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Additional Up-Front Thoracic Ultrasound in the Workup of Patients with Unilateral Pleural Effusion: A Prospective Observational Pilot Study

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Keywords
Thoracic ultrasound · Pleural effusion · Malignant pleural effusion · Pleural disease

Abstract
Background: In patients with pleural effusion, specific ultrasound characteristics are associated with pleural malignancy. ***Objectives:*** This study aimed to evaluate the added value of an additional, up-front, systematic thoracic ultrasound (TUS) to standard imaging in patients with unilateral pleural effusion of unknown cause in a clinical setting. ***Methods:*** In a prospective observational pilot study, patients referred for workup and thoracentesis of a unilateral pleural effusion received up-front TUS following a set protocol in addition to available imaging and US guiding the thoracentesis or diagnostic puncture. The primary outcome was the proportion of cases where systematic TUS changed the planned diagnostic workup. Follow-up took place 26 weeks after inclusion. ***Results:*** From February to December 2020, 55 patients were included. Thirty-six (65%) patients had other chest imaging available before TUS. Twenty-one (38%) were diagnosed with malignant pleural effusion. Three patients (5%) had clinically relevant changes in the diagnostic workup after additional systematic TUS. ***Conclusions:*** Additional up-front, systematic TUS had limited clinically relevant effect on the planned diagnostic workup in patients with unilateral pleural effusion in a setting where chest CT scans often are available at referral.

Introduction

Pleural effusion describes fluid, which accumulates in the pleural space due to increased production and/or decreased absorption. The incidence in Denmark is estimated to be 20,000 cases per year [1]. Malignant pleural effusion (MPE) accounts for approximately 20% of

Study registration: The study is registered at ClinicalTrials.gov, number NCT04235998.

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effusions [1] and typically presents unilaterally [2]. It is defined as the presence of malignant cells in the pleural fluid or an effusion in the context of cancer where other causes have been excluded. Still, in order to guide treatment, the "gold standard" diagnosis of malignancy requires cytological or histopathological evidence of malignant cells from the pleural space.

Initial workup of a unilateral pleural effusion includes a medical history, physical examination, chest X-ray, and subsequent ultrasound-guided thoracentesis for cytological and biochemical characterization [2]. If the cause thereafter is still unclear, guidelines suggest contrast-enhanced (CE) chest computed tomography (CT) [2, 3]. The upcoming BTS guideline for pleural disease states that ultrasound should be used to change the diagnostic pathway if it reveals a good biopsy target site [4].

Thoracic ultrasound (TUS) has the advantage of being a non-invasive, real-time diagnostic procedure with no exposure to radiation. TUS has proven to be useful in the evaluation of dyspnoea in an acute setting [5, 6] and as guidance for pleural interventions [7]. Specific ultrasound (US) characteristics have been associated with malignancy including pleural/diaphragmatic nodules, parietal pleura thickness >10 mm, diaphragmatic pleura thickness >7 mm, liver metastasis, absence of lung air bronchogram signs, and absence of fibrinous septations in the pleural effusion [8, 9]. However, a limitation of the technique is that it cannot provide the same assessment as CT in areas which are not accessible to TUS, like intraparenchymal tumours and enlarged mediastinal lymph nodes [9]. In diagnosing MPE, the sensitivity of TUS varies from 73% to 80%, the specificity from 83.6% to 100%, the positive predictive value from 82.8% to 100%, and the negative predictive value from 79% to 81.2% [8, 9].

In Denmark, patients referred for workup of unilateral pleural effusion often have a CE chest CT and occasionally positron emission tomography (PET)-CT performed prior to the first consultation with a pulmonologist [10]. This consultation will usually involve a diagnostic or therapeutic aspiration being performed under ultrasound guidance, making it the ideal opportunity to perform a broader US assessment. However, the potential value of adding a more comprehensive, systematic assessment of the lungs and thorax, exploring the nature of the pleural effusion and concomitant signs of extrathoracic malignancy, is unknown. For this reason, we aimed to investigate the clinical impact of additional systematic TUS and focused assessment of possible extrathoracic malignancy in the workup of unilateral pleural effusion in an outpatient respiratory medicine clinic.

