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Early View

Original article

Complications following symptom limited thoracentesis using suction

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Key Words: re-expansion pulmonary edema, thoracentesis, complications, pneumothorax, suction, cancer

ABSTRACT

Background: Thoracentesis using suction is perceived to have increased risk of complications including pneumothorax and re-expansion pulmonary edema (REPE). Current guidelines recommend limiting drainage to 1.5 L to avoid REPE. Our purpose was to examine the incidence of complications with symptom limited drainage of pleural fluid using suction and identify risk factors for REPE.

Methods: A retrospective cohort study of all adult patients who underwent symptom limited thoracentesis using suction at our institution between 1/1/2004 and 8/31/2018 was performed, and a total of 10344 thoracenteses were included.

Results: Pleural fluid $\geq$1.5 L was removed in 19% of the procedures. Thoracentesis was stopped due to chest discomfort (39%), complete drainage of fluid (37%), and persistent cough (13%). Pneumothorax based on chest radiograph was detected in 3.98%, but only 0.28% required intervention. The incidence of REPE was 0.08%. The incidence of REPE increased with Eastern Cooperative Oncology Group performance status (ECOG) $\geq$3 compounded with $\geq$1.5 L (0.04 to 0.54%, 95% CI 0.13-2.06). Thoracentesis in those with ipsilateral mediastinal shift did not increase complications, but less fluid was removed ($p<0.01$).

Conclusions: Symptom limited thoracentesis using suction is safe even with large volumes. Pneumothorax requiring intervention and REPE are both rare. There were no increased procedural complications in those with ipsilateral mediastinal shift. REPE increased with poor performance status and drainage $\geq$1.5 L. Symptom limited drainage using suction without pleural manometry is safe.

INTRODUCTION

Thoracentesis is a common pleural intervention used to relieve respiratory symptoms and to assist with diagnosis. However, complications such as pneumothorax and re-expansion pulmonary edema (REPE) increase morbidity, health care costs, and hospital lengths of stay.[1-3] In an effort to minimize adverse events, avoidance of suction for drainage, limitation of volume removed and pleural manometry have all been proposed, but supporting evidence for these recommendations is sparse.[4-8] Interestingly, most of the published literature on thoracentesis includes manual aspiration of pleural fluid. A recent study suggests the overall complication rate with suction drainage may be higher, but the small sample size limits the interpretation of these results.[9] Standard guidelines recommend limiting drainage to less than 1.5 L to minimize the risk of REPE.[10] However, the pathophysiology of REPE, its true etiology and risk factors remains elusive.[1,11] Pleural manometry has also been proposed as an adjunctive tool to minimize complications, but its use is time consuming, requires additional setup, does not alter procedure related chest discomfort, and is not widely adopted.[12-14]

Arbitrary limitations including the 1.5 L removal and avoidance of suction drainage creates constraints for the proceduralist. For example in those with large effusions, restricting the amount of fluid removal may not adequately relieve symptoms, require additional interventions, or result in suboptimal evaluation of unexpandable lung after the procedure.

Similarly, for patients that present with pleural effusions with ipsilateral mediastinal shift, recommendations have been made advising against drainage of more than 300 mL of fluid without pleural manometry.[7] Interestingly, none of the studies supporting these recommendations have taken into account the amount drained in relation to the size of the chest cavity. Since predictive equations of total lung capacity directly correlate with an individual's height, the mechanical effects of draining a fixed amount of pleural fluid vary between individuals of different heights.[15-17] Thus, our purpose was to examine the incidence of thoracentesis related complications, including pneumothorax and REPE, in patients

undergoing symptom limited suction drainage. A secondary aim was to identify risk factors associated with REPE.

MATERIALS AND METHODS

Subjects. This is a retrospective cohort study of all thoracenteses in adult patients by the pulmonary department between January 1, 2004 and August 31, 2018. Patients without post-procedure chest imaging within 48 hours after thoracentesis were excluded. The study protocol (DR09-0666) was approved by our Institutional Review Board. The procedures were identified with ICD-9 codes. All procedures were assessed for 7 days after intervention, and those without adequate information were excluded.

Data Collection. Data collected from the electronic medical record at the time of the procedure included the following: demographics; cancer diagnosis; size of effusion estimated by chest radiograph prior to the thoracentesis (very small effusion only visible on lateral decubitus film, small effusion blunting the costophrenic angle, moderate effusion extending from the costophrenic angle to below the hilum, large effusion extending above the hilum and complete opacification of the hemithorax); radiographic position of the mediastinum in relation to pleural effusion before thoracentesis (ipsilaterally deviated, contralaterally deviated or central); volume of fluid removed; Eastern Cooperative Oncology Group performance status (ECOG) was either extracted or inferred from clinical records; any reported finding suggestive of a complication on imaging or in the medical record.

In order to normalize the fluid drained to the chest cavity size, the predicted ipsilateral lung capacity was used as a surrogate with height (H) at the time of the thoracentesis. This was calculated using the following equations: total lung capacity=7.99 x H-7.08 for men; total lung capacity=6.60 x H-5.79 for women.[18] Based on prior studies, the right lung has been estimated as accounting for 52.5% of the total

lung capacity.[19] Thus, the ipsilateral lung capacity was estimated by multiplying the estimated total lung capacity by 0.525 for right pleural effusions and by 0.475 for left pleural effusions.

