EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Jiang B, Li X-lian, Yin Y, *et al*. Ultrasound elastography: a novel tool for the differential diagnosis of pleural effusion. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.02018-2018).

Ultrasound elastography: a novel tool for the differential diagnosis of pleural effusion

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Summary: Pleural ultrasound elastography is a better technique than traditional thoracic ultrasound for diagnosing malignant pleural effusion.

Abstract

Introduction: Traditional thoracic ultrasound (TUS) is often the initial tool used to help diagnose malignant pleural effusion (MPE). Ultrasound elastography (UE), a relatively new technique, has been used to differentiate malignant disease from benign disease by evaluating tissue "stiffness". However, no studies evaluating the efficacy of UE for diagnosing MPE are available. We assessed the value of UE for diagnosing MPE prospectively.

Methods: All 244 enrolled patients were divided into a development set and a validation set in chronological order. The cut-off elasticity index (EI) was established using a receiver operating characteristic curve constructed from the continuous data of the patients in the development set. The diagnostic performance of UE was compared with that of TUS in the validation set.

Results: In the development set, the mean EI (47.25 kPa) was the optimal cut-off. In the validation set, pleural UE had a sensitivity of 83.64%, a specificity of 90.67%, a positive predictive value of 86.79%, a negative predictive value of 88.31%, a positive likelihood ratio of 8.96, and a negative likelihood ratio of 0.18 for diagnosing MPE. The sensitivity of UE was significantly higher (p=0.006) than that of TUS (60.00%).

Conclusion: Pleural UE is a better technique than TUS for differentiating MPE from benign pleural disease.

Key Words: malignant pleural effusion, ultrasound elastography, tuberculosis, pleurisy

Introduction

Pleural effusion is an extremely common problem; however, the diagnosis of pleural effusion remains challenging due to its diverse etiologies. Malignant pleural effusion (MPE) is one of the leading causes of unilateral pleural effusion, and many clinical guidelines have recommended diagnostic strategies for MPE [1, 2]. Radiographic techniques, such as contrast-enhanced computed tomography (CECT) and thoracic ultrasound (TUS), have been shown to be valuable in the diagnosis of MPE. Ultrasound imaging is convenient, free of radiation and can be used to diagnose pleural disease, guide closed pleural biopsy and assess the characteristics of pleural effusion [1]. Ultrasound elastography (UE) is a recently developed, novel ultrasound technology that can be used to quantitatively assess tissue stiffness by measuring the degree of distortion under the application of an external force (shear waves). Since tumor tissue is stiffer than normal tissue, UE has been used to evaluate tissue stiffness and is a very valuable imaging method for differentiating malignant from benign disease, such as breast [3], thyroid [4], and liver diseases [5, 6]. However, to the best of our knowledge, no published studies have assessed the diagnostic value of UE in MPE. We conducted this prospective study to determine the cut-off elasticity index (EI) for the diagnosis of MPE and to assess the diagnostic accuracy of UE compared with TUS for differentiating MPE from benign pleural effusion.

Methods:

Study design

The study was prospectively conducted at the First Hospital of China Medical University between October 2012 and October 2017. Patients with unilateral or bilateral pleural effusion were enrolled in this study. The inclusion criteria were as follows: (1) patients with pleural effusion, as demonstrated by chest radiography; (2) undiagnosed effusions (malignant or otherwise) at the first patient encounter or presentation; (3) patients who did not undergo thoracentesis, drainage and analysis of pleural effusions before enrollment; and (4) patients who, in clinical practice, would have undergone further examination to establish the cause of pleural effusion. The exclusion criterion was patients who were unable or declined to undergo further examination to establish the cause of pleural effusion. All enrolled patients were divided into a development set and a validation set based on the chronological order in which they presented to the hospital (Figure 1). The primary outcome was the capacity of UE to identify MPE compared with traditional TUS. The secondary outcome was the influence of different etiologies on the diagnostic performance of UE. This study was approved by the Institutional Ethical Review Board of the First Hospital of China Medical University (reference number: 201-9126-2), and written informed consent was obtained from all patients.