Materials and Methods

We undertook a prospective, observational pilot study of patients referred for outpatient workup of unilateral pleural effusion (ClinicalTrials.gov, number NCT04235998). Participants were recruited from the outpatient clinics of the Department of Respiratory Medicine, Zealand University Hospital, Denmark. The department performs all invasive diagnostics on patients suspected of pulmonary malignancy or MPE in Region Zealand consisting of approximately 850,000 inhabitants.

Inclusion criteria: age ≥18 years, unilateral pleural effusion of unknown cause, and the ability to give informed consent. Exclusion criteria: bilateral pleural effusion, life expectancy <3 months, or inability to understand written or spoken Danish were excluded.

Written informed consent was obtained from all participants and the study was approved by the Danish Committee of Health Research Ethics (project number: SJ-789). All participants underwent systematic TUS, developed by the research group, in addition to the standard, targeted TUS to guide the thoracentesis. Thus, TUS was not an alternative to other potentially available imaging, but a supplement. TUS was performed by two medical doctors (K.F., J.K.P.) who had completed evidence-based training programme and competency assessment in accordance with DLS recommendations and were fully independent and experienced practitioners in lung ultrasound. In performing simple focused US of heart, liver, and neck, they had received bedside training, supervision, and assessment by the mentor, but no formal training/competency assessment since no guidelines or evidence-based training programme is currently available. Results of chest radiology and blood tests were available to the operators.

Thoracic Ultrasound Protocol

US assessments were performed using LOGIQ S8 (GE Healthcare, Wauwatosa, USA) at Zealand University Hospital, Naestved and ALOKA ARIETTA V60 (Hitachi, Tokyo, Japan) at Zealand University Hospital, Roskilde. The TUS was performed with the patient seated erect, using a C1-5 curved abdominal transducer (2–5 MHz) and abdominal preset with the LOGIQ S8 and a C42 micro convex transducer (4–8 MHz) and liver preset when using ALOKA Arietta V60. Operators conducted a systematic assessment, using an approach in which each hemithorax was divided into 7 scanning zones as previously described [11] (see Figure 1). In each zone, the following aspects were assessed:

- Size of pleural effusion (small: <1/3 of hemithorax, moderate: 1/3–2/3 of hemithorax, and large >2/3 of hemithorax).
- Sonographic characteristic of the effusion (simple, complex non-septated, complex septated, homogeneously echogenic).
- Septation score [12] (septations visible in a single US field at the area of maximum septations: no septations, 1–2, 3–4, >5).
- Swirling sign [8](present, non-present).
- Signs of trapped lung (a subjective assessment on likely trapped lung based on impaired movement of the underlying lung).
- Parietal pleura (thickness of the thickest part, structure [homogeneous or irregular], pleural nodules, and rib/chest invasion).
- Visceral pleura (normal, abnormal).
- Diaphragmatic pleura (thickness of the thickest part, structure [homogeneous or irregular], pleural nodules, and mobility [normal, impaired, immobile]).