Procedures. All patients in our department undergo thoracentesis in a uniform fashion. All procedures included in the study were performed by a pulmonary faculty or fellow. Each procedure was either performed in our dedicated suite or at the bedside, and post-procedure chest radiograph was obtained immediately after. As per our departmental guidelines, all procedures were performed using sterile technique, ultrasound guidance, local anesthesia and symptom limited drainage. A thoracentesis safety needle was used to introduce an 8 French catheter into the pleural space, and it was then connected to a 1 L vacuum bottle (before May 2009) or to a 2 L plastic canister attached to wall suction on the maximum setting (May 2009 and after). The 1 L vacuum bottle generates a suction pressure of -590 mmHg (-802 cmH_2O).[20] The maximal pressure generated by the wall suction was -527 mmHg (-716 cmH_2O). We found that the average negative pressure generated from the wall suction in our institution was -482.6mmHg (-656 cmH20). Although time was not measured in our study, thoracentesis using active aspiration decreases procedure time when compared to gravity drainage.[21] Drainage was stopped after complete drainage of the pleural space or if the patient developed symptoms including chest pain/discomfort or persistent cough. After thoracentesis, our routine *modus operandi* was to contact the patient within 3 business days to discuss results, evaluate complications and either to schedule a definitive pleural intervention or arrange further diagnostic workup for both outpatients and inpatients. Independent of our efforts, the primary services were also in contact with the patient, and all interactions were in the electronic medical record.

Definitions. Pneumothorax was documented as a complication if absent within 7 days prior to the procedure. Patients without imaging were assumed not to have a pneumothorax. Unexpandable lung (pneumothorax ex vacuo) was also included as pneumothorax. Although ultrasound is a useful tool in detecting pneumothorax, chest radiograph was used to detect pneumothorax and to evaluate lung

expansion.[22] The diagnosis of REPE required: 1) acute clinical decompensation (respiratory and/or cardiovascular, including new or worsening dyspnea, additional oxygen supplementation, cough, hypotension, cardiovascular collapse); 2) diagnostic image with findings compatible with REPE; 3) within a 48 hour time period following thoracentesis. Radiographic findings consistent with REPE included interstitial or alveolar infiltrates in regions previously obscured by the effusion. All suspect cases for REPE were independently reviewed by a panel of 3 experts, and they were specifically asked to confirm or exclude REPE. A concordance between 2 out of 3 experts was used. Hemothorax was defined as a pleural fluid hematocrit $\geq$50% of serum hematocrit. Incomplete information refers to patients who lacked adequate follow up or key data points (i.e. amount of fluid drained, no ECOG performance status) and to patients who pursued care elsewhere.

Statistical Analysis. The primary outcome was the incidence of pneumothorax and REPE following symptom limited thoracentesis using suction. Secondary outcomes were: 1) incidence of other complications (bleeding, hemothorax, death); 2) associations between REPE and the absolute amount of fluid drained, amount of fluid drained normalized by the predicted ipsilateral chest cavity size (V/LC), the patient's ECOG and the radiographic position of the mediastinum prior to thoracentesis.

We used descriptive statistics to summarize the patients' characteristics. Kappa coefficient was used to measure inter-rater agreement for the diagnosis of REPE. The proportions of positive and negative agreement were reported, particularly since the prevalence of the event affects the value of kappa (low prevalence of the main outcome will decrease the value of kappa as the proportion of agreement by chance will increase, known as the kappa paradox).[23,24] Wilcoxon rank sum test with a two-tale alpha level of 0.05 was used to compare the incidence of REPE on continuous variables with skewed distributions. Odds ratios were estimated using logistic regression. We postulated a logistic model represented the hypothetical relationship between the probability of REPE and volume drained, and then volume normalized by the predicted lung capacity of the affected hemithorax (V/LC). Tables and plots

were generated in order to select cutoff points for both continuous variables. A p-value of 0.05 or less was considered significant. Ninety-five percent confidence intervals (CI) were reported when appropriate. Statistical software used was Stata® version 15.1 (College Station, Texas). Study data were collected and managed using REDCap (Research Electronic Data Capture).[25]

RESULTS

A total of 11,074 procedures were screened for eligibility, and 730 did not meet criteria (296 with incomplete information, 276 performed by another department, 112 without post-procedure imaging, 18 procedures were cancelled, 22 had a different procedure, 6 duplicate entries). Our final cohort included 7,206 patients that underwent 10,344 thoracenteses.

Patient demographics and clinical characteristic are shown on Table 1. The etiology of non-malignant effusions included volume overload, paramalignant or parapneumonic. Figure 1 displays the distribution of pleural fluid drained during each procedure. Large volumes of fluid ($\geq$1.5 L) were removed in 19.4%. Table 2 provides reasons for discontinuation of drainage and complications. The vast majority of the procedures were symptom limited; however, a few (4%) listed as "Other" included those with vasovagal episodes, dry taps, loculated effusions resulting in minimal drainage, and patient discomfort/pain unrelated to the procedure. In those terminated due to physician discretion, they were either small effusions, a diagnostic procedure or the fluid was left to allow for definitive pleural intervention. The incidence of pneumothorax was 3.98%, but only 0.28% required intervention. Malignant pleural effusion in breast (OR 1.65, 95% CI 1.21-2.23) and lung (OR 1.57, 95% CI 1.19-2.07) cancer were associated with a higher risk of pneumothorax when compared to non-malignant pleural effusion. Mortality from thoracentesis was 0.03%, and 3 patients (2 from REPE, 1 hemothorax) died as a direct result of the

procedure. The patient that died from a hemothorax had advanced cancer and was treated with comfort measures only.

