Current evidence for lung ultrasound elastography in the field of pneumology: a systematic review

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Shareable abstract (@ERSpublications)
Ultrasound elastography is a promising tool for pulmonologists and has the potential to improve patient care, although the current evidence is heterogeneous. The absence of standardisation prevents its widespread application in clinical practice. https://bit.ly/4c5UyVr

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Abstract

Background and objectives Elastography is a technology that has strongly impacted several medical specialties; however, it is not yet applied as part of standard clinical practice in the field of pulmonology. The objective of this systematic review is to analyse the evidence available to date in relation to pleuropulmonary ultrasound elastography, focusing on the three pathologies with the most publications: subpleural consolidations, interstitial lung diseases and pleural effusion.

Methods Original *in vivo* studies published up until 12 August 2023 in the Embase, MEDLINE or Web of Science databases were included. The QUADAS-2 tool was applied to analyse bias.

Results We found 613 records in database search. After duplicates removal, we screened 246 records and finally included 18 papers. The average cohort sample size was 109 patients. The elastography modes most frequently used were strain (22.2%), transient elastography (22.2%), point shear-wave elastography (38.9%) and two-dimensional shear-wave elastography (22.2%). The possibility of a meta-analysis was ruled out because of the heterogeneity of the studies included.

Discussion The currently available literature indicates that pleuropulmonary ultrasound elastography produces promising and consistent results, although the lack of standardisation in the use of the technique and in the elastography modes employed still impedes its use in daily clinical pneumology practice. The development of a clinical guideline establishing a common nomenclature and standardised techniques for pleuropulmonary elastography will be imperative to generate quality scientific evidence in this field.

Introduction

Elastography is a technology that, although only developed as recently as the 1990s, has been implemented in numerous areas of medicine as a complement to conventional ultrasound for the study and characterisation of the elasticity of tissues. This technique calculates the Young's modulus of elasticity of a given tissue after the application of an external tension (stress). This tension or stress can be generated by manual compression by the operator, by external vibration or through the emission of an acoustic radiation force through the ultrasound probe itself. Depending on whether the stress applied is a form of longitudinal compression/traction tension (strain) or a transverse tension using a shear wave, the technique will be referred to as strain elastography or shear-wave elastography (SWE), respectively.

Longitudinal waves only allow qualitative calculation of elasticity by measuring the relative strain of the tissue, while with shear waves it is possible to obtain quantitative data as a result of their differential physical characteristics [1]. Thus, using the propagation speed of the shear waves in $m \cdot s^{-1}$, the shear

modulus (G) can be calculated. We can infer Young's modulus (E) mathematically by using the values of G and the speed of propagation of the shear wave previously obtained, while also considering the density of the tissue studied.

Therefore, in strain elastography we can only obtain qualitative or semiquantitative values (the strain ratio) because of the type of wave used, whereas with SWE we can obtain quantitative values in the form of shear wave speed (in $m \cdot s^{-1}$) or the elastic modulus (in kPa). Although the elastic modulus can be expressed as G or as E, the latter is usually used as a reference [1–5]. The European Federation for Ultrasound in Medicine and Biology (EFSUMB) recommends the use of wave speed over elastic modulus because its calculation implies fewer assumptions about the tissue under study [6]. Moreover, there are multiple elastography modes, which can be classified according to the type of wave used, information processing or mechanism used to produce the wave [5].

Importantly, the elasticity of tissues has been related to different pathologies, especially neoplastic or fibrosing diseases, meaning that these tissues can be differentiated from healthy tissue because they are more rigid. Elastography was initially described in 1991 by Ophir *et al*. [7] and was designed for use in patients with breast cancer or liver cirrhosis. The use of this tool has been consolidated and standardised in its respective specialties. However, its use in other medical fields has been progressively increasing and it has proven useful in the study of liver, thyroid, breast, prostate and pancreatic tissue [5].

Despite this, the use of this technology in lung tissue developed later. This is because the lungs were considered organs in motion with air inside them, and it was thought that any measurements would be invalid or not reproducible in clinical practice. However, multiple publications have shown that elastography can be useful in the exploration of pleuropulmonary pathologies, especially in subpleural lesions, interstitial lung diseases (ILDs) and cases of pleural effusion. The superficial locations of these pathologies allow longitudinal or shear waves to propagate adequately through them, and their values can be more reliably recorded. Nonetheless, obtaining these measurements is still complex and their values can easily change if the wave does not present a good signal [8].

In 2019, the EFSUMB published their most recent recommendations for the use of elastography in organs other than the liver [9]; however, these guidelines did not consider lung tissues. Therefore, no specific guidelines on performing pulmonary elastography are currently available, meaning that the technique is not standardised and no common nomenclature or reference values have yet been published in the academic literature.

The objective of this current systematic review was to group together all the evidence related to pleuropulmonary ultrasound elastography available to date and, thus, assess the usefulness of its everyday application in pulmonology services, focusing on the three pathologies for which the most evidence is currently available in this field: subpleural consolidations, ILDs and pleural effusion.

Methods

This systematic review was conducted following the recommendations set out in the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) declaration [10, 11].

Eligibility criteria

All original *in vivo* studies published in English and/or Spanish up until 12 August 2023 on the use of elastography in subpleural consolidations, ILDs or pleural effusion reported in the academic literature were considered. Publications on elastography in the context of echobronchoscopy or magnetic resonance (MR) elastography, as well as conference communications, technique feasibility studies or work published without providing detailed results in the article or its supplementary material, were discarded.

