Prediction of time to next therapeutic thoracentesis and identification of risk factors of rapid pleural fluid recurrence: a prospective observational study.

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Short title: Risk factors of rapid pleural fluid recurrence

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Abstract

Background:

The value of pre-booked repeated thoracenteses in patients with recurrent pleural effusion is reliant on the estimation of time to next drainage. Identifying factors associated with rapid pleural fluid recurrence, could be supportive.

Objective:

We aimed to evaluate the ability of the patient and physician to predict the time to next therapeutic thoracentesis and to identify characteristics associated with rapid pleural fluid recurrence.

Method:

In a prospective, observational study, patients with recurrent unilateral pleural effusion and the physician were to predict the time to next symptom-guided therapeutic thoracentesis. Primary outcome was difference between days to actual thoracentesis and days predicted by the patient and the physician. Factors associated with pleural fluid recurrence within 60 days follow-up was assessed using Cox regression analysis.

Results:

A total of 98 patients were included, 71% with malignant pleural effusion. Patients' and physicians' predictions numerically deviated with 6 days from the actual number of days to re-thoracentesis (IQR 2-12 and 2-13, respectively). On multivariate analyses, factors associated with increased hazard of pleural fluid recurrence included daily fluid production (HR 1.35 (1.16-1.59), p>0.001) and large effusion size (HR 2.76 (1.23-6.19), p=0.01). Septations were associated with decreased hazard (HR 0.48 (0.24-0.96), p=0.04).

Conclusion:

Patients and physicians were equally unable to predict the time to next therapeutic thoracentesis. Daily fluid production and large effusion size was associated with increased risk of rapid pleural fluid recurrence, while septations was associated with a decreased risk. This may guide patients and physicians in when to expect a need for therapeutic thoracentesis.

Background

Dyspnoea is the most common symptom in patients with pleural effusion, and repeated therapeutic thoracentesis is a simple method to achieve relief[1]. The optimal time interval between repeated therapeutic thoracentesis is highly individual[2] which may challenge the patients ability to plan everyday life. In daily practice, a pleural clinic may either pre-book the next therapeutic thoracentesis or ask the patient to call for a subacute thoracentesis based on patient-led symptom relief.

Though a definitive management of patients with recurrent pleural effusion is recommended[3], indwelling pleural catheters (IPC) or pleurodesis are not universally available. Also, some patients simply prefer repeated therapeutic thoracentesis over IPC. Pre-booking therapeutic thoracentesis relies on the patient's and caregivers' ability to predict the appropriate time span to next therapeutic thoracentesis. An approach guided by patient's symptoms relies on accurate perception of day-to-day worsening of symptoms. Acute admissions with rescue thoracentesis should be avoided, since it is both costly, strains health care systems and exposes the patient to an unnecessary discomfort[4]. Thus, knowledge of factors associated with time to the next thoracentesis might support shared decision making between patient and caregiver.

Previous studies have investigated factors associated with pleural fluid recurrence in patients with malignant pleural effusion. A small, prospective study identified larger volume drained and a higher increase in dyspnoea following maximal relief after thoracentesis as risk factors of re-thoracentesis within 30 days[2]. Two larger, retrospective studies found large effusion size on chest x-ray[5], [6], larger volume drained[6], high pleural fluid lactate dehydrogenase[5], [6] and malignant pleural fluid cytology[5], [6] to be associated with an increased hazard of pleural fluid recurrence. Yet, pleural fluid specimens and recent chest x-rays may not always be available. Currently, real-time thoracic ultrasound (TUS) has widely replaced chest x-ray to assess presence of effusion and effusion size, since TUS is more sensitive[7] and ultrasound (US)-guided thoracentesis is standard-of-care[8]. Identifying US characteristics associated with pleural fluid recurrence, could be a useful clinical tool. Another poorly understood factor in is the impact of the underlying condition and comorbidity causing dyspnoea. Recurrent

pleural effusion is often caused by multiple coexisting conditions such as malignancy, heart failure, or malnutrition[9], [10].

On this background, we decided to investigate the ability of the patient and treating physician to predict time to next therapeutic thoracentesis. In addition, we aimed to identify possible baseline characteristics, with focus on US, associated with rapid pleural fluid recurrence.

Methods

In a prospective, observational study, patients with unilateral pleural effusion and repeated need for therapeutic thoracentesis were recruited from the outpatient clinics of the Department of Respiratory Medicine, Zealand University Hospital Næstved and Roskilde, Denmark. Inclusion criteria were age ≥18 years, unilateral pleural effusion, ≥2 previous therapeutic thoracentesis, and ability to give informed consent. Exclusion criteria were inability to understand written or spoken Danish. The protocol was registered at clinical.trial.gov (ID: 19-000067). We collected data on basic demographics, smoking status, cause of pleural effusion, number of previous thoracenteses, time since recent thoracentesis, volume drained and co-morbidities possibly contributing to dyspnoea.