To obtain the desired level of statistical power for evaluating the accuracy of the diagnostic test, the minimal sample size required was calculated based on the estimated sensitivity and specificity [7], as follows:

$$N_{Se} = \frac{Z_{\frac{\alpha}{2}}^2 \times \widehat{Se} \times (1-\widehat{Se})}{d^2 \times Prev}; N_{Sp} = \frac{Z_{\frac{\alpha}{2}}^2 \times \widehat{Sp} \times (1-\widehat{Sp})}{d^2 \times (1-Prev)};$$

We estimated the sensitivity (Se) and specificity (Sp) for the mean EI to diagnose MPE as 85% and 85%, respectively, according to our preliminary pilot study of a small sample of 20 cases; we estimated the prevalence of MPE in patients with pleural effusion as 43% according to data from our center in 2012. For a maximum marginal error of the estimate not exceeding 10% with a 95% confidence level, the total required sample size was 114 patients. All 114 patients needed were enrolled in the development set to measure the accuracy of interest (the sensitivity/specificity and the area under the receiver operating characteristic (ROC) curve (AUC)), and another 130 patients were enrolled in the validation set.

Transthoracic ultrasound and UE

Before pleural ultrasound, a respiratory expert (GH) reviewed each patient's most recent chest radiographs to determine which side of the thorax to assess via ultrasound. In patients with bilateral pleural effusion, the side with the greater amount of effusion was assessed since this was usually considered the clinically relevant side. Two operators with different seniority levels (the senior operator was a radiologist with more than 8 years of experience, while the junior operator was a radiologist with 3 years of experience) who were blinded to the patients' clinical history and thoracic imaging (computed tomography/magnetic resonance imaging (CT/MRI)) data separately performed all ultrasound examinations.

Grayscale ultrasound was performed with an Aixplorer ultrasound scanning system

(SuperSonic Imagine, Aix-en-Provence, France) with a 4- to 15-MHz linear-array transducer, as described in previous studies [8-10]. The ultrasound imaging features of pleural nodules and focal pleural thickening are shown in Figure 2a, b.

Measurements of pleural stiffness were performed using shear wave elastography (SWE) [11, 12] (Figure 2c). Using the device's software (OsiriX, version 6.0; Pixmeo, Berne, Switzerland), a circular region of interest was placed inside the pleural elastogram, and the diameter of the circle was increased as much as possible to between 1 and 8 mm, taking care not to surpass the limits of the analyzed pleurae. The default setting for the pleural 2D-SWE scale was used (range, 0 to 100 kPa). A summary of the quantitative stiffness data was automatically displayed. The following parameters for the EI, expressed in kPa, were provided by the system: the mean EI (SWE-Mean), the maximum EI (SWE-Max), the minimum EI (SWE-Min), and the EI standard deviation (SWE-SD) [13]. Precise details of the TUS and UE technique are provided in the supplementary materials.

Criteria for malignant pleural disease on TUS

The operators separately recorded an initial diagnosis of malignant or benign pleural disease pro forma on the basis of anonymized TUS data. If patients had any one of the following criteria upon TUS examination, then a TUS-based diagnosis of malignant disease was recorded: (1) diaphragmatic or parietal pleural nodule(s); (2) pleural thickening >1 cm; or (3) hepatic metastasis [14]. If patients had none of those three criteria, benign pleural effusion based on TUS would be recorded.

Pleural effusion types and the criteria for definitive diagnosis

The diagnosis of malignant pleural lesions was confirmed by the histocytological examination of biopsy samples obtained by semirigid thoracoscopy or closed pleural biopsy or by the cytopathological examination of pleural effusion samples using a liquid-based thin-layer cytopathology technique [1]. When disseminated malignancy was present with no alternative explanation for exudative effusion, probable MPE was diagnosed.

All definitive diagnoses of benign pleural effusion were determined based on comprehensive clinical data, including imaging, laboratory results and histocