. The VCU Institutional Review Boards approved this study (IRB# HM20002940). Details of aspiration procedure are listed in appendix.¹³

Data Collection

Collected data included: number and date of thoracenteses per patient, proceduralists' level of training, admission status, procedure site, volume of fluid removed and complications. Specific evidence of the following complications were recorded in all cases: pneumothorax, cardiovascular compromise/syncope, hemothorax, infection, re-expansion pulmonary edema and death. Other collected data included patient demographics, etiology of liver disease and non-HH pleural effusion. Laboratory data were retrieved from within 72 hours prior to and preferably closest to the procedure. Post procedure pleural fluid analysis labs were retrieved.

Complication definitions

All prospectively documented complications were recorded, to include all major clinical complications of interest with the following pre-hoc definitions:

- Trapped vs non-trapped lung were recorded separately. When pneumothorax-ex vacuo was suspected, Chest X-ray was reviewed to verify air in a non-gravity dependent location with no continued expansion of the air space on follow up chest Xray obtained within 6-12 hours. Pneumothorax-ex vacuo requiring hospitalization or observation was reported under pneumothorax as a complication.
- Re-expansion pulmonary edema (REPE) was diagnosed if there was acute respiratory decompensation with increased work of breathing or oxygen requirement with unilateral pulmonary edema within 24 hours.
- Patients were diagnosed with a hemothorax if there was a drop in hemoglobin with rapid re-accumulation of effusion on chest imaging and verified by pleural/serum hematocrit >50%.
- Complications such as continued leak from thoracentesis site were recorded under "other complications".

Complications were categorized in to major (pneumothorax requiring chest tube placement, hemothorax, REPE and death) and minor (pneumothorax not requiring chest tube placement, pneumothorax ex-vacuo, vasovagal syncope and fluid leak from puncture site) complications.

Statistical Analysis:

Simple descriptive statistics were used to describe patient demographics and outcomes. Participants' characteristics were described for the total study sample. Binary and categorical data were reported as percent frequencies. Continuous variables were displayed as mean and

standard deviation. Multivariate logistic regression was used to identify the association between severity of liver disease to hemothorax and total complications within the HH group as well as between the two study groups. Severity of liver disease was measured by Model for End-Stage Liver Disease (MELD score), which was used as a continuous variable. Platelet count was used as a binary variable with platelet counts above and below $50 \times 10^3/\text{microliter}$. Akaike Information Criterion (AIC) was used to assess for goodness of fit and the relative quality of the statistical models.

The Fisher's exact test was performed to compare the rate of complications of the first thoracentesis in HH to control patients. For specific complications, e.g., pneumothorax and hemothorax, the Fisher's exact test was performed to compare rates of occurrence between hepatic hydrothorax and control patients. To analyze the complication rate of repeated thoracentesis, the median number of complications were compared between the patients who had more than one thoracentesis, in both HH and non-HH groups. To account for correlated data from repeated procedures in the same patients, the cumulative rate of complications according to number of procedures was estimated using the empirical distribution function around the percentage of subjects with complications up to the n^{th} procedure. For each hepatic hydrothorax procedure, data were analyzed using associated number of complications, immediate previous complication status, and the accumulated number of complications up to that particular hepatic hydrothorax procedure, in order to assess for increase complications risk when the subject had positive complication history.

All statistical analyses were performed with SAS version 9.4. P-values <0.05 were considered significant.

Results:

Baseline data

462 procedures were recorded and retained in the analysis. A total of 182 patients were included in the study (82 HH and 100 non-HH). Mean age and standard deviation (SD) in the HH group was 57 (8.9) and 29 (35.4%) of patients were female. Mean age (SD) in the non-HH group was 63 (14.3) and 57 (57%) of the patient were female (for procedure characteristics comparing the two groups please see Table 2). Procedure characteristics within the HH group comparing those with and without complications are shown in Table 3.

Procedures and Complication Analysis

There was a median number of 5 (IQR 3 to 8) procedures/patient in the HH group and 2 (IQR: 1 to 4) procedures/patient in the non-HH group. A total of 32.9% (27/82) of HH patients underwent a single thoracentesis during the study period. 55 patients in the HH group (total number of 192 repeat thoracenteses) and 42 patients in the non-HH group (total number of 88 repeat thoracenteses) had more than one thoracenteses recorded. Complications details are shown in table 4.