Patient reported outcomes

On the day of inclusion, prior to thoracentesis all participants completed a questionnaire concerning level of dyspnoea measured by the modified Borg 0-10 Scale[11] (MBS) and the Medical Research Council dyspnoea score[12] (MRC). MBS was repeated 10 minutes after completion of drainage. Then the patient and the physician were both asked to predict number of days to next therapeutic thoracentesis. The patient were asked first by a member of the research team. The treating physician was not blinded towards the patient response. The patient was instructed to contact the pleura clinic - based on symptoms - for a subacute thoracentesis typically performed within 0-2 days.

Thoracic ultrasound (TUS)

Before thoracentesis, a systematic TUS was performed by two experienced operators (KF and JP) using C1-5 curved abdominal transducer (2 - 5 MHz), abdominal preset, LOGIQ S8 (GE Healthcare Wauwatosa, USA) or a C42 micro convex transducer (4-8 MHz), liver preset. ALOKA ARIETTA V60 (Hitachi, Tokyo, Japan)). The patient was placed in an erect position. TUS involved an assessment of size of pleural effusion (small: < 1/3 of hemi thorax, moderate: 1/3-2/3 and large: > 2/3), sonographic characteristic of the effusion (simple, complex non-septated, complex septated, homogenously echogenic[13]), septa score[14] (septations visible in a single US field at area of maximum septations: no septations, 1-2, 3-4, >5), swirling sign (present, non-present), signs of trapped lung (a subjective assessment of impaired mobility of the compressed lung, registered as suspected trapped lung or not), diaphragmatic shape (domed, non-domed) and diaphragmatic movement by M-mode[15] and the Area method as described by Skaarup et al[16]. After drainage ended, diaphragm shape and movement were reassessed, and drainage completion was evaluated.

Thoracentesis

KF and JP performed all thoracentesis US-guided according to guidelines[8] using either a 7 French or up to 16 French pigtail catheter. After drainage of one liter, drainage was paused for 10 minutes. Drainage was protocolised as following: drainage until the effusion was considered fully drained or when the patient experienced symptoms of symptoms of trapped lung (cough and chest pain). There was no standard minimum or maximum volume drained but larger volumes (>1500 mL) where drained with pauses for each 500 mL. A drainage was considered completed if less than 0.1L fluid was left in the pleural cavity, assessed by eyeballing.

Outcomes

Primary outcome was difference between days to actual patient-reported therapeutic thoracentesis and days predicted by the physician and the patient, respectively. Both were defined as the actual time minus the predicted time measured in days, i.e. positive values represent underestimation and negative values represent overestimation. Secondary outcome was assessment of risk factors of rapid pleural fluid recurrence at follow-up. Follow-up was at the time of re-thoracentesis or after 60 days, whichever was sooner.

Statistical considerations

Power calculations concerning the primary outcome estimated the need of 97 included patients (Power of 80%; alfa 5%; estimated best guess by one group in 60% vs. 40% in other group). Categorical data was described as number (*n*) and percentage (%), continuous variables as median and IQR and normally distributed data as mean (± SD). Intergroup differences in categorical variables was analysed with Chi^2-test or Fisher´s test as appropriate, and differences in continuous variables with Wilcoxon signed rank test or Mann-Whitney *U*-test. Factors associated with risk of re-thoracentesis during follow-up were assessed using univariate and multivariate cox proportion hazard regression, adjusted for variables with p>0.05 in the initial analysis. Patients without re-thoracentesis at follow-up or who died before re-thoracentesis were right censored. Test of the proportional hazard assumptions was performed using Schoenfeld residuals.

To make the study findings more translatable to a clinical setting, factors associated with risk of re-thoracentesis within 14 days were assessed using logistic regression analysis. Day 14 was chosen, since early recurrence indicates a need of an IPC[3].

MBS as a predicting variable was dichotomised, since some categories contained very few patients. A cut-off of MBS score ≥ 4 was chosen to distinguish mild to moderate from severe level of dyspnoea, see Table A in supplementary material.

Missing data were considered missing at random and level of significance was p< 0.05. All statistics were performed using STATA/BE 17 (Texas, US).