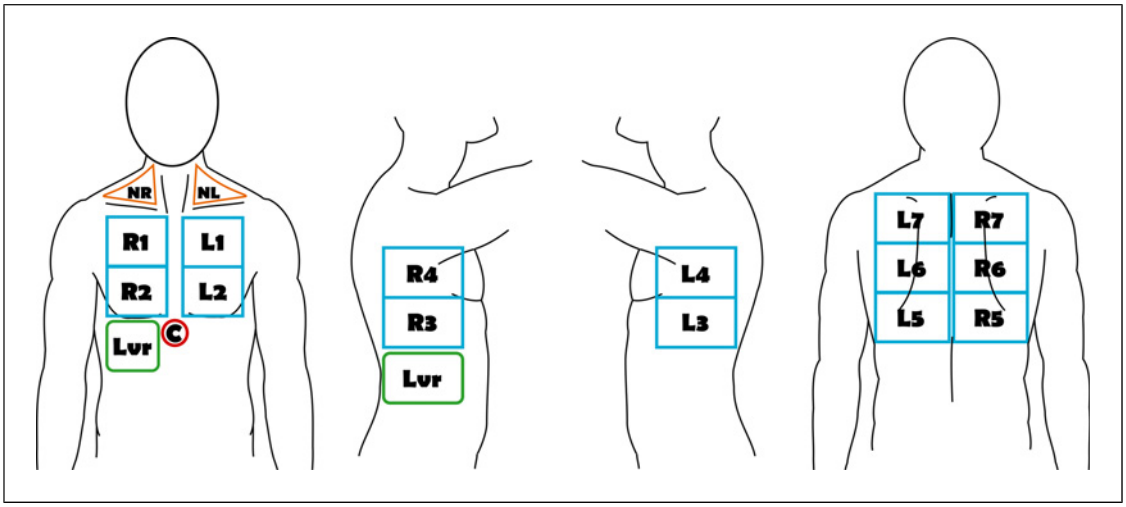

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Fig. 1. The systematic TUS. Lung assessment: the seven lung ultrasound zones on each hemithorax corresponding to the anterior, lateral, and posterior thorax wall. Extrapulmonary assessment: neck, liver, and heart. L, left; R, right; N, neck; C, cardiac; Lvr, liver.

- Lung parenchyma (visible consolidation [most likely to be pneumonia, obstructive atelectasis, compression atelectasis, tumour, pulmonary embolism, or non-specific consolidation]).

TUS was supplemented with focused assessment of signs of possible extrathoracic metastasis and cardiac cause of the pleural effusion (see Fig 1). The examination was performed with the patient in a supine position.

- Neck assessment: Infraclavicular, supraclavicular, and cervical lymph nodes (regions III, IV, Va, Vb [13]). Lymph node metastasis was suspected if the shortest diameter >1 cm, using an ML6-15 linear transducer (4.5–15 MHz) and SM-P preset when using LOGIQ S8 and a microconvex transducer (4–8 MHz) and liver preset when using Arietta V60.
- Upper abdominal assessment: Hepatic metastasis was suspected in the presence of focal lesions in the liver, using a C1-5 curved abdominal transducer (2–5 MHz) and abdominal preset when using LOGIQ S8 and a microconvex transducer (4–8 MHz) and a lever preset when using Arietta V60.
- Cardiac assessment: The presence of the following conditions was assessed: pericardial effusion, dilation of right ventricle (RV) (RV inner diameter > left ventricle inner diameter), obvious impairment of left ventricle systolic function, or other obvious pathology, assessed by an M5S-D phased array transducer (1.5–4.5 MHz) and a cardiac preset when using LOGIQ S8 and an S211 sector transducer (1–5 MHz) and a cardiac preset when using ARIETTA V60.

Outcomes

The primary endpoint was proportion of cases where systematic TUS and the supplementary extrapulmonary focused US assessment led to a change from the scheduled diagnostic management of the pleural effusion. Secondary endpoints included (a) proportion of cases where this change led to demonstration of the cause of the pleural effusion, (b) proportion of cases where findings of clinical importance on systematic US were not identified on the initial imaging (as assessed by a radiologist or a clinician at the initial planning of diagnostic workup), (c) extra time spent on the additional systematic US, and (d) patient experience.

Patient experience was assessed following US and pleural procedures and included measurement of pain using a visual analogue scale pain score, patient experienced time consumption, measured by a 3-point Likert-type scale (1: not, 2: slightly and 3: very time consuming), and the patients willingness to have the same examination again in the future if necessary, measured by a 5-point Likert-type scale (1: being definitely willing and 5: being definitely not willing to have the examination again).

Follow-up was 26 weeks after the day of inclusion and involved a review of the electronic medical file to evaluate the diagnostic workup and confirm the final diagnosis. Reference test for MPE was histological or cytological results. Otherwise, the registered cause of the pleural effusion was the diagnosis established by the pulmonologist.