Information sources

The literature search was carried out in the Embase, MEDLINE and Web of Science databases.

Search strategy

The following search terms were used to retrieve relevant articles: (elasto*[Title]) AND (pleur*[Title]), (elasto*[Title]) AND (lung[Title]), (elasto*[Title]) AND (pulmo*[Title]), (elasto*[Title]) AND (effusi*[Title]), (Elasticity Imaging Techniques"[Mesh]) AND (lung[Mesh]), (Elasticity Imaging Techniques"[Mesh]) AND (pleura[Mesh]) and (Elasticity Imaging Techniques"[Mesh]) AND (pleural effusion[Mesh]).

Selection process

The selection process was carried out by the main author of this current article and was reviewed by the second author to ensure correct inclusion and exclusion of the reviewed publications. In case of any disagreements, a third author was consulted to establish a majority.

Data collection process, data items and synthesis methods

The following data were collected from each publication: author, study year, study design, country, sample size, elastography mode employed, measurements (number of measurements, qualitative and quantitative values described, units, and size of the region of interest), probe type used, patient position during the measurement, measurement area, respiratory cycle stage during the measurement, adverse effects/complications during the examination or after the examination, gold standard for diagnosis, pathology subtype (neoplastic strain, ILD subtype or benign aetiology subtype), statistical significance, intraobserver and/or interobserver correlation, and suggested cut-off point. Structured tables were designed to separately collect the data from each study, facilitating comparison of their different characteristics and the numerical values extracted.

The heterogeneity of the publications was analysed by comparing the extracted characteristics in terms of the elastography technique (probe, position and respiratory cycle stage), elastography modes used, measurement types and study design. The nomenclature used to describe the elastography modes varied greatly according to different authors and commercial brands employed and so, to avoid confusion, we used a common nomenclature adapted from the EFSUMB guidelines and based both on the type of wave (longitudinal or shear) used and the method applied to generate it (manual compression, external vibration or radiating acoustic force) [1, 6], as follows. “Strain” refers to qualitative elastography based on longitudinal waves generated by manual compression. “Acoustic radiation force impulse (ARFI)-strain” refers to qualitative elastography based on the use of longitudinal waves generated by acoustic radiation force generated through the ultrasound probe. “Transient elastography (TE)” is quantitative elastography based on shear waves generated by external vibration. “Point shear-wave elastography (pSWE)” is quantitative elastography based on shear waves generated by applying an acoustic radiation force through the ultrasound probe at a specific point on the ultrasound image chosen by the operator. Of note, some authors refer to this elastography mode using the nomenclature “ARFI”. “Two-dimensional shear-wave elastography (2D-SWE)” is quantitative elastography based on shear waves generated by acoustic radiation force *via* the ultrasound probe in an area of the ultrasound image chosen by the operator, generating a colour elastography map of the chosen region in real time.

Study risk of bias assessment

To analyse the possible biases of the included publications, we used the QUADAS-2 tool to assess the quality of the diagnostic accuracy studies included in this systematic review, after adapting it for use in this study according to the recommendations of its original authors [12]. Given the absence of current guidelines standardising the technique, establishing reference values for interpretating results or indicating the elastography mode that should be applied for pleuropulmonary pathologies, the applicability section of the QUADAS-2 index test was excluded. Furthermore, we developed a quality scale for the publications included in this systematic review (rated from 0 to 10, as detailed in supplementary table 4S) according to the following items: total sample size, study centres, study design, elastography modes, measurement types and number of measurements.

Results

Study selection

We found 613 records in the database search. After removing duplicates, we screened 246 records, reviewed 37 full-text documents and finally included 18 articles. The selection of publications, the number of excluded publications and the reasons for their exclusion are detailed in figure 1.

Study characteristics

Tables 1, 2 and 3 show the characteristics of the publications describing the use of elastography in cases of subpleural consolidations (n=10 articles), ILDs (n=5 articles) and pleural effusion (n=3 articles).

Risk of bias in studies

The QUADAS-2 tool [12], designed to analyse bias and applicability in systematic reviews focused on diagnostic accuracy studies, was applied to analyse possible bias in the studies included in this systematic review. Supplementary tables 1S, 2S and 3S describe the bias analysis in more detail.

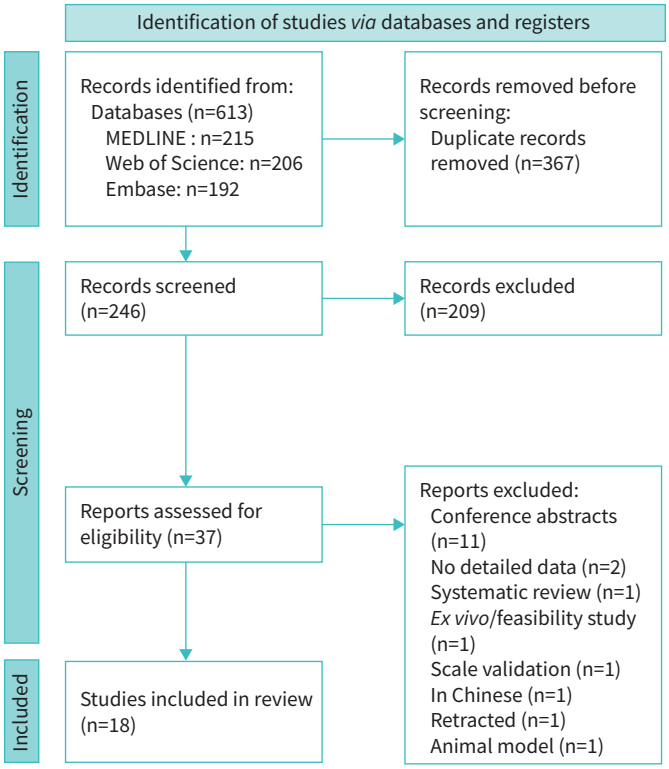

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram.