Results

January 2020 to December 2021, 98 patients were included, by screening 458 (see Figure 1). The mean age was 74 years (SD 10), 40/98 (41%) were female and 49/98 (50%) had comorbidity associated with dyspnoea (see Table 1). Malignant pleural effusions constituted 67/98 (71%) predominantly caused by lung cancer 34/67 (51%). The median number of prior thoracenteses within one year was three (IQR 2-4) and median days since most recent thoracentesis was 18 (IQR

11-42). At inclusion, mean volume drained was 1.3L (SD 0.7). 43/98 (44%) of effusions were fully drained (see Table 2). At follow-up (on day 60), re-thoracentesis was performed in 74 (76%) patients with a median of 14 (IQR 7-29) days. A total of 16 patients died before day 60, of whom 13 had a re-thoracentesis. No deaths were considered related to the thoracentesis.

Prediction of time to next thoracentesis:

There was no significant difference between the actual days to re-thoracentesis and the patients' or physicians' predictions (p = 0.42 and 0.81, respectively, see Figure A in supplementary material). The differences between predictions and actual days to thoracentesis are shown on Figure 2. There was no sign of systematically over- or underestimation of time in any of the groups. Both patients' and physicians' predictions numerically deviated with 6 days from the actual number of days to re-thoracentesis (IQR 2-12 and 2-13, respectively), see Figure 3.

Factors associated with rapid pleural fluid recurrence

Results of cox regression analysis are presented in Table 2. On univariate analyses, factors associated with an increased hazard of pleural fluid recurrence within the 60 days follow-up included daily fluid production (volume drained divided by the number of days since the latest therapeutic thoracentesis) (HR 1.35 (95%CI 1.16-.159), p<0.001)), moderate and large size pleural effusion (HR 2.29 (1.23-4.26), p=0.009 and HR 3.76 (1.80-7.86), p<0.001, respectively) and a MBS score after thoracentesis ≥ 4 (HR 1.76 (1.07-2.90), p=0.03). The presence of septations were associated with a decreased hazard of re-thoracentesis (HR 0.51 (0.27-0.97), p=0.04). On multivariate analyses, factors associated with an increased hazard of pleural fluid recurrence included daily fluid production since previous thoracentesis (HR 1.35 (1.16-1.59), p>0.001) and large effusion size (HR 2.76 (1.23-6.19), p=0.01). Septations were still associated with decreased hazards (HR 0.48 (0.24-0.96), p=0.04). There was only a tendency of MBS score after thoracentesis ≥ 4 to be associated with an increased hazard of re-thoracentesis (HR 1.71 (1.00-2.95), p=0.05).

Table B in the supplementary material show factors associated with re-thoracentesis within 14 days after inclusion. On unadjusted daily fluid production since previous thoracentesis (OR 3.36

(1.83-6.18), p<0.001), MBS score before thoracentesis ≥ 4 (OR 3.27 (1.41-7.62), p=0.01), moderate and large effusion size (OR 3.12 (1.02-9.50), p=0.046 and OR 6.60 (1.69-25.7), p=0.01, respectively) and MBS score after thoracentesis ≥ 4 (OR 3.04 (1.22-7.58), p=0.02) were associated with increased odd ratio of re-thoracentesis. No factors were associated with a decreased odds ratio. On adjusted analysis daily fluid production since previous thoracentesis (OR 3.30 (1.03-9.38), p<0.001) and MBS score before thoracentesis ≥ 4 (OR 3.11 (1.03-9.37), p=0.04 were associated with an increased odd ratio.

Discussion

In this study, we found no difference in the patients' or physicians' ability to predict the number of days to next therapeutic thoracentesis. Both predictions were numerically incorrect by a median of 6 days, with no clear tendency of over- or underestimating. This result emphases the need of flexibility in the treatment with repeated therapeutic thoracentesis.

We identified increased daily fluid production and moderate and large effusion size on TUS to be associated with an increased hazard of re-thoracentesis within 60 days. The association between daily production rate and risk of pleural fluid recurrence is intuitive for both patients and physicians. Daily production rate of pleural fluid as a predictor for recurrence has been noted earlier. Both by a small, prospective study by Boshuizen *et al*[2] (n=49) and two large retrospective studies by Grosu *et al*[5] (n=988) and Schwalk *et al*[6] (n=396) finding large volume drained to be associated with increased risk of re-thoracentesis in patients with malignant pleural effusion.

Grosu *et al* and Schwalk *et al* identified larger effusions on chest x-ray to be associated with increased hazard of re-thoracentesis. We have shown that assessment of effusion size by US is an alternative. This was expected, as US assessment is real-time while the chest x-rays included in the above-mentioned studies were up to two weeks old. The studies by Grosu *et al* and Schwalk *et al* only included patients at their first thoracentesis and excluded patients with prior thoracenteses. Thus, our study confirms their findings in patients with known recurrent pleural effusion. One might assume that the effect of larger effusion was caused by a larger amount of fluid drained,

however, the results of the multivariate analysis in Table 2 does not chance when adding volume drained as a variable.