Statistical Considerations

Estimated number of patients to be included was 56 patients (power [1-beta] = 90%; alpha 5% [$p = 0.05$]; estimated incidence of changes by US performed to guide diagnostic puncture/thoracentesis: 0%, estimated incidence of changes by additional TUS: 30%). Descriptive and analytical statistics was performed using dedicated statistical software (STATA/IC 17, TX, USA). Categorical data were described as number (n) and percentage (%), and continuous variables as median and range or interquartile range.

Results

Between February and December 2020, 57 participants were included by screening 139 patients (see Figure 2). TUS and thoracentesis were not performed in 1 patient

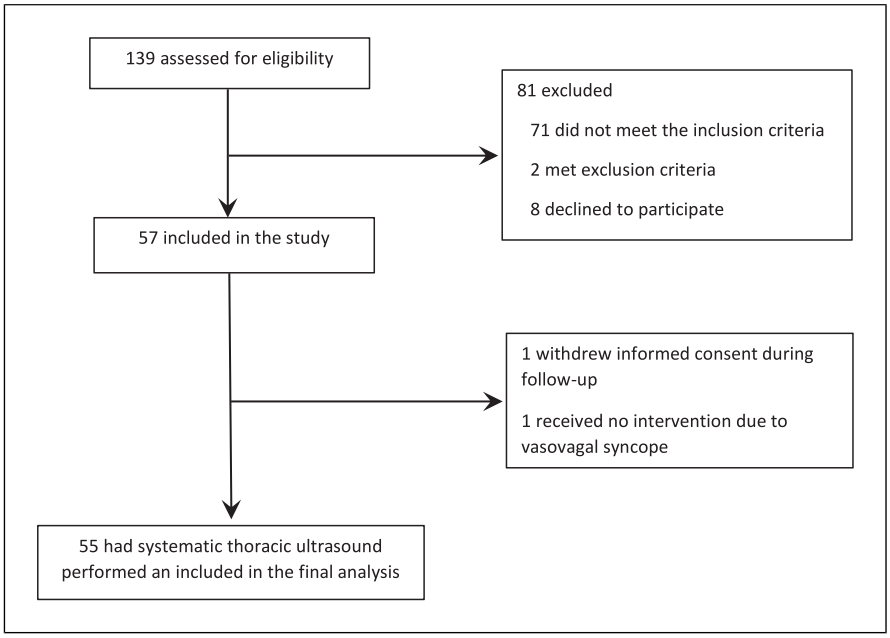

Fig. 2. Flowchart showing the inclusion of patients.

due to a vasovagal episode, and 1 patient withdrew informed consent during the follow-up; hence, 55 patients were included for the final analysis. Baseline characteristics are provided in Table 1. The mean age was 71, 38% were female, and 9% had a recent diagnosis of non-pleural malignancy. In 36/55 patients (65%), cross-sectional imaging was performed <30 days prior to inclusion, including 30 CE chest CT, 7 PET-CT, 3 low-dose CT, 1 high-resolution CT, and 1 pulmonary angiography.

The type and incidence of abnormal findings are shown in details in Table 2 and online supplementary Table A.1 (for all online suppl. material, see www.karger.com/doi/10.1159/000529871). In all, 26/55 cases (47%) had normal ultrasonographic findings. The majority of effusions were right-sided (40/55, 73%), simple (26/55, 47%), and involved <1/3 of hemithorax (36/55, 65%). TUS characteristics known to be associated with malignancy were rare (rib/chest invasion [1/55, 2%], pleural/diaphragmatic nodules [5/55, 9%], parietal pleural thickness >10 mm [1/55, 2%], suspected lever metastasis [1/55, 2%], consolidation most likely to be tumour [3/55, 5%], no cases of cervical lymphadenopathy) except diaphragmatic pleura thickness >7 mm found 17/55 cases (31%). Cardiac pathology was found in 8/55 (15%), dominated by pericardial effusion in 5/55 (9%). A total of 21/55 patients (38%) were eventually diagnosed with MPE (see Table 3). US characteristics in MPE and non-malignant effusions, and their diagnostic accuracy are shown in Table 2 and online supplementary Table A.2, respectively.