Re-expansion pulmonary edema (REPE)

A total of 126 cases were suspected to have REPE based on radiographic or clinical information. REPE was confirmed (Table 3) in only 8 patients (0.08%). Kappa coefficient was 0.73 for the diagnosis of REPE, with a proportion of positive agreement of 0.75. In the remaining 118 cases which were not REPE, 7 were initially identified due to acute decompensation, and 111 due to radiographic findings. In these 118 cases, 2/3 concordance was present in 3 cases, and 3/3 concordance was present in the remaining 115. The proportion of negative agreement was 0.98. Two of the 8 patients died within 9 days of the procedure from REPE (25% mortality). One additional patient with REPE expired due to cardiac comorbidities. All patients with REPE received supportive care (Table 3).

Seventy-five patients with dry taps were excluded from the statistical analyses for REPE (Tables 4 and 5). Volume of pleural fluid drained, V/LC and ECOG 3 or 4, were associated with increased risk of REPE. Using tables and plots of probability of REPE generated from the logistic regressions of volume drained and V/LC, 1.5 L, 2 L, 0.6, 0.7 and 0.8 were selected as cutoff points for volume drained and V/LC respectively (Figure 2). Table 6 shows the risk of REPE using these cutoff points for the entire cohort and for patients with ECOG 3 or 4. The incidence of REPE increases to 0.30% (95% CI 0.05-1.23) when draining $\geq$1.5 L and to 0.61% (95% CI 0.15-2.35) when draining $\geq$2 L. In patients with ECOG 3 or 4, the incidence of REPE increased to 0.54% when draining $\geq$1.5 L (95% CI 0.13-2.06) and to 1.29% (95% CI 0.31-5.53) when draining $\geq$2 L.

Position of the mediastinum

Table 7 elucidates procedure information in those with and without ipsilateral deviation of the mediastinum. The majority of REPE (7 out of 8) had no shift in mediastinal structures before the

procedure. One case of REPE had a contralateral mediastinal deviation due to prior radiation therapy. Patients who had an ipsilateral shift in the mediastinum had less volume drained when compared to patients with central and contralateral mediastinal shift (median 850 ml vs. 1000ml, $p<0.01$). In patients with pre-procedure ipsilateral deviation of the mediastinum, there was no increase in the incidence of post-procedure pneumothorax (40 vs. 372, $p=0.18$) or pneumothorax requiring intervention (2 vs. 27, $p=1.00$).

DISCUSSION

Symptom limited suction drainage of pleural fluid is a safe intervention, and there is a low risk of complications even in those with large volumes drained. Our data suggests the incidence of pneumothorax was less than 4%, and only 0.28% required an intervention. The incidence of REPE was 0.08%, and in patients with drainage of 2 L or more, the highest estimated probability was 2.35%. However, patients with poor performance status had a significantly increased risk of REPE with removal of $\geq$1.5 L. As expected, the amount of pleural fluid drained was smaller when ipsilateral mediastinal shift was present but there was no increase in adverse events. In our cohort, mortality related to thoracentesis was 0.03%, but a quarter of those with REPE expired within 9 days after the procedure. Our results represent the largest study to date for symptom limited thoracentesis using suction.

Similar to other studies, we report a low incidence of complications, but differences in procedural aspects and methodology exist. The largest published study included 9,320 thoracentesis performed via manual aspiration.[1] There were 0.61% iatrogenic pneumothoraces, 0.10% REPE and 0.18% bleeding episodes. Iatrogenic pneumothorax was associated with removal of >1.5 L fluid ($p<0.01$), unilateral procedures ($p=0.01$) and more than one needle pass through the skin ($p=0.03$). Of note, chest radiograph was not routinely ordered after the procedure, so asymptomatic pneumothoraces were likely missed. Use of suction drainage has been suggested to increase the risk of pneumothorax. In a separate study (278

thoracenteses), the authors reported an odds ratio of 4.6 for pneumothorax in those with vacuum drainage compared to manual aspiration. However, their overall pneumothorax complication rate was high (6.5%) and potentially could have included cases with unexpandable lung.[26] A more recent study evaluated 100 patients that were randomized to manual aspiration or vacuum drainage.[9] These investigators reported a higher complication rate in the vacuum group (5 vs 0; p=0.03) with 3 cases of pneumothorax, 1 case with hemothorax and 1 case with REPE. Their small sample size precludes confirmation that suction was the culprit. In our study, the incidence of pneumothorax detected radiographically was 3.98% (412 cases). In a prior study with ultrasound guided thoracentesis and post-procedure radiographs, the investigators reported a pneumothorax rate of 5.4% with 0.78% requiring additional intervention.[27] Since many other studies do not use ultrasound guidance or standard post-procedure radiograph, our incidence of pneumothorax and need for intervention are similar if not lower compared to other studies. In addition, our cohort of cancer patients likely has an overall increased incidence of unexpandable lung.[28-30]

REPE is a rare but potentially fatal complication, and symptoms typically occur 24 to 48 hours after the pleural intervention.[31] Findings on a plain radiograph are not pathognomonic, and the differential diagnosis includes atelectasis, pneumonia and malignancy. Correlation with the clinical scenario is paramount. Potential rationales for REPE include the application of negative pressure during drainage, airway obstruction, chronicity of the lung collapse, loss of surfactant, pleural pressure below -20 cm H_20, and increased airway permeability.[4,32]

A retrospective study which examined the incidence of REPE in 185 patients undergoing large volume ($\geq$1 L) thoracentesis reported 1 case of clinical REPE and 4 cases of radiographic REPE.[11] Criteria for REPE required at least 2 of the following: worsening dyspnea, hypoxia, cough lasting more than 20 minutes, tachypnea, and hemodynamic instability. Unfortunately, post-procedure chest radiograph was not routinely performed. All 4 cases of radiographic REPE had symptomatic improvement after fluid drainage despite the radiographic findings, so the association of radiographic changes and the diagnosis of