Results of individual studies

Tables 4, 5 and 6 describe the individual results of each publication corresponding to subpleural consolidations, ILDs and pleural effusion, respectively.

Results of syntheses

After applying the inclusion and exclusion criteria, 18 publications that had focused on the use of elastography in pleuropulmonary pathologies were analysed in this systematic review. The mean patient cohort sample size was 109 patients and the average patient age was 62.2 years. Most of the patients studied in publications examining pleural effusion and consolidations were male, while the majority of the patients with ILDs were female. Publications focusing on subpleural consolidations, ILDs and pleural effusion had a total sample size of 1125, 433 and 402, respectively; 60% (six out of 10) of the articles on subpleural consolidation were published after 2020, while this figure was 10% (one out of five) for ILD and 33% (one out of three) for pleural effusion. The earliest study included in this systematic review dated from 2014 [16].

The application of elastography also varied between studies, with an average of 6.2 measurements per area studied. Some 72.2% of the studies (13 out of 18) were performed with apnoea: 38% (five out of 13) at the maximum inspiration point and 15.4% (two out of 13) at mid-inspiration, with 46% (six out of 13) not describing how the apnoea had been produced. The elastography was performed with spontaneous breathing in 5.5% studies (one out of 18), while the point in the respiratory cycle at which the measurements had been made was not described in 22.2% (four out of 18). No adverse effects resulting from the elastography exploration were reported in any of the publications.

A convex probe was used in all studies relating to subpleural consolidations, whereas a linear probe was used in studies relating to pleural effusion and ILDs. The technique was performed with the patient in a sitting position in 44% of the publications (eight out of 18) and in the supine or a variable position in 22.2% (four of 18); this information was unknown or not stated in the other 33.3% (six out of 18).

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TABLE 1 Characteristics of studies about subpleural consolidations

Study	Study design	Country	Sample size	Gold standard	Elastography mode	Measurements	Transducer (ROI size)	Position (time of measurement[#])	Number of measurements (end result[¶])
Li *et al.*, 2021 [13]	Prospective consecutive	China	153	Biopsy	Strain	Qualitative $(1–5)^{+}$	Convex (variable)	Variable (apnoea)	1 (qualitative)
Kuo *et al.*, 2021 [14]	Mixed (prospective and retrospective)	Taiwan	354	Biopsy, microbiology and/or evolution in 6 months	2D-SWE	Quantitative (kPa)	Convex (3 mm)	UNK (apnoea)	1 or 3 (mean of the 4 highest values)
Alhyari *et al.*, 2021 [15]	Prospective consecutive	Germany	87	Biopsy and/or clinical-radiological evolution	pSWE	Quantitative ($m·s^{-1}$)	Convex (10×5 mm)	UNK (apnoea)	11 (mean of all values)
Sperandeo *et al.*, 2014 [16]	Prospective consecutive	Italy	95	Biopsy in malignancies, rest UNK	Strain	Qualitative $(1–5)^{+}$	Convex (whole lesion)	UNK (apnoea)	UNK (qualitative)
Boccatonda *et al.*, 2021 [17]	Prospective non-consecutive non-randomised	Italy	14	Not explicitly described	pSWE and strain	Qualitative $(1–3)^{+}$ and quantitative ($m·s^{-1}$)	pSWE: Convex (whole lesion) Strain: (whole lesion)	Supine (spontaneous breathing)	3 (mean of all measurements)
Unlu *et al.*, 2021 [18]	Prospective non-consecutive non-randomised	Turkey	63	Biopsy	pSWE	Quantitative ($m·s^{-1}$)	Convex (10×5 mm)	UNK (apnoea)	3–10 (highest value of all measurements)
Wei *et al.*, 2018 [19]	Retrospective	China	91	Biopsy	Strain, ARFI and pSWE	Qualitative $(1–4)^{+}$ and quantitative ($m·s^{-1}$)	Convex (6×5 mm)	UNK (UNK)	7 (mean of all measurements removing extreme values)
Lim *et al.*, 2016 [20]	Retrospective	Taiwan	45	Biopsy except in pneumonia: symptoms and radiological evolution	Strain	Semiquantitative (strain ratio)	Convex (centre of the lesion and a nearby subcutaneous muscle layer)	Variable (apnoea)	3 (mean of all measurements)
Quarato *et al.*, 2022 [21]	Prospective unspecified	Italy	190	Symptoms, microbiology and/or histology	pSWE	Quantitative ($m·s^{-1}$ and kPa)	Convex (variable)	Sitting (apnoea)	10 (median of all reliable measurements)
Ozgokce *et al.*, 2018 [22]	Prospective unspecified	Turkey	33	Symptoms, microbiology and/or histology	pSWE	Quantitative ($m·s^{-1}$)	Convex or linear (1×1 mm)	UNK (apnoea)	24–30 (mean of all measurements)

ROI: region of interest; 2D-SWE: bidimensional shear-wave elastography; UNK: unknown; pSWE: point shear-wave elastography; ARFI: acoustic radiation force impulse. [#]: time of the respiratory cycle when measurement is taken; [¶]: way of calculating the final result of the measurement; [+]: qualitative scales given with lower numbers demonstrating the most elasticity and highest numbers the least elasticity.