The rate of any minor and major complication in the non HH group was 2/188 (1.06%, 95% CI: 0.4, 2.5) with both complications occurring following a first thoracentesis. Four patients in the HH group had a minor or major complication following their first thoracentesis (4.9%, 95% CI:

1.6% to 12.7%). The rate of any major and minor complication was higher with the first thoracentesis in the HH group compared to non-HH group but did not reach statistical significance. (4.9% vs 2%, $p=0.41$). Similarly, The complication rate of second thoracentesis in the HH and non-HH groups were 7.3% (4/55) and 0 (0/42) respectively but did not reach statistical significance ($p=0.12$). Additional comparisons were not performed due to a small number of patients with 3, 4, or more thoracenteses in the non-HH group.

No infections in the form of empyema, parapneumonic effusion or cellulitis were recorded, as a result of thoracentesis. All procedures including diagnostic thoracentesis, were also therapeutic. Thoracentesis occurred with the purpose of complete drainage of the pleural space unless limited by trapped lung physiology as per our practice protocol.

Adjusted Analysis

Overall complication rate between HH and non-HH population, overall complication in the HH group alone and hemothorax in the HH group were assessed in multivariate analysis.

Within the HH group, the odds of developing a hemothorax was 1.2 times higher for every 1 unit increase in MELD score, after adjusting for INR and platelet count (OR: 1.19, 95% CI: 1.03, 1.36, $p=0.012$) in multivariate analysis. Additionally the odds of developing a hemothorax was nearly 10 times higher when platelet count was less than $50 \times 10^3/\text{microliter}$, compared to counts of $> 50 \times 10^3/\text{microliter}$ (OR: 9.67, 95% CI: 1.16 to 80.42, $p=0.035$).

In multivariate analysis including variables of age, sex, INR and MELD score within the HH group, MELD score did not have any significant effect on the total rate of complications (OR: 1.03, $p=0.39$). For every unit increase in INR, there was a 1.9 times higher overall complication rate (CI: 1.87, 95% CI: 1.08 to 3.24, $p=0.024$).

On univariate analysis the odds of having a complication (minor and major) was 6 times higher in the HH than the non-HH group (OR: 6.15, 95% CI: 1.4 to 26.9, $p=0.015$). In multivariate analysis including variables of HH status, BUN and creatinine, the HH group still had higher odds of complication than the non-HH group (OR: 4.91, 95% CI: 1.08 to 22.2, $p=0.038$). Additionally, the odds of developing any complication was 4.2 times higher in the HH group after platelet counts were included in the model, but was not statistically significance. (OR: 4.2, 95% CI: 0.9 to 19, $p=0.066$)

Repeat Thoracentesis

Repeat thoracentesis was required and performed with shorter intervals in the HH group. Median time interval between repeat thoracentesis was 14 days (IQR: 6, 49) in the HH group and 35 days (IQR: 11, 115) in the non-HH group. The median number of all complications of repeated thoracentesis was compared between HH and non-HH group, demonstrating an 8.1% risk (from 2nd to nth thoracenteses) in the HH group compared with a 0% risk in the non-HH group ($p=0.016$, 95% CI: 1.5% to 14.6%).

Ten patients (12.2%) in the HH group had at least one minor or major complication at any point. Detail review of the data showed that out of the 10 patients with 20 complications in 17

procedures, 6 patients had one complication only, and the remaining 4 patients had a total of 14 complications.

The cumulative rate of complications increased with the increased number of thoracentesis. The complication rate for repeated thoracentesis in the non-HH group was zero, regardless of the number of thoracenteses (Table 5 and Figure 1).

In multivariate analysis adjusted for INR, platelet count and MELD score, having an immediate previous complication significantly increased the risk of having another complication (OR=17.1, $p=0.0013$). Having more than 1 previous complication (not necessarily an immediate previous complication) significantly increased the risk of future complications (OR=15.0, $p<0.001$).

Details of each complication can be found in table 6 (appendix).

Discussion:

Although repeat thoracentesis is considered as a treatment for refractory symptomatic effusion in HH, the risk of repeat thoracentesis is not well reported in the literature. To our knowledge, this is the first study to examine the safety of repeat thoracentesis in HH patients compared to a non-HH control group.^{9, 10, 14, 15}

We have demonstrated that the major complication rate in our cohort of 462 patients is comparable to the world published literature for thoracentesis.^{9-11, 16, 17} Total and major complication rates were found to be higher in the HH than the non-HH group.

Castellote et al, retrospectively reviewed the complications of thoracentesis in cirrhotics with HH assessing complication rate in 69 patients (245 thoracentesis). Pneumothorax rate in the diagnostic group was 4.4%, but rose to 7.7% in the first therapeutic thoracentesis. By thoracentesis number 4, the pneumothorax rate was 34% (95% CI: 22.1-47.2).¹² The authors concluded that therapeutic thoracentesis (\geq thoracentesis number 2) is a risk factor for pneumothorax and the risk increases with consecutive thoracenteses. Our data does not show a significant change in pneumothorax rate associated with repeat thoracentesis. Although in our cohort, overall complication rate was higher in HH vs non-HH group, total pneumothorax rate was very low. While it is difficult to consider the possible causes of high pneumothorax rate in Castellotes' study, we speculate that these findings may be explained by the lack of ultrasound use for puncture site identification, among other possible reasons such as trapped lung physiology and pneumothorax *ev-vacuo*.

Our data shows that having a previous thoracentesis complication of any kind increased the chance of having a complication with another thoracentesis by 15 fold. This risk was even higher if the previous complication involved the immediate last thoracentesis. While it is impossible to prove the causality of these findings with a retrospective design, we hypothesize that in a patient with end-stage liver disease, the presence of a complication may indicate abnormal pleural space anatomy or physiology (for example, intercostal varicose veins are reported in patients with end stage liver disease¹⁸). Higher complication rate following a prior complication may indicate worsening downstream effects of liver failure, hypoalbuminemia resulting in hypotension and

rapid flux of fluid through the diaphragm, worsening coagulopathy, and scar tissue formation at the site of prior puncture site, resulting in future procedural complexities. In multivariate analysis, overall complication rate remained significantly higher in the HH group. MELD score and platelet count were independent predictors of hemothorax. The role of transfusion was not evaluated in this study. Whether thrombocytopenia is a marker of bone marrow dysfunction and poor health state or the primary cause of hemothorax is not known.

In this study, univariate analysis showed that among the HH group, total complications (but not REPE alone) were more likely to occur following a larger volume thoracentesis ($P=0.0412$, table 3). A study by Feller-Kopman and colleagues noted that large volume thoracentesis was not associated with REPE.¹⁹ Additional trials are required to further investigate this question.

The results of this study highlight the risks and safety of thoracentesis in pleural effusion management in HH. This is particularly important when patients are poor candidates for TIPS and/or are awaiting liver transplant evaluation.²⁰⁻²⁵ Chest tube drains are shown to carry a high complication rate with electrolyte imbalance, renal failure, infection and death²⁶⁻²⁸. In a prospective study of 24 patient with HH, Chen et al²⁹, has shown that the use of indwelling pleural catheters (IPC) with a regimented drainage schedule of 1 liter fluid removal on every other day bases may be a feasible and safe approach. Although IPCs are often used in the management and palliation of malignant pleural effusion³⁰⁻³², a growing body of literature proves their utility and safety in benign pleural effusions^{29,33-35}. This is however paired with an overall higher complication rate and lower spontaneous pleurodesis rate in the HH population receiving IPC compared to malignant pleural effusion.^{29,36} This study shows that repeat thoracentesis is an overall low-risk procedure in both HH and non-HH population. However, when repeat thoracentesis is clinically required in the HH population, we suggest that particular attention be paid to the history of prior complications, severity of liver disease and presence of thrombocytopenia.

There are a number of limitations in our study. Firstly, this is a single-center retrospective design lending itself to the possibility of missing or inaccurate data. We have a dedicated policy in place to stop anticoagulation, where patients are allowed to continue Aspirin, whereas other anticoagulants are ceased according to half-life and pharmacokinetics. In this study, we did not specifically review every case to assess the length of time that anticoagulation was discontinued in those receiving such medications, accepting that the policy as above was operational. Additionally, due to few overall complications in the cohort, model building was limited to a small number of variables per model. The results of this study will need to be evaluated and confirmed in a larger prospective design.

This study does not assess the efficacy of repeat thoracentesis in symptom management. Large scale and prospective randomized trials are needed to fully evaluate safety and assess quality of life, using repeat thoracentesis compared with other modes of management.