REPE are suspect. Another study with 941 thoracentesis (>1 L) estimated an incidence of REPE of 0.5% (2 out of 373 cases). However, modality of drainage and the criteria to diagnose REPE were unclear.[33] In our cohort, the incidence of REPE was 0.08%, patients with REPE had both clinical and radiographic changes, and the diagnosis was confirmed by our expert panel. All our cases used suction for drainage, and our cohort had a significant number (2,009) of large volume ($\geq$1.5 L) procedures. In addition, the majority of our thoracenteses were symptom limited and meticulously reviewed for complications 7 days after the procedure; thus, it appears unlikely that the use of suction increases the incidence of REPE. Some have suggested that the risk of REPE increases by 0.18% for every 1 ml of fluid removed while other authors did not find a relationship between the volume drained and REPE.[1,11] To the contrary, our analysis highlights a logistic risk model in Figure 2A. Although the curve never reaches a risk of 1.0, the risk for REPE slowly ascends as the volume removed increases, thus the relationship is likely dose dependent (as seen in many biological models) and not linear. The risk of REPE compounds with higher ECOG scores and larger volumes drained (Table 6), and we postulate this is multifactorial reflecting poor overall health condition. We also explored the association of REPE and the volume drained in relationship to the size of the ipsilateral hemithorax. As expected, the risk of REPE increases with higher V/LC. Finally, pre-procedure ipsilateral mediastinal shift yields removal of less fluid, but does not increase the risk of REPE. Thus, REPE is a rare but serious complication, and those with the highest risk include patients with poor performance status (ECOG 3 or 4), combined with volume drained $\geq$1.5 L or V/LC $\geq$0.6.

Evidence for the use of pleural manometry during large volume thoracenteses is limited, and only one of the recent clinical practice guidelines recommends its use.[34] Pleural manometry can be time consuming, labor intensive and potentially costly. Also, as seen with the adoption of other technologies, unexpected harm can occur with widespread but poor implementation and inadequate interpretation of the data.[35] Another publication also found a close correlation between the development of chest discomfort during

drainage and drop in pleural pressures estimated by manometry, suggesting that chest discomfort was a valuable surrogate to pleural manometry.[14] Our study supports that symptom limited drainage is safe with a lower incidence of REPE than previously reported with pleural manometry.[11] In addition, a recent multicenter study comparing active aspiration and gravity drainage concluded that both methods are safe.[21] At our institution, all thoracentesis patients are monitored with telemetry, and fluid is removed with suction. The procedure is stopped after the development of chest discomfort or persistent cough independent of the amount of fluid drained. Post-procedure imaging is routinely obtained. Given our results, we believe that performance of symptom limited thoracentesis is safe, and that pleural manometry has no additive clinical benefit.

The limitations of our study are those inherent to any retrospective study. Our study was performed in a specialized cancer center, and whether our results are generalizable might be subject to debate. Our findings may not be extrapolated to intubated or sedated patients, for whom symptoms cannot be assessed. We were also unable to quantify the degree of chest discomfort/pain as well as the duration of cough before drainage was stopped. Although lung capacity may closely correlate with chest cavity size, it might not be a perfect surrogate. The chest cavity size may increase with pleural fluid accumulation due to the loss of the chest wall recoil, the displacement of the diaphragm caudally, and the contralateral shifting of the mediastinum. The potential for bias in our study is minimal. We used radiographic and laboratory data that were not influenced by personnel conducting the research, and for our primary outcomes, sufficient information was available from the medical record. Incomplete information was noted in a very small percentage of our cohort, and we believe this data is missing completely at random. Our study is unique as it closely resembles how thoracentesis is performed in the community setting. To our knowledge, this is the largest cohort to date examining the complications of symptom limited thoracentesis with suction drainage using both clinical and radiographic assessments.

In conclusion, symptom limited thoracentesis with suction drainage may be performed safely without an increased risk of complications. Both pneumothorax requiring intervention and REPE are rare. In those with ipsilateral mediastinal shift, there was no increase in complications, but the volume extracted was less. Risk factors for REPE included poor performance status compounded with volume drainage of $\geq$1.5 L and V/LC $\geq$0.6. Our study establishes that restriction of drainage based on volume is not warranted, but we recommend exercising caution when removing large volumes in those with poor performance status. Symptom limited suction drainage should be integrated into daily practice and guidelines for thoracentesis.

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Figure Legends

Figure 1. Distribution of pleural fluid volume drained during thoracentesis

Figure 2. Probability of re-expansion pulmonary edema by volume drained (A) and by volume drained normalized by the ipsilateral chest cavity size (V/LC) (B)

Table Legends

Table 1. Demographics and clinical characteristics for all thoracenteses

Table 2. Reason to stop pleural fluid drainage and complications post-thoracentesis (n=10,344)

Table 3. Summary of re-expansion pulmonary edema (REPE) cases (n=8)

Table 4. Analysis of continuous variables for re-expansion pulmonary edema (REPE)

Table 5. Univariate logistic regression analysis for re-expansion pulmonary edema (REPE)

Table 6. Probabilities of re-expansion pulmonary edema (REPE)

Table 7. Volume of pleural fluid drained and complications of patients with and without ipsilateral deviation of the mediastinum (n=10,344)