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TABLE 2 Characteristics of studies on ILD

Study	Study design	Country	Sample size	ILD subtype	Elastography mode	Measurements	Transducer (ROI size)	Position (time of measurement[#])	Number of measurements (end result[¶])	Measurement area[+]
Zhang *et al.*, 2017 [23]	Unspecified	USA	I: 41 C: 30	SSc	TE	Quantitative ($m \cdot s^{-1}$)	Linear (UNK)	Sitting (apnoea)	3 (mean of all measurements)	3 bilateral intercostal spaces (A, P, L)
Clay *et al.*, 2018 [24]	Unspecified	USA	I: 77 C: 19	SSc (39%), RA (12%), antisynthetase syndrome (8%), IPF (7%), polymyositis (5%), Sjögren (4%), other CTD (14%), others (12%)	TE	Quantitative ($m \cdot s^{-1}$)	Linear (UNK)	Sitting (apnoea)	3 (UNK)	3 bilateral intercostal spaces (A, P, L)
Huang *et al.*, 2022 [25]	Prospective consecutive	China	I: 65 C: 60	Associated with CTD	2D-SWE	Quantitative ($m \cdot s^{-1}$ and kPa)	Linear (1 mm)	Sitting and supine (apnoea)	3 (mean of all measurements)	50 lung sites
Zhang *et al.*, 2017 [26]	Unspecified	USA	I: 10 C: 10	Associated with CTD (90%) and IPF (10%)	TE	Quantitative ($m \cdot s^{-1}$)	Linear (UNK)	Sitting (apnoea)	3 (mean of all measurements)	3 bilateral intercostal spaces (A, P, L)
Zhou *et al.*, 2019 [27]	Prospective unspecified	USA	I: 91 C: 30	NSIP (50%), fibrotic NSIP (11%), UIP (10%), others (29%)	TE	Quantitative ($m \cdot s^{-1}$)	Linear (UNK)	Sitting (apnoea)	3 (UNK)	3 bilateral intercostal spaces (A, P, L)

ILD: interstitial lung disease; ROI: region of interest; I: case group; C: control group; SSc: systemic sclerosis TE: transient elastography; UNK: unknown; A: anterior; P: posterior; L: lateral; RA: rheumatoid arthritis; IPF: idiopathic pulmonary fibrosis; CTD: connective tissue disease; 2D-SWE: bidimensional shear-wave elastography; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia. [#]: time of the respiratory cycle when measurement is taken; [¶]: way of calculating the final result of the measurement; [+]: places on the chest where transducer is positioned to take the measurement.

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TABLE 3 Characteristics of studies about pleural effusion

Study	Study design	Country	Sample size	Gold standard	Elastography mode	Measurements	Transducer (ROI size)	Position (time of measurement[#])	Number of measurements (end result[¶])
Ozgokce *et al.*, 2019 [28]	Prospective unspecified	Turkey	60	Analysis of pleural fluid	pSWE	Quantitative ($m \cdot s^{-1}$)	Linear (UNK)	Sitting (UNK)	8–12 (mean of all measurements)
Jiang *et al.*, 2019 [29]	Prospective unspecified	China	244	Biopsy in malignancies; symptoms, complementary tests (analytical, imaging and microbiology) and evolution in at least 1 year for benignity	2D-SWE	Quantitative (kPa)	Linear (1–8 mm)	Sitting (UNK)	UNK (mean, maximum and minimum index)
Deng *et al.*, 2023 [30]	Prospective unspecified	China	98	Biopsy	2D-SWE	Quantitative (kPa)	Linear (variable)	Sitting (UNK)	3 (maximum measurement or measurement ⩾47.25 kPa)

ROI: region of interest; pSWE: point shear-wave elastography; UNK: unknown; 2D-SWE: bidimensional shear-wave elastography. [#]: time of the respiratory cycle when measurement is taken; [¶]: way of calculating the final result of the measurement.

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TABLE 4 Results of studies on subpleural consolidations

Study	Elastography mode	Measurements	Elasticity and measure of variability (benign)	Elasticity and measure of variability (malignancy)	Statistical significance	Cut-off point	Correlation	Quality scale (0–10)[#]
Li *et al.*, 2021 [13]	Strain	Qualitative (1–5)[#]	Mean±SD: 3.41±0.99 (n=64)	Mean: 4.24±0.85 (n=89)	p<0.05	No	No	4
Kuo *et al.*, 2021 [14]	2D-SWE	Quantitative (kPa)	Median (IQR): Bacterial pneumonia (n=62): 42.64 (22.77–57.45) Fungal pneumonia (n=23): 54.33 (33.03–65.73) Tuberculosis (n=13): 77.53 (71.29–89.10)	Median (IQR): Adenocarcinoma (n=120): 103.09 (92.20–113.98) SCLC (n=23): 95.09 (69.28–105.36) Metastasic lung cancer (n=20): 105.22 (94.29–122.76) Lung lymphoma (n=8): 109.09 (98.22–120.97)	p<0.05	65 kPa S: 89.7% E: 70.6%	Interobserver: 0.93	4
Alhyari *et al.*, 2021 [15]	pSWE	Quantitative ($m \cdot s^{-1}$)	Mean±SD: 1.82±0.97 (n=58)	Mean±SD: 3.05±0.73 (n= 29)	p<0.001	2.21 $m \cdot s^{-1}$ S: 89.7% E: 75.9%	No	5
Sperandeo *et al.*, 2014 [16]	Strain	Qualitative (1–5)[#]	Not specified: 2.35±0.48 (all pneumonia, n=34)	Not specified: 4.19±0.55 (n=61)	p <0.0001	4 S: 86.9% E: 99.7%	No	3
Boccatonda *et al.*, 2021 [17]	pSWE and strain	Qualitative (1–3)[#] and quantitative ($m \cdot s^{-1}$)	Mean±SD: 3.36±1.20 $m \cdot s^{-1}$ (n=8), qualitative not specified	Mean±SD: 5.92±2.8 $m \cdot s^{-1}$ (n=6), qualitative not specified	Unspecified	pSWE: 3.6 $m \cdot s^{-1}$ Strain: 2.5	No	3
Unlu *et al.*, 2021 [18]	pSWE	Quantitative ($m \cdot s^{-1}$)	Mean±SD: 3.55±0.71 (n=19)	Mean±SD: 4.13±0.59 (n=64)	p<0.001	4.08 $m \cdot s^{-1}$ S: 68.2% E: 84.2%	No	3
Wei *et al.*, 2018 [19]	Strain, ARFI-strain and pSWE	Qualitative (1–4)[#] and quantitative ($m \cdot s^{-1}$)	Total (n=36) SWE (mean±SD): 1.85±0.92 Strain: Score 1: 10 (71.4%) Score 2: 17 (33.3%) Score 3: 5 (29.4%) Score 4: 4 (44.4%) ARFI-strain: Score 1: 15 (93.8%) Score 2: 4 (33.3%) Score 3: 15 (37.5%) Score 4: 2 (8.7%)	Total (n=55) SWE (mean±SD): 2.47±0.92 Strain: Score 1: 4 (28.6%) Score 2: 34 (66.7%) Score 3: 12 (70.6%) Score 4: 5 (55.6%) ARFI-strain: Score 1: 1 (6.3%) Score 2: 8 (66.7%) Score 3: 25 (62.5%) Score 4: 21 (91.3%)	SWE: p<0.002 Strain: p=0.542 ARFI-strain: p<0.001	pSWE: 1.951 $m \cdot s^{-1}$ S: 70.9% E: 69.4% ARFI-strain: score 3 S: 83.6% E: 52.8%	No	4
Lim *et al.*, 2016 [20]	Strain	Semiquantitative (strain ratio)	Mean±SD: 21.03±16.51 (n=7)	Mean±SD: 41.07±20.32 (n=25)	Not statistically significant	No	Intraobserver: 0.955	1
Quarato *et al.*, 2022 [21]	pSWE	Quantitative ($m \cdot s^{-1}$ and kPa)	Mean±SD: 2.73±0.60 $m \cdot s^{-1}$; 24.87±10.64 kPa (n=46)	Mean±SD: 2.59±0.55 $m \cdot s^{-1}$; 22.32±8.97 kPa (n=144)	Not statistically significant	No	No	5
Ozgokce *et al.*, 2018 [22]	pSWE	Quantitative ($m \cdot s^{-1}$)	Mean±SD: 2.18±0.49 $m \cdot s^{-1}$ (n=13)	Mean±SD: 3.50±0.69 $m \cdot s^{-1}$ (n=20)	p<0.001	No	No	3

2D-SWE: bidimensional shear-wave elastography; SCLC: small cell lung cancer; S: sensitivity; E: specificity; pSWE: point shear-wave elastography; ARFI: acoustic radiation force impulse. [#]: qualitative scales given with lower numbers demonstrating the most elasticity and highest numbers the least elasticity.

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TABLE 5 Results of studies on ILD

Study	Elastography mode	Measurements	Elasticity and measure of variability (control)	Elasticity and measure of variability (ILD)	Statistical significance	Cut-off point	Correlation	Quality scale (0 –10)
Zhang *et al.* 2017 [23]	TE	Quantitative ($m \cdot s^{-1}$)	Mean±SD (n=30): 100 Hz: 1.98±0.26 150 Hz: 2.61±0.22 200 Hz: 3.12±0.33	Mean±SD (n=41): 100 Hz: 2.98±0.42 150 Hz: 3.64±0.45 200 Hz: 4.84±0.87	p<0.0001	No	Intraobserver and interobserver (all frequencies): >0.9	2
Clay *et al.* 2018 [24]	TE	Quantitative ($m \cdot s^{-1}$)	Median (n=19): 100 Hz: 2.31 150 Hz: 3.35 200 Hz: 4.32	Median (n=77): 100 Hz: 2.83 150 Hz: 4.23 200 Hz: 5.47	p<0.01	No	No	2
Huang *et al.* 2022 [25]	2D-SWE	Quantitative ($m \cdot s^{-1}$ and kPa)	Median (IQR) (n=60): 15.2 kPa (12.30–18.40 kPa); 2.20 $m \cdot s^{-1}$ (2.00–2.50 $m \cdot s^{-1}$)	Median (IQR) (n=65): 17.90 kPa (12.20–25.68 kPa); 2.40 $m \cdot s^{-1}$ (2.00–2.90 $m \cdot s^{-1}$)	p<0.001 (both)	15.81 kPa: S: 65% E: 67% 2.31 m/s: S: 59% E: 73%	Intraobserver and Interobserver: >0.97 (p<0.01)	6
Zhang *et al.* 2017 [26]	TE	Quantitative ($m \cdot s^{-1}$)	Mean±SD (n=10): 100 Hz: 2.01±0.2 150 Hz: 2.8±0.26 200 Hz: 3.39±0.2	Mean±SD (n=10): 100 Hz: 3.2±0.23 150 Hz: 4.1±0.26 200 Hz: 5.68±0.38	p<0.05	No	No	1
Zhou *et al.* 2019 [27]	TE	Quantitative ($m \cdot s^{-1}$)	Unspecified	Unspecified	Unspecified	5.47 $m \cdot s^{-1}$ (200 Hz) S: 92% E: 89%	No	3

ILD: interstitial lung disease; TE: transient elastography; 2D-SWE: bidimensional shear-wave elastography; S: sensitivity; E: specificity.

TABLE 6 Results of studies on pleural effusion

Study	Elastography mode	Measurements	Elasticity and measure of variability (transudate)	Elasticity and measure of variability (exudate)	Statistical significance	Cut-off point	Correlation	Quality scale (0–10)
Ozgokce *et al.* 2019 [28]	pSWE	Quantitative ($m \cdot s^{-1}$)	Mean±SD (n=17): 2.29±0.41	Mean±SD (n=43): 3.29±0.63	p<0.001	2.52 $m \cdot s^{-1}$: S: 91% E: 76.5%	Intraobserver: >85%	4
Jiang *et al.* 2019 [29]	2D-SWE	Quantitative (kPa)	Unspecified	Unspecified	Unspecified	47.25 kPa (mean): S: 90.6% E: 86.9%	Interobserver: not statistically significant	4
Deng *et al.* 2023 [30]	2D-SWE	Quantitative (kPa)	Unspecified	Unspecified	Not applicable	S: 88.7% E: 100%	No	4

pSWE: point shear-wave elastography; S: sensitivity; E: specificity; 2D-SWE: bidimensional shear-wave elastography.

All but one of the studies considered here were single centre (94%; 17 out of 18). 66.7% (12 out of 18) were prospective studies, 16.7% (three out of 18) were mixed or retrospective and 16.7% (three out of 18) had not specified the study design. Among the prospective articles, none were randomised and 33.3% (four out of 12) were defined as consecutive. Only two out of the 18 publications (11.1%) had described the source of the participating individuals (recruited hospitalised patients), while the origin of the patients was not stated in the remaining manuscripts.

The elastography modes that were used were as follows: 22.2% strain (four out of 18), 22.2% TE (four out of 18), 5.5% ARFI-strain (one out of 18), 38.9% pSWE (seven out of 18) and 22.2% 2D-SWE (four out of 18). In the quantitative modes, 33.3% (five out of 15) analysed the elastic modulus (in kPa) and 80% (12 out of 15) had measured the shear-wave speed (in $m \cdot s^{-1}$). Qualitative measurements had only been applied in four of the publications about subpleural consolidations, two of which had used the classification by Sperandeo *et al.* [16], which is itself an adaptation of the qualitative classification applied by Itoh *et al.* [31] in breast elastography analyses. One publication had applied a semiquantitative method that used the term "strain ratio" to compare the qualitative values of strain elastography of the chest wall to that of the analysed tissue [20].

The studies included for every respiratory pathology subtype all presented biases, especially in relation to patient selection (as individually presented in supplementary tables 1S–3S according to the results from the QUADAS-2 tool [12]). In addition, in this systematic review we developed a numerical scale to reflect the level of importance we assigned to each publication considered (supplementary table 4S). Finally, given the heterogeneity of the publications, as reflected in the study characteristics section (tables 1–3) in terms of the case mixes, study design, technique used, elastography modes employed, measurements collected and measurement acquisition methods, we were unable to perform a meta-analysis.

Discussion

To the best of our knowledge, this is the first systematic review of the use of ultrasound elastography for pleuropulmonary pathologies conducted to date that meets the PRISMA statement criteria [10]. One brief systematic review on this topic was published in 2020 [8] but it did not meet these aforementioned quality criteria and is already outdated given the various new lines of evidence that have become available in the intervening period. Our review collates, updates and critically analyses the knowledge generated regarding pleuropulmonary elastography when employed in the three main pathologies that scientific research in this area has mainly focused on: subpleural consolidations, ILDs and pleural effusion.