In the 36 patients with chest CT scans available at inclusion, pleural malignancy was suspected in 10 individuals (see online supplementary Table A.3). Additional TUS identified pleural nodules and pericardial effusions, not identified on the initial chest CT scan, in 4 and 2 cases, respectively. However, 2 cases of pleural nodules and pericardial effusions and a single case of enlarged cervical lymph nodes and suspected lever metastasis were identified solely on chest CT scans.

The diagnostic workup was changed due to findings on systematic TUS in 3 of the 56 included patients (5%) (see Table 3). In 2 of the 3 cases, systematic TUS led to instant US-guided biopsies due to parietal pleural thickening or tumour invasion of the thorax. Both patients had a recent CE chest CT available at visitation and inclusion. Thus, these procedures could have been booked up-front at patient visitation. In the third case, the patient did not have recent chest radiology performed prior to inclusion. TUS revealed a persistent consolidation, compared to a previous CE chest CT, which led to the booking of a PET-CT. In this case, the additional TUS added an important clinical value to the diagnostic workup of the patient. However, the consolidation would probably have been visible on chest X-ray, if this had been performed prior to thoracentesis. None of the changes in the workup led to the exact cause of the pleural effusion. However, in the first 2 cases, the change led to investigations ruling out malignancy. The change in diagnostics planned did not lead to other new findings of clinical importance in any patients. Going through the

Table 1. Baseline characteristics of the included patients

Characteristic	Population (n = 55)
Age, years, mean (IQR)	71 (65–81)
Sex, *n* (%)	
Female	21 (38)
Male	34 (62)
Smoking, *n* (%)	
Never	15 (27)
Ever	40 (73)
Pack years, mean (IQR)	36 (15–50)
Asbestos exposure, *n* (%)	11 (20)
Comorbidities*, *n* (%)	
Malignancy	
Current treatment/palliation	5 (9)
Previous malignancy	17 (31)
Heart failure	4 (7)
Hepatic insufficiency	2 (4)
Nephropathy	3 (5)
Thromboembolic disease	10 (18)
Known pleural disease	3 (5)
Current exposure to drugs[a] known to cause pleural effusion, *n* (%)	13 (24)
Chest CT scan performed within 30 days prior to inclusion, *n* (%)	
Patients with recent scans	36 (65)[b]
CE CT	30 (55)
PET-CT	7 (13)
HRCT	1 (2)
Low-dose CT	3 (5)
Pulmonary angiography	1 (2)

*Heart failure: left ventricle ejection fraction <40% or ICD10 code including DI50, DI110, DI113, or DI97. Hepatic insufficiency: medical file with diagnose of hepatic insufficiency. Nephropathy: dialysis, chronic GFR <30, or acute nephropathy diagnosed by the clinician. Thromboembolic disease: any current thromboembolic event. [a]Beta-blockers, phenytoin, nitrofurantoin, amiodarone, methotrexate. [b]CT, computed tomography; PET-CT, positron emission tomography-CT; HRCT, high-resolution CT. Six patients had both CT and PET-CT. One patient had both low-dose CT and HRCT.

findings on systematic US retrospectively, we found that 5 additional patients could have had a clinical relevant change in their management, if action had been taken on all positive US findings. This included 1 case of pericardial effusion, not referred to the cardiologists, and 4 cases of parietal pleural thickening. Biopsy of the parietal pleural was not performed in 3 cases due to only very small amounts of pleural fluid, so the result of pleural fluid examination was awaited before further invasive procedures, to limit the risk of pneumothorax. In 1 case, the patient was randomized in another study for local anaesthesia thoracoscopy.

The median additional time spent on systematic TUS was 9 min (range 5–21 min). By patients, systematic TUS was perceived as a painless and acceptable procedure, and most patients would accept re-examination if needed (see online supplementary Table A.4).

Discussion

Our study showed that additional, systematic TUS was a well-tolerated procedure, which changed the planned diagnostic workup of unilateral pleural effusion in three of 55 (5%) of the patients. The changes included same day US-guided biopsies and requesting a PET-CT.

The additional amount of minutes spent on the systematic TUS varied from 5 to 21 min, due to varying image quality. Operator US assessment time did not differ between operators and varied throughout the study period, indicating that time spent was experience-independent.