References

1. Ault MJ, Rosen BT, Scher J, Feinglass J, Barsuk JH. Thoracentesis outcomes: a 12-year experience. *Thorax*. 2015;70(2):127-132.
2. 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.
3. Mercaldi CJ, Lanes SF. Ultrasound guidance decreases complications and improves the cost of care among patients undergoing thoracentesis and paracentesis. *Chest*. 2013;143(2):532-538.
4. Light RW, Jenkinson SG, Minh VD, George RB. Observations on pleural fluid pressures as fluid is withdrawn during thoracentesis. *Am Rev Respir Dis*. 1980;121(5):799-804.
5. Villena V, Lopez-Encuentra A, Pozo F, De-Pablo A, Martin-Escribano P. Measurement of pleural pressure during therapeutic thoracentesis. *Am J Respir Crit Care Med*. 2000;162(4 Pt 1):1534-1538.
6. Lan RS, Lo SK, Chuang ML, Yang CT, Tsao TC, Lee CH. Elastance of the pleural space: a predictor for the outcome of pleurodesis in patients with malignant pleural effusion. *Ann Intern Med*. 1997;126(10):768-774.
7. Antony VB, Loddenkemper R, Astoul P, et al. Management of malignant pleural effusions. *Eur Respir J*. 2001;18(2):402-419.
8. Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(7):839-849.
9. Senitko M, Ray AS, Murphy TE, et al. Safety and Tolerability of Vacuum Versus Manual Drainage During Thoracentesis: A Randomized Trial. *J Bronchology Interv Pulmonol*. 2019;26(3):166-171.
10. Havelock T, Teoh R, Laws D, Gleeson F. Pleural procedures and thoracic ultrasound: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*. 2010;65 Suppl 2:ii61-76.

11. 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.

12. Lentz RJ, Lerner AD, Pannu JK, et al. Routine monitoring with pleural manometry during therapeutic large-volume thoracentesis to prevent pleural-pressure-related complications: a multicentre, single-blind randomised controlled trial. *Lancet Respir Med.* 2019;7(5):447-455.

13. Pannu J, DePew ZS, Mullon JJ, Daniels CE, Hagen CE, Maldonado F. Impact of pleural manometry on the development of chest discomfort during thoracentesis: a symptom-based study. *J Bronchology Interv Pulmonol.* 2014;21(4):306-313.

14. 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.

15. Cook CD, Hamann JF. Relation of lung volumes to height in healthy persons between the ages of 5 and 38 years. *J Pediatr.* 1961;59:710-714.

16. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis.* 1981;123(6):659-664.

17. Crapo RO, Morris AH, Clayton PD, Nixon CR. Lung volumes in healthy nonsmoking adults. *Bull Eur Physiopathol Respir.* 1982;18(3):419-425.

18. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. *Eur Respir J.* 1995;8(3):492-506.

19. Cheng CP, Taur AS, Lee GS, Goris ML, Feinstein JA. Relative lung perfusion distribution in normal lung scans: observations and clinical implications. *Congenit Heart Dis.* 2006;1(5):210-216.

20. Kelil T, Shyn PB, Wu LE, et al. Wall suction-assisted image-guided therapeutic paracentesis: a safe and less expensive alternative to evacuated bottles. *Abdom Radiol (NY).* 2016;41(7):1333-1337.

21. Lentz RJ, Shojaee S, Grosu HB, et al. The Impact of Gravity vs Suction-driven Therapeutic Thoracentesis on Pressure-related Complications: The GRAVITAS Multicenter Randomized Controlled Trial. *Chest.* 2020;157(3):702-711.

22. Shostak E, Brylka D, Krepp J, Pua B, Sanders A. Bedside sonography for detection of postprocedure pneumothorax. *J Ultrasound Med.* 2013;32(6):1003-1009.

23. Feinstein AR, Cicchetti DV. High agreement but low kappa: I. The problems of two paradoxes. *J Clin Epidemiol.* 1990;43(6):543-549.

24. Cicchetti DV, Feinstein AR. High agreement but low kappa: II. Resolving the paradoxes. *J Clin Epidemiol.* 1990;43(6):551-558.

25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.

26. Petersen WG, Zimmerman R. Limited utility of chest radiograph after thoracentesis. *Chest.* 2000;117(4):1038-1042.

27. Colt HG, Brewer N, Barbur E. Evaluation of patient-related and procedure-related factors contributing to pneumothorax following thoracentesis. *Chest.* 1999;116(1):134-138.

28. Huggins JT, Maldonado F, Chopra A, Rahman N, Light R. Unexpandable lung from pleural disease. *Respirology.* 2018;23(2):160-167.

29. Boland GW, Gazelle GS, Girard MJ, Mueller PR. Asymptomatic hydropneumothorax after therapeutic thoracentesis for malignant pleural effusions. *AJR Am J Roentgenol.* 1998;170(4):943-946.

30. Dresler CM, Olak J, Herndon JE, 2nd, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest.* 2005;127(3):909-915.

31. Trachiotis GD, Vricella LA, Aaron BL, Hix WR. As originally published in 1988: Reexpansion pulmonary edema. Updated in 1997. *Ann Thorac Surg.* 1997;63(4):1206-1207.

32. Mahfood S, Hix WR, Aaron BL, Blaes P, Watson DC. Reexpansion pulmonary edema. *Ann Thorac Surg.* 1988;45(3):340-345.

33. Jones PW, Moyers JP, Rogers JT, Rodriguez RM, Lee YC, Light RW. Ultrasound-guided thoracentesis: is it a safer method? *Chest.* 2003;123(2):418-423.

34. Reddy CB, DeCamp MM, Diekemper RL, et al. Summary for Clinicians: Clinical Practice Guideline for Management of Malignant Pleural Effusions. *Ann Am Thorac Soc.* 2019;16(1):17-21.