In terms of publication volumes and the variety of elastography modes used, most of the evidence available in this field to date is related to the applications of elastography in the context of subpleural consolidations. For the most part, these results were statistically significant in terms of the aetiological differentiation of benign and malignant lesions, both when using qualitative modes such as strain, and quantitative modes such as pSWE or 2D-SWE. However, the results from different studies related to subpleural consolidations are also the most controversial compared to the other pathologies under review. For example, the study by Quarato *et al.* [21] included a wide range of cases but the use of pSWE showed no significant differences between the different aetiologies of these pathologies, except for

community-acquired pneumonia compared to pneumonia that was refractory to standard treatment. Furthermore, both the absolute numerical results and the cut-off points established in these different publications were inconsistent and showed great variability, as shown in table 4. These discrepancies were probably because of the lack of standardisation in the elastography techniques and modes used between publications. It is also worth mentioning the study by Wei *et al*. [19], which was the only analytical research that employed different elastography modes (strain, pSWE and ARFI). These authors showed statistically significant results for the aetiological differentiation of lesions using pSWE and ARFI, but not the strain mode. However, given its retrospective nature and that it did not directly compare the pSWE, ARFI and strain modes, among other biases, the aforementioned study had several limitations.

Furthermore, some of the sub-analyses in the studies included in this review suggest that elastography can differentiate between not only benign and malignant tissues, but also different types of benign [14, 21] or malignant [20] consolidation pathologies. However, the sub-analyses performed in different publications were inconsistent and so further work considering a wider range of cases will probably be required to clarify these results. Nevertheless, there is a consensus that consolidations associated with granulomatous diseases (especially tuberculosis) or pulmonary infarctions produce qualitative and quantitative elastography values similar those of neoplasms. In other words, they are both less elastic [13–15].

In the case of ILDs, most of the available evidence has employed TE technology and four of the five studies included in our review were conducted by the same Mayo Clinic (USA) group [23, 24, 26, 27]. Of note, these authors applied a homogeneous methodology in terms of the elastography technique and mode utilised. The majority of ILD cases studied in these four publications were associated with connective tissue diseases, especially those secondary to systemic sclerosis. In every case, elasticity was measured at the level of the pleural line.

Importantly, the results from elastography performed in patients with ILDs were consistent in all five publications considered here, including in the Chinese study by Huang *et al*. [25], which used a different measurement methodology alongside the pSWE mode. Both the TE and pSWE modes detected a significantly higher wave velocity in patients with ILDs than in people with no previous lung pathologies. This was demonstrated even with different wavelengths (100, 150 and 200 Hz) for the TE mode, although the variability of the data between these studies was striking despite having been published by the same authors, using very similar methodology and the same elastography mode [23, 24, 26, 27]. There were conflicting results as to whether elastography could differentiate the severity of ILDs among already diagnosed patients [24, 25, 27] and there are no data to suggest that elastography is useful in the long-term follow-up of ILDs. Furthermore, the sensitivity and specificity of the cut-off points proposed by the two groups responsible for these studies were very different, perhaps because of the heterogeneity of the cases considered and the methodologies and elastography modes employed [25, 27]. In short, in our opinion, the level of evidence for the use of elastography for ILDs is low given that there is only one publication from a group other than that of X. Zhang (Mayo Clinic) and colleagues. Furthermore, they used the TE mode, which was not employed in any other publications examining pleuropulmonary pathologies. Notwithstanding, we believe it is important to continue expanding the evidence regarding the use of elastography in the field of early detection and, above all, in the long-term follow-up of ILDs. This is especially relevant because elastography is a safe and rapid method that does not involve using radiation.

Finally, the lowest amount of evidence for the use of elastography in the field of pulmonology was available for pleural effusion. However, application in this context also produced the most promising results. Only three studies, by Ozgokce *et al*. [28], Jiang *et al*. [29] and Deng *et al*. [30], examining the use of elastography in this context have been published to date, and all of them had different objectives. The first aimed to differentiate between transudates and exudates by using pSWE, the second tried to differentiate benign and malignant aetiologies of pleural effusion by comparing 2D-SWE with conventional ultrasound, and the third performed 2D-SWE-guided pleural biopsies. Finally, we found no published data regarding the use of strain elastography in the context of pleural effusion. All three studies showed positive results (using the cut-off points described in table 6), with a sensitivity close to 90% in each case. The 2019 publication from Jiang *et al.* [29] demonstrated that, compared to conventional B-mode ultrasound, 2D-SWE was better at detecting malignant effusions, except for mesotheliomas, and established a malignancy cut-off point of 47.25 kPa. This group subsequently used this cut-off point to select a pleural biopsy site for effusions in cases where conventional ultrasound had provided insufficient information (absence of pleural nodules or pleural thickening), and achieved a sensitivity of 88.7% [30]. Of note, this result exceeded the sensitivity reported in a meta-analysis on blind pleural biopsy (77%) and was close to the results of medical thoracoscopy (93%) [32]. Thus, if these results are confirmed, elastography would represent a very useful tool both for the early and noninvasive diagnosis of malignant

pleural effusion and for improving the effectiveness of pleural biopsies, making it an alternative to medical thoracoscopy, especially in locations difficult to assess with the latter [30].

It is important to note that none of these three publications measured the shear-wave speed specifically in the pleural effusion because these waves are not transmitted through low viscosity liquids [5]; rather, they were measured in the pleura, specifically in the area between the anterior and posterior costal margins where the pleura and all intercostal fatty and muscular structures are located. The pleura is not normally visible with ultrasound but is anatomically located at this measurement point (the location that is traditionally referred as the pleural line is, in reality, the lung surface itself) [33].