We did not find any cases of enlarged infraclavicular, supraclavicular, or cervical lymph nodes. Previous studies have found a high prevalence of ultrasound-verified enlarged cervical lymph nodes in patients with

Table 2. US characteristics in malignant and non-malignant effusions

US characteristics	Malignant effusions (n = 21)	Non-malignant effusions (n = 34)	p value*
Right side	14	26	0.428
Effusion size			
Small	14	22	0.882
Moderate	6	10	0.947
Large	1	2	0.859
Sonographic characteristics			
Simple	5	21	**0.006**
Complex non-septated	7	4	0.052
Complex septated	3	3	0.528
Homogeneously echogenic	6	6	0.341
Swirling sign	11	4	**0.001**
Suspected trapped lung	4	1	0.044
Septations			
0	18	31	0.528
1–2	2	0	0.067
3–4	1	1	0.726
≥5	0	2	0.258
Parietal pleura			
Thickness >10 mm	1	0	0.428
Nodules present	4	1	0.044
Irregular structure	8	7	0.157
Signs of rib/chest invasion	1	0	0.277
Diaphragmatic pleura			
Thickness >7 mm	10	7	**0.035**
Irregular structure	14	7	**0.001**
Nodules present	5	0	**0.003**
Visceral pleura abnormal	3	3	0.528
Lung consolidation with tumour	3	0	**0.023**
Extrapulmonary US			
Hepatic metastasis	1	0	0.199
Cervical lymph nodes[a]	0	0	
Cardiac findings			
Pericardial effusion	3	2	0.292
Dilation of right ventricle	0	2	0.258
Obvious impaired left ventricle	0	2	0.258
Other obvious pathology	0	1	0.428
Pooled characteristics that indicates malignancy[b]	14	8	**0.002**

*p values generated by χ^2. [a]Infraclavicular, supraclavicular, and cervical lymph nodes (regions III, IV, Va, Vb). [b]Parietal pleura >10 mm, parietal pleural nodules, diaphragmatic pleura >7 mm, diaphragmatic pleural nodules, signs of rib/chest invasion, signs of hepatic metastasis, and lung consolidation most likely to be tumour.

suspected lung cancer [14] and a high diagnostic yield of instant ultrasound-guided biopsies [15]. In our study, a minority were diagnosed with lung cancer, while several patients had mesothelioma where spread to cervical lymph nodes is rare [16]. Thus, our study does not support routine assessment of the neck in patients presenting with unilateral pleural effusion a recent chest CT.

TUS revealed cardiac abnormalities in 8/55 patients (14%), whereas it was not possible to obtain images with sufficient image quality to assess the heart in 4/55 (7%). TUS resulted in one (2%) referral to cardiologist, since the cardiac abnormalities were already known in the remainder, either pericardial effusions seen on the recent chest scan, or as clinically known cardiac disease. Thus, in our study, additional cardiac ultrasound had a limited value in a setting where recent chest CT scan and echocardiography are available.

No previous study has investigated the effect of additional up-front systematic TUS on the planned diagnostic workup of patients with unilateral pleural effusion.

Table 3. The value of additional systematic TUS in the workup of unilateral pleural effusion

Outcomes	*n* = 55
Systematic TUS changed the planned diagnostic management, *n* (%)	3 (5)
Change in diagnostic management led to the cause of the pleural effusion, *n* (%)	0 (0)
Potential change in the planned diagnostic management, *n* (%)	8 (15)
Additional minutes spend on systematic TUS, median (range)	9 (5–21)
Patient alive at follow-up, *n* (%)	49 (89)
Final diagnosis	
Malignant pleural effusion, *n* (%)	21 (38)
Lung cancer	9 (16)
Malignant mesothelioma	7 (13)
Breast cancer	5 (9)
Non-malignant pleural effusion, *n* (%)	34 (62)
Cardiac failure	7 (13)
Nephropathy	1 (2)
Nephropathy and cardiac failure	1 (2)
Hepatic insufficiency	1 (2)
Infectious	
Simple parapneumonic	4 (7)
Empyema	1 (2)
Post-infectious	2 (4)
Post-operative	3 (5)
RA-associated	2 (2)
Pleuritis	7 (13)
Post-radiation therapy	1 (2)
Benign asbestos-related	1 (2)
Traumatic	2 (4)
Meigs syndrome	1 (2)