35. Connors AF, Jr., Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA.* 1996;276(11):889-897.

Table 1. Demographics and clinical characteristics for all thoracenteses (Ts)

Characteristic	All Ts n (%) n=10344^	Ts with PTX+ n=412	Ts with REPE n=8
Median age (range), years	62.0 (17-98)	62.5 (17-95)	50.5 (41-72)
Gender			
Women	5451 (53)	225 (55)	4
Men	4893 (47)	187 (45)	4
Side			
Left	4693 (45)	184 (45)	3
Right	5651 (55)	228 (55)	5
Suction method			
Vacuum bottle	2764 (27)	110 (27)	1
Wall suction	7580 (73)	302 (73)	7
Volume			
Median volume drained, mL (range)	1000 (0-5350)	1000 (0-5350)	2025 (1050-3100)
<1.5 L	8335 (81)	326 (79)	2
≥1.5 L	2009 (19)	86 (21)	6
Median V/LC (range)	0.34 (0-1.65)	0.35 (0-1.63)	0.61 (0.41-1.17)
ECOG			
0	478 (5)	17 (4)	0
1	2960 (29)	113 (27)	1
2	3154 (30)	118 (29)	1
3	3200 (31)	137 (33)	3
4	552 (5)	27 (7)	3
Cause of pleural fluid			
Breast cancer	1351 (13)	72 (18)	2
Lung cancer	1987 (19)	101 (25)	1
Hematological cancer	1397 (13)	47 (11)	1
Other solid cancer	2343 (23)	84 (20)	0
Non-malignant	3266 (32)	108 (26)	4
Size of pleural effusion			
Very small effusion	47 (1)	1 (0)	0
Small effusion	877 (8)	22 (5)	0
Moderate effusion	6917 (67)	278 (68)	4
Large effusion	1803 (17)	79 (19)	3
Complete opacification	407 (4)	17 (4)	1
No pre-procedure diagnostic image	293 (3)	15 (4)	0
Position of the mediastinum pre-thoracentesis			
Centered	7337 (71)	278 (67)	7
Ipsilaterally deviated	819 (8)	40 (10)	0
Contralaterally deviated	1895 (18)	79 (19)	1
No pre-procedure diagnostic image	293 (3)	15 (4)	0

^75 dry taps

+PTX, pneumothorax. Only 29 (0.28%) required intervention

REPE, re-expansion pulmonary edema

V/LC, volume normalized by estimated lung capacity of the affected hemithorax

ECOG, Eastern Cooperative Oncology Group performance status

Table 2. Reasons to stop pleural fluid drainage and complications for all thoracentesis (n=10,344)

Reason to stop drainage	**n (%)**
Chest discomfort/pain	4015 (39)
Complete drainage of fluid	3841 (37)
Persistent cough	1323 (13)
Not documented	768 (7)
Other^	397 (4)
Complication	
Hemothorax	2 (0.02)
Bleeding at puncture site requiring prolonged pressure	8 (0.08)
Pneumothorax	412 (3.98)
Requiring intervention	29 (0.28)
REPE	8 (0.08)
Vasovagal episode	137 (1.32)
Death	3 (0.03)
REPE	2
Hemothorax	1

^Dry tap, vasovagal episode and physician's discretion

REPE, re-expansion pulmonary edema

Table 3. Summary of re-expansion pulmonary edema (REPE) cases (n=8)*

Gender	Cancer	Pleural fluid	Side	Volume drained (mL)	V/LC	ECOG	Position of the mediastinum	Size of effusion	Reason to stop drainage	Respiratory support	Length of hospital stay after procedure	Death during admission
W	Breast cancer	Malignant	L	1350	0.64	3	Centered	Large	No more fluid	Mechanical ventilation	4	Yes
M	Laryngeal cancer	Non malignant	R	2500	0.74	1	Centered	Moderate	No more fluid	Low flow oxygen	1	No
W	Hodgkin's lymphoma	Malignant	L	2500	1.06	4	Contralateral	Moderate	No more fluid	Non-invasive ventilation	14	No
M	Lung adenocarcinoma	Malignant	R	1550	0.43	3	Centered	Complete opacification	Chest discomfort /pain	Mechanical ventilation	9	Yes
W	Multiple myeloma	Non malignant	R	1050	0.41	4	Centered	Moderate	No more fluid	High flow oxygen	38	No
M	Lung squamous cell carcinoma	Non malignant	L	1500	0.46	2	Centered	Large	Not documented	Mechanical ventilation	19	Yes^
W	Breast cancer	Malignant	R	3100	1.17	3	Centered	Moderate	Chest discomfort /pain	Low flow oxygen	11	No
M	Prostate cancer	Non malignant	R	2500	0.58	4	Centered	Large	Persistent cough	Mechanical ventilation	36	No

*All patients with REPE received supportive care including diuretics when clinically indicated
^ Patient expired due to cardiac comorbidities
W, woman; M, man; L, left; R, right
V/LC, Volume normalized by estimated lung capacity of the affected hemithorax
ECOG, Eastern Cooperative Oncology Group performance status

Table 4. Analysis of continuous variables for re-expansion pulmonary edema (REPE)^

	median	IQR	p value*
Age			
No REPE	62.00	53.00-70.00	0.24
REPE	50.50	49.50-67.00	
Volume drained			
No REPE	1000	650-1300	<0.01
REPE	2025	1425-2500	
V/LC			
No REPE	0.34	0.23-0.46	<0.01
REPE	0.61	0.44-0.90	

^REPE=8; no REPE=10261

*Wilcoxon rank-sum; IQR, interquartile range

V/LC, Volume normalized by estimated lung capacity of the affected hemithorax

Table 5. Univariate logistic regression analysis for re-expansion pulmonary edema (REPE)^