Of other US characteristics, only the presence of septations was associated with a reduced hazard of re-thoracentesis, also when adjusted for daily fluid production. The underlying mechanism is unknown. A possible explanation is that septations are a sign of chronicity and a more fixed visceral pleura. This theory is supported by an increased incidence of suspected trapped lung in patients with septations, see Table C in supplementary. Maybe septations leads to less improvement in dyspnoea following therapeutic thoracentesis. This hypothesis is supported by a previous study showing a negative correlation between number of septations and dyspnoea improvement following pleural drainage[14]. In our study, however, we did not find any association between septations or septa score and degree of baseline dyspnoea or relief, see Table C and D in the supplementary material. In addition, it should be noted that the presence of septations was not significantly associated with re-thoracentesis at day 14 after drainage on adjusted logistic regression. This could indicate that the role of septations is more important in the time following day 14 after drainage.

Our study has several limitations. First, we chose the difference between patients' and physicians' estimation of days to next thoracentesis as primary outcome, while the accuracy of the estimation may be more clinical relevant. In addition, the day of re-thoracentesis may not always represent be the exact day of patient-needed thoracentesis, since there could be two days delay on available time-slots in the pleura clinic. Second, we did not reach the estimated sample size, which reduces the power of the study and may lead to further type two errors. Third, neither physicians nor patients were blinded to each other's prediction of time to next thoracentesis, which obviously could introduce bias yet predictions were only identical in 14/74 cases. We chose not to blind the participants, since the physician hopefully always takes the patients perspective into account. Fourth, testing several factors' association with rapid pleural fluid recurrence in a relative small study population may lead to type one errors. Fifth, patients may be affected by their own prediction of time to next thoracentesis, thus introducing confirmation bias. However, this is unlikely since the prediction was not noted by the patient, who hardly remembered their guess. Sixth, our study includes patients with repeated need of therapeutic thoracentesis and both benign and malignant effusions. One should be aware of this when generalising the results to

specific patients groups. Seventh, we chose not to use competing risk regression analysis[17], since only 3/98 patients died before re-thoracentesis.

Conclusion

In this study, we found the physicians and patients to be equally unable to predict the time to next therapeutic thoracentesis. We identified daily fluid production and large effusion size to be associated with an increased risk of rapid pleural fluid recurrence, while the presence of septations was associated with a decreased risk. This may guide patients and physicians in when to expect a need for therapeutic thoracentesis.

Statement of Ethics

The Danish Committee of Health Research Ethics assessed that an approval was not required. The Danish Data Protection Agency (REG-077-2019) approved the study. All participant signed an informed consent form.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

Author Contributions

Katrine Fjaellegaard contributed to the research protocol, performed clinical examinations, contributed to the data analysis and interpretation and was the primary author of the manuscript.

Jesper Koefod Petersen contributed to the research protocol, performed clinical examinations, contributed to the data analysis and interpretation and the writing of the manuscript.

Daniel Beck Rasmussen contributed to the data analysis and interpretation and the writing of the manuscript.

Paul Frost Clementsen initiated the research project, contributed to the research protocol, the data analysis and interpretation and the writing of the manuscript.

Christian B. Laursen initiated the research project, contributed to the research protocol, the data analysis and interpretation and the writing of the manuscript.

Rahul Bhatnagar contributed to the data analysis and interpretation and the writing of the manuscript.

Uffe Bodtger initiated the research project, contributed to the research protocol, the data analysis and interpretation and the writing of the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Figure Legends

Fig. 1. Flowchart showing the inclusion of patients.

Fig. 2. Differences between patients' and physicians' prediction and actual number of days to re-thoracentesis. N=74. A: Positive values represent underestimation of time and negative values represent overestimation. P-value calculated by Wilcoxon signed rank test. Boxes contain the 25th and 75th percentile, and the center line denotes the median. The "whiskers" mark the 5th and 95th percentiles, and values marked with dots are considered outliers. B: Positive values represent underestimation of time and negative values represent overestimation.

Fig. 3. Numeric differences between actual number of days to re-thoracentesis and predictions by patients and physicians. N=74, p-value calculated by Wilcoxon signed rank test. Boxes contain the 25th and 75th percentile, and the center line denotes the median. The "whiskers" mark the 5th and 95th percentiles, and values marked with dots are considered outliers.

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