By recruiting from a centre covering the workup of pleural effusions in the entire Region Zealand, we ensured a broad representation of patients. Therefore, our results can most likely be extrapolated to other Danish regions. However, it should be emphasized that our results are very dependent on our specific clinical setting. Results may be affected by the recentness of available chest scans, the quality of the radiologists' description of scans, and the pulmonologist doing the initial visitation. Other variables include the expertise of the US operator and the access to pleural biopsies. In our study, two of the changes after systematic TUS involved instantly US-guided biopsies. Thus, a clinical set-up with access to instant pleural biopsies is to prefer.

Additional, systematic TUS would most likely have a higher impact on the planned diagnostic workup, if chest CT scans were lacking at visitation. Our study was not powered to bear a subgroup analysis in patients without available scans. However, our results of findings by TUS and chest CT in online supplementary Table A.3 suggest that additional cases of pleural nodules and pericardial effusions can be identified by TUS. Also, our results of diagnostic accuracy in online supplementary Table A.2 suggest that in setting without prior chest CT scans, positive swirling sign, pleural thickening, or nodules and lung consolidation most likely to be tumour and suspected hepatic metastasis have a high specificity for malignancy. This is in line with the findings of previous studies [8, 9]. Our finding of a high specificity of trapped lung should be taken with cautions, since our definition of trapped lung was very vague. It was based on a subjective assessment of the underlying lung and not on, e.g., patient symptoms during drainage and post procedure X-ray [17] or movement of the compressed lung at breath hold using M-mode [18]. This could have led to misclassification.

In this study, we chose not to blind the US operators to available imaging, blood tests, or other diagnostics performed prior to inclusion. This may have introduced confirmation bias. However, we wanted to make a study as close to a real-life clinical setting as possible.

A final limitation was the fact that positive findings on systematic TUS not always led to the expected action. Thus, in total, 8 of 55 patients (15%) had findings on systematic TUS that could lead to a change from the scheduled diagnostic management.

For future studies, we suggest to investigate the value of additional up-front systematic TUS in a randomized trial, which enables more solid outcomes, e.g., time to diagnosis, number of visits to diagnosis, and number of invasive investigations. The study should be powered to do subgroup analysis on patients with and without available chest CT at inclusion. The TUS protocol should include assessment of pleural thickening and nodules, rib/chest invasion, and pulmonary consolidation likely to be a tumour and liver metastasis, since these variables have a high specificity MPE. It should include assessment of lung consolidations to consider differential diagnosis. In a setting without up-front chest CT, a simple cardiac assessment could be including, with regard to the findings of pericardial effusions in our study. Furthermore, the study should have a clear action plan for each positive TUS finding to prevent deviations from the protocol. For now, TUS remains a helpful tool in guiding pleural interventions, as the value of an additional, systematic TUS appears limited.

Conclusions

In our study population, additional up-front, systematic TUS had limited diagnostic effect in patients with unilateral pleural effusion in a setting where chest CT is often available at referral. We cannot recommend TUS following our protocol as routine in these patients.

Statement of Ethics

The study was approved by the Danish Committee of Health Research Ethics (project number: SJ-789) and the Danish Data Protection Agency (REG-076-2019). Written informed consent was obtained from participants.

Conflict of Interest Statement

None of the contributing authors have any conflict of interest to report.

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Author Contributions

P.F.C., C.B.L., and U.B. initiated the research project. K.F., J.K.P., P.F.C., C.B.L., and U.B. contributed to the research protocol. K.F. and J.K.P. performed all clinical examinations. All authors have discussed the results and participated in the writing of the manuscript.

Data Availability Statement

All data from the study are presented in this manuscript or in the online supplementary material. For questions concerning data, please contact the corresponding author.

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