	No REPE n=10,261	Clinical REPE n=8	p value	OR (95% CI)
Median age, years	62	50.5	0.33	0.98 (0.93-1.02)
Gender				
Women	5412	4		Ref (1.00)
Men	4849	4	0.88	1.12(0.28-4.47)
Cause of pleural fluid				
Non-malignant	3236	4		Ref (1.00)
Breast cancer	1340	2	0.83	1.21 (0.22-6.60)
Lung cancer	1966	1	0.43	0.41 (0.05-3.68)
Hematological	1391	1	0.63	0.58 (0.06-5.21)
Other Solid cancer	2328	0	-	-
ECOG				
ECOG 0/1/2	6544	2		Ref (1.00)
ECOG 3/4	3717	6	0.04	5.28 (1.07-26.18)
Side				
Right	5604	5		Ref (1.00)
Left	4657	3	0.66	0.72 (0.17-3.02)
Mediastinum position				
Centered	7281	7		Ref (1.00)
Ipsilateral	810	0		-
Contralateral	1878	1	0.58	0.55 (0.07-4.50)
No image[&]	292	0		-
Size of pleural effusion				
Very small	46	0	-	Ref (1.00)
Small	869	0	-	1
Moderate	6868	4	0.20	0.23(0.03-2.10)
Large	1783	3	0.74	0.68 (0.07-6.54)
Complete opacification	403	1	-	1
No image[&]	292	0	-	1
Reason to stop				
Chest discomfort	4010	3		Ref (1.00)
Persistent cough	1321	1	0.99	1.01(0.11-9.74)
Fluid stopped	3826	3	0.95	1.05(0.21-5.20)
Other	338	0	-	-
Not documented	766	1	0.63	1.74(0.18-16.80)

Volume drained				
Volume (continues)			<0.01	1.002(1.001-1.002)
<1.5 L	8258	2		Ref (1.00)
≥1.5 L	2003	6	<0.01	12.37 (2.49-61.33)
<2 L	9607	4		Ref (1.00)
≥2 L	654	4	<0.01	14.69 (3.67-58.87)
Volume/Lung Capacity				
V/LC (continuous)			<0.01	197.56 (27.75-1406.25)
<0.6	9417	4		Ref (1.00)
≥0.6	844	4	<0.01	11.16(2.79-44.69)
<0.7	9903	5		Ref (1.00)
≥0.7	358	3	<0.01	16.60(3.95-69.72)
<0.8	10100	6		Ref (1.00)
≥0.8	161	2	<0.01	20.91(4.19-104.39)
Suction method				
Vacuum bottle	2732	1		Ref (1.00)
Wall suction	7529	7	0.38	2.54 (0.31-20-65)

^ 75 dry taps excluded

[&]No pre-procedure diagnostic image

OR, odds ratio

ECOG, Eastern Cooperative Oncology Group performance status

V/LC, volume normalized by estimated lung capacity of the affected hemithorax

Table 6. Probabilities of re-expansion pulmonary edema (REPE)

	Procedures (n=10269)		Incidence	Probability (%) 95% CI^	
	No REPE	REPE	(%)	Lower	Higher
ECOG					
<3	6544	2	0.03		
≥3	3717	6	0.16	0.03	0.78
Volume drained					
<1.5 L	8258	2	0.02		
≥1.5 L	2003	6	0.30	0.05	1.23
<2 L	9607	4	0.04		
≥2 L	654	4	0.61	0.15	2.35
V/LC					
<0.6	9417	4	0.04		
≥0.6	844	4	0.47	0.11	1.79
<0.7	9903	5	0.05		
≥0.7	358	3	0.83	0.20	3.49
<0.8	10100	6	0.06		
≥0.8	161	2	1.23	0.25	6.26
Volume drained + ECOG					
<1.5 L + ECOG<3	9522	4	0.04		
≥1.5 L + ECOG≥3	739	4	0.54	0.13	2.06
<2 L + ECOG<3	10032	5	0.05		
≥2 L + ECOG≥3	229	3	1.29	0.31	5.53
V/LC + ECOG					
<0.6 + ECOG<3	9944	5	0.05		
≥0.6 + ECOG≥3	317	3	0.94	0.22	3.96
<0.7 + ECOG<3	10128	6	0.06		
≥0.7 + ECOG≥3	133	2	1.48	0.30	7.62
<0.8 + ECOG<3	10201	6	0.06		
≥0.8 + ECOG≥3	60	2	3.23	0.67	17.19

^Using odds ratios of univariate analyses.

ECOG, Eastern Cooperative Oncology Group performance status

V/LC, Volume normalized by estimated lung capacity of the affected hemithorax

Table 7. Volume of pleural fluid drained and complications of patients with and without ipsilateral deviation of the mediastinum (n=10,344)

	Position of Mediastinum		**p value**
	Ipsilateral deviation (n=819)	**Other positions (n=9525)**	
Pneumothorax	40	372	0.16*
Requiring chest tube	2	27	1.00*
Volume drained, median (IQR)	850 (550-1200)	1000 (650-1300)	<0.01[+]
Vasovagal episodes	10	127	1.00*
REPE	0	8	1.00*

*Fisher's exact, [+]Wilcoxon rank-sum, IQR, interquartile range
REPE, re-expansion pulmonary edema