Conclusion: Repeat thoracentesis is an overall low-risk procedure in HH and non-HH population but the safety profile is lower in the HH group. Cirrhotic patients with refractory

hepatic hydrothorax with a history of a previous thoracentesis complication have a significantly higher risk of developing future thoracentesis complications. Hemothorax risk is increased with higher MELD score and thrombocytopenia in HH. We recommend meticulous study of the patients' physical and clinical state to reconsider the indications of thoracentesis, in patients with a thoracentesis complication history. Candidacy for alternative methods such as TIPS, and transplantation should be reexamined when possible. Other modes of management such as IPC placement in this patient population are under investigation and should be compared with repeat thoracentesis in refractory HH management. Additional studies are required to evaluate the efficacy of repeat thoracentesis in symptom management and palliation in HH.

REFERENCES

1. Kinasewitz GT, Keddissi JI. Hepatic hydrothorax. *Curr Opin Pulm Med*. 2003;9(4):261-265.
2. Light RW, Macgregor MI, Luchsinger PC, Ball WC, Jr. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med*. 1972;77(4):507-513.
3. Romero S, Candela A, Martin C, Hernandez L, Trigo C, Gil J. Evaluation of different criteria for the separation of pleural transudates from exudates. *Chest*. 1993;104(2):399-404. doi: S0012-3692(16)35348-X [pii].
4. Giacobbe A, Facciorusso D, Barbano F, Andriulli A, Frusciante V. Hepatic hydrothorax. Diagnosis and management. *Clin Nucl Med*. 1996;21(1):56-60.
5. Lieberman FL, Peters RL. Cirrhotic hydrothorax. Further evidence that an acquired diaphragmatic defect is at fault. *Arch Intern Med*. 1970;125(1):114-117.
6. Singh A, Bajwa A, Shujaat A. Evidence-based review of the management of hepatic hydrothorax. *Respiration*. 2013;86(2):155-173. doi: 10.1159/000346996 [doi].

7. Sese E, Xiol X, Castellote J, Rodriguez-Farinas E, Tremosa G. Low complement levels and opsonic activity in hepatic hydrothorax: its relationship with spontaneous bacterial empyema. *J Clin Gastroenterol*. 2003;36(1):75-77.
8. Borchardt J, Smirnov A, Metchnik L, Malnick S. Treating hepatic hydrothorax. *BMJ*. 2003;326(7392):751-752. doi: 10.1136/bmj.326.7392.751 [doi].
9. Gordon CE, Feller-Kopman D, Balk EM, Smetana GW. Pneumothorax following thoracentesis: a systematic review and meta-analysis. *Arch Intern Med*. 2010;170(4):332-339. doi: 10.1001/archinternmed.2009.548 [doi].
10. Grogan DR, Irwin RS, Channick R, et al. Complications associated with thoracentesis. A prospective, randomized study comparing three different methods. *Arch Intern Med*. 1990;150(4):873-877.
11. Ault MJ, Rosen BT, Scher J, Feinglass J, Barsuk JH. Thoracentesis outcomes: a 12-year experience. *Thorax*. 2015;70(2):127-132. doi: 10.1136/thoraxjnl-2014-206114 [doi].
12. Castellote J, Xiol X, Cortes-Beut R, Tremosa G, Rodriguez E, Vazquez S. Complications of thoracentesis in cirrhotic patients with pleural effusion. *Rev Esp Enferm Dig*. 2001;93(9):566-575.
13. Feller-Kopman D, Walkey A, Berkowitz D, Ernst A. The relationship of pleural pressure to symptom development during therapeutic thoracentesis. *Chest*. 2006;129(6):1556-1560. doi: S0012-3692(15)50759-9 [pii].
14. Shojaee S, Argento AC. Ultrasound-guided pleural access. *Semin Respir Crit Care Med*. 2014;35(6):693-705. doi: 10.1055/s-0034-1395794 [doi].

15. Rahman NM, Singanayagam A, Davies HE, et al. Diagnostic accuracy, safety and utilisation of respiratory physician-delivered thoracic ultrasound. *Thorax*. 2010;65(5):449-453. doi: 10.1136/thx.2009.128496 [doi].
16. Bass J, White DA. Thoracentesis in patients with hematologic malignancy: yield and safety. *Chest*. 2005;127(6):2101-2105. doi: S0012-3692(15)49815-0 [pii].
17. Wilcox ME, Chong CA, Stanbrook MB, Tricco AC, Wong C, Straus SE. Does this patient have an exudative pleural effusion? The Rational Clinical Examination systematic review. *JAMA*. 2014;311(23):2422-2431. doi: 10.1001/jama.2014.5552 [doi].
18. Casoni GL, Gurioli C, Corso R, Gurioli C, Poletti V. Hemothorax by intercostal varicose veins in alcoholic liver cirrhosis. *Respiration*. 2010;80(1):71-72. doi: 10.1159/000233446 [doi].
19. Feller-Kopman D, Berkowitz D, Boiselle P, Ernst A. Large-volume thoracentesis and the risk of reexpansion pulmonary edema. *Ann Thorac Surg*. 2007;84(5):1656-1661. doi: S0003-4975(07)01344-6 [pii].
20. Dhanasekaran R, West JK, Gonzales PC, et al. Transjugular intrahepatic portosystemic shunt for symptomatic refractory hepatic hydrothorax in patients with cirrhosis. *Am J Gastroenterol*. 2010;105(3):635-641. doi: 10.1038/ajg.2009.634 [doi].
21. Siegerstetter V, Deibert P, Ochs A, Olschewski M, Blum HE, Rossle M. Treatment of refractory hepatic hydrothorax with transjugular intrahepatic portosystemic shunt: long-term results in 40 patients. *Eur J Gastroenterol Hepatol*. 2001;13(5):529-534.

22. Spencer EB, Cohen DT, Darcy MD. Safety and efficacy of transjugular intrahepatic portosystemic shunt creation for the treatment of hepatic hydrothorax. *J Vasc Interv Radiol*. 2002;13(4):385-390.
23. Everhart JE, Lombardero M, Detre KM, et al. Increased waiting time for liver transplantation results in higher mortality. *Transplantation*. 1997;64(9):1300-1306.
24. Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Transplantation*. 1998;66(7):956-962.
25. Cardenas A, Kelleher T, Chopra S. Review article: hepatic hydrothorax. *Aliment Pharmacol Ther*. 2004;20(3):271-279. doi: 10.1111/j.1365-2036.2004.02081.x [doi].
26. Liu LU, Haddadin HA, Bodian CA, et al. Outcome analysis of cirrhotic patients undergoing chest tube placement. *Chest*. 2004;126(1):142-148. doi: 10.1378/chest.126.1.142 [doi].
27. Runyon BA, Greenblatt M, Ming RH. Hepatic hydrothorax is a relative contraindication to chest tube insertion. *Am J Gastroenterol*. 1986;81(7):566-567.
28. Orman ES, Lok AS. Outcomes of patients with chest tube insertion for hepatic hydrothorax. *Hepatol Int*. 2009;3(4):582-586. doi: 10.1007/s12072-009-9136-z [doi].
29. Chen A, Massoni J, Jung D, Crippin J. Indwelling Tunneled Pleural Catheters for the Management of Hepatic Hydrothorax. A Pilot Study. *Ann Am Thorac Soc*. 2016;13(6):862-866. doi: 10.1513/AnnalsATS.201510-688BC [doi].

30. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA*. 2012;307(22):2383-2389. doi: 10.1001/jama.2012.5535 [doi].
31. Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. *Chest*. 2006;129(2):362-368. doi: S0012-3692(15)38758-4 [pii].
32. Koegelenberg CF, Vorster MJ. Chemical Pleurodesis for Malignant Pleural Effusion: How Far Have We Come in 80 Years?. *Respiration*. 2015;90(5):355-356. doi: 10.1159/000441308 [doi].
33. Freeman RK, Herrera A, Ascoti AJ, Dake M, Mahidhara RS. A propensity-matched comparison of cost and outcomes after esophageal stent placement or primary surgical repair for iatrogenic esophageal perforation. *J Thorac Cardiovasc Surg*. 2015;149(6):1550-1555. doi: 10.1016/j.jtcvs.2015.01.066 [doi].
34. Majid A, Kheir F, Fashjian M, et al. Tunneled Pleural Catheter Placement with and without Talc Poudrage for Treatment of Pleural Effusions Due to Congestive Heart Failure. *Ann Am Thorac Soc*. 2016;13(2):212-216. doi: 10.1513/AnnalsATS.201507-471BC [doi].
35. Mercky P, Sakr L, Heyries L, Lagrange X, Sahel J, Dutau H. Use of a tunnelled pleural catheter for the management of refractory hepatic hydrothorax: a new therapeutic option. *Respiration*. 2010;80(4):348-352. doi: 10.1159/000282493 [doi].
36. Bhatnagar R, Reid ED, Corcoran JP, et al. Indwelling pleural catheters for non-malignant effusions: a multicentre review of practice. *Thorax*. 2014;69(10):959-961. doi: 10.1136/thoraxjnl-2013-204563 [doi].