Studies related to elastography in other lung pathologies, such as TE in acute lung oedema [34], have also been published. In the latter, Wiley *et al*. [34] demonstrated significant differences in shear-wave velocity measurements after treatment with diuretics for 1–2 days. Moreover, 2D-SWE has also been applied to monitor cases of COVID-19, although the results for the detection of sequelae after discharge were not significant [35]. Similarly, publication of elastography in patients with COPD showed that decreased diaphragmatic elasticity correlated to disease severity on the Global Initiative for Chronic Obstructive Lung Disease grade stratification [36]. Finally, a sign called “elasto-lung point” when strain elastography is applied to pneumothorax has been described and can help identify and confirm the conventional “lung point” [37]. To test for the presence of this sign, a colour map that qualitatively grades lung elasticity is generated on a B-mode ultrasound image in which the pneumothorax area is highlighted in a different colour (blue or red, depending on the settings) with respect to the healthy lung area. This occurs because the device mistakenly identifies the pneumothorax as a more rigid location. Identifying this sign can facilitate the diagnosis of pneumothorax by ultrasound, especially in doubtful cases, although its usefulness in other elastography modes must still be confirmed.

Lung elastography is not only limited to ultrasound, it can also be applied to other imaging tests. MR lung elastography is a promising technique, which has been shown in the work of Marinelli *et al*. [38], who were able to differentiate individuals with ILD from healthy subjects. However, most of the available evidence is either from animal models or from feasibility studies [39, 40], so at present it is not possible to draw conclusions about its usefulness. In addition, the lack of availability and the cost of this imaging test, in contrast to ultrasound elastography, may add great difficulty to its inclusion in routine clinical practice in the case it proves valuable in the field of ILD.

The most important limitation to this present systematic review lies in the variability of the techniques employed by the authors of the studies included, as well as the multitude of elastography modes now available for use. These were the two main reasons we ruled out the possibility of conducting a meta-analysis of these studies. One of the biggest arguments against the use of elastography is the reproducibility of the measurements obtained as a result of the complexity of the technique. However, excellent interobserver and/or intraobserver correlation (>0.9 in most publications) have been reported, even when using strain elastography (which is a qualitative mode that depends on the force applied by the operator) [20], in cases of consolidations [14, 20], pleural effusion [28, 29] and ILDs [23, 25]. Another aspect of the technique that remains undefined is the appropriate wave frequency for use. In this sense, only X. Zhang (Mayo Clinic) and colleagues have studied this question and they did not find significant differences between the results obtained at 100, 150 or 200 Hz [23, 24, 26].

Importantly, no adverse effects were recorded for elastography performed using any of its different frequencies or modes in any of the publications included in this systematic review. The EFSUMB guidelines recommend that examinations be as short as possible because of the risk of damaging sensitive tissues with acoustic radiation force. This is because prolonged exposure in simulations are associated with increased local heat, especially in bone tissues [9]. Initially, there was some concern about the use of elastography in lung tissue, justified by the risk of acoustic cavitation due to the amount of air present in the alveoli [41]. However, commercially available elastographs are designed to operate within established limits of mechanical index, thermal index and transmit power, and there are no currently published adverse effects from the use of lung elastography in humans [41]. Studies conducted in rats have related the use of elastography based on acoustic radiation force with the presence of pulmonary capillary haemorrhages, although this also occurred when other modes most commonly used in clinical practice (B or pulsed doppler modes) were used in these studies [42, 43]. To date, there is no evidence that elastography can have this effect in humans. Given the safety data extracted in this present review, we consider elastography a safe technique (although long-term data are still required to confirm this), thereby supporting the EFSUMB safety recommendations in the context of lung explorations [9].

Another limitation of this current work is that practically all the studies we analysed were single centre and many of them were not randomised and did not use a consecutive recruitment approach. Furthermore, we did not explore possible publication biases. Moreover, many of the studies we included had established strict criteria to exclude patients unable to perform apnoea and so a significant portion of patients with pulmonary disease were not considered. Thus, results from these publications may not be valid for a significant number of patients. Therefore, given the heterogeneity of the evidence currently available, it is imperative to create clinical guidelines that establish a common nomenclature using standardised techniques in order to generate quality scientific evidence on pulmonary elastography, in line with other areas of medicine in which this technology has been applied.

Conclusions

Ultrasound elastography is a promising tool for the study of pleuropulmonary pathologies. However, interpreting the evidence generated to date is a complex task. The multiple elastography modes used and lack of technique standardisation currently prevents the widespread application of elastography into daily clinical practice. The greatest core of evidence for the use of this technology is for subpleural consolidations, with multiple studies supporting its utility for the aetiological differentiation of benign and malignant tissues in practically every elastography mode, although this evidence still remains controversial.

Furthermore, the use of elastography for other pathologies such as ILDs or pleural effusion still requires further study to provide certainty about the usefulness of this technology. To date, the available results are consistent and favourable for both pathologies, but its applicability is very limited to the results of a single publication or to a specific elastography mode. However, if these positive results are confirmed, elastography has the potential to substantially improve the care of patients with pulmonary pathologies because it would allow for early diagnosis and follow-up of serious diseases at the bedside, thereby avoiding unnecessary radiation with safe techniques that are accessible to any trained clinician. Lastly, the development of a clinical guide that establishes a common nomenclature and standardised techniques for pleuropulmonary elastography will be imperative to generate quality scientific evidence in this field.

Provenance: Submitted article, peer reviewed.

This systematic review was registered in the international prospective register of systematic reviews (PROSPERO) with registration number CRD42023472828. The review protocol was not published or deposited in a public repository at the time of registration. The materials and data extracted for the preparation of this publication are not available in online public repositories.

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