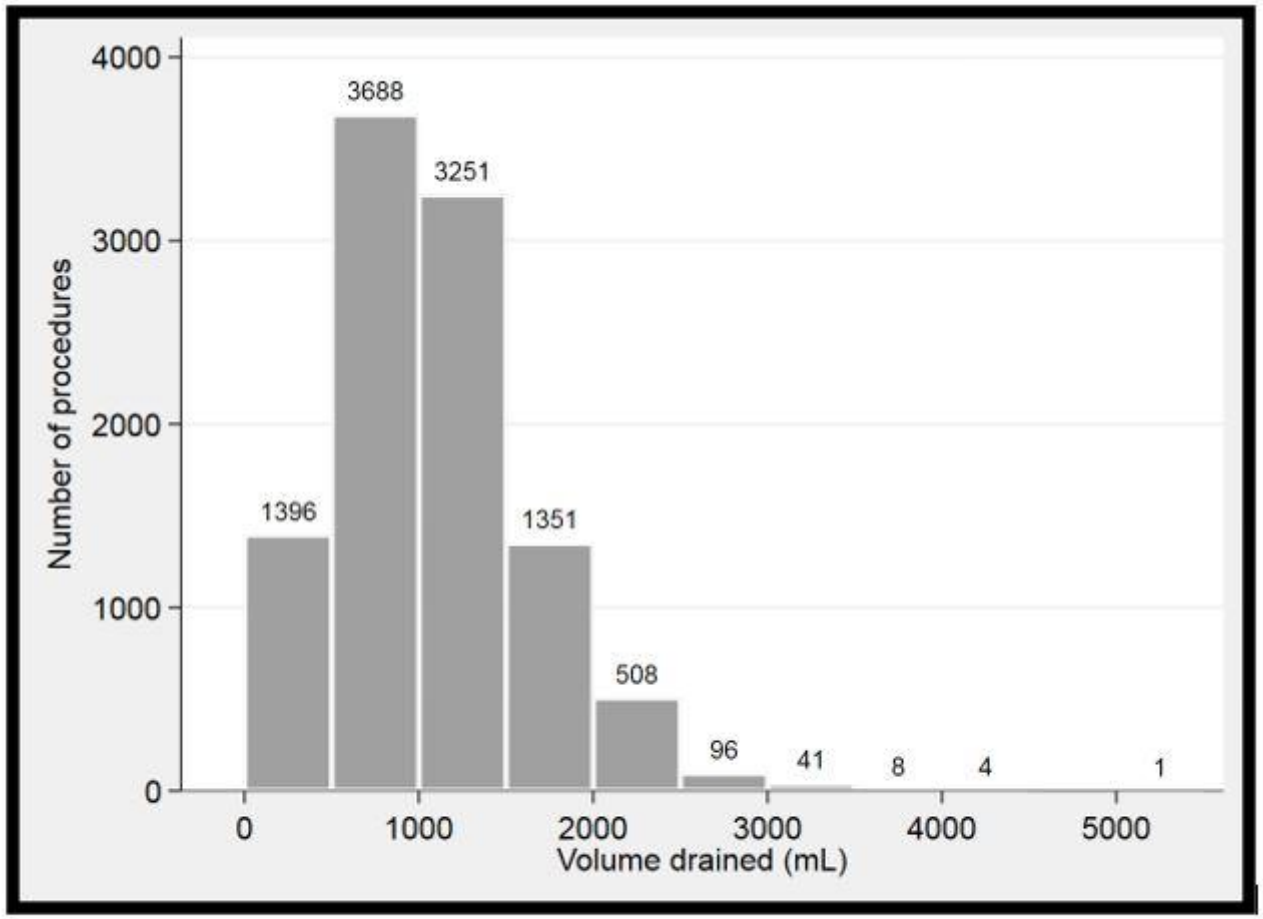

Figure 1. Distribution of pleural fluid volume drained during thoracentesis

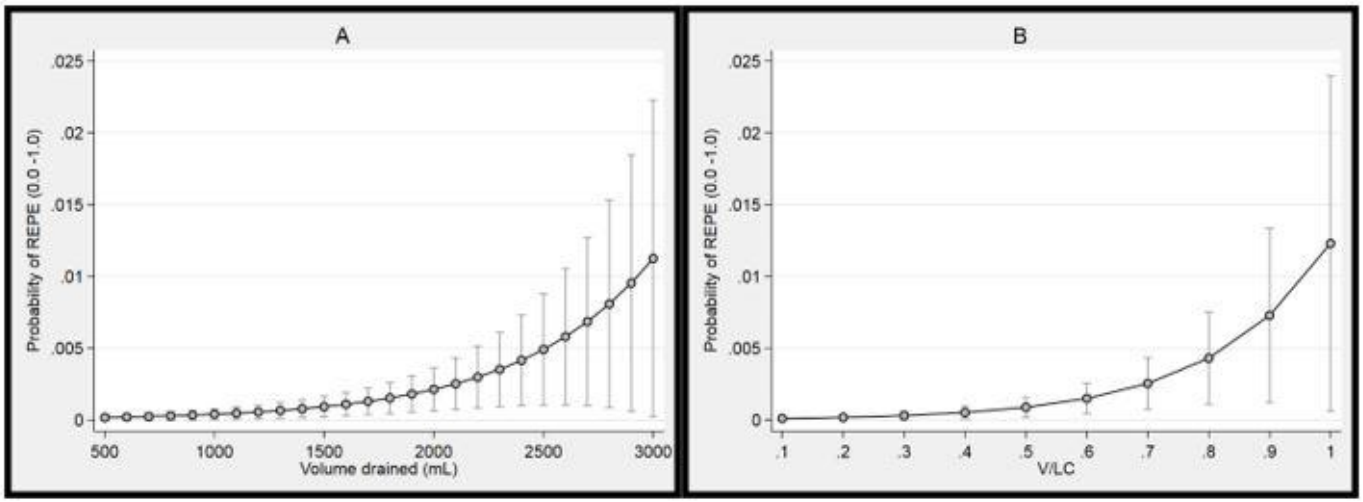

Figure 2. Probability of re-expansion pulmonary edema by volume drained (A) and by volume drained normalized by the ipsilateral chest cavity size (V/LC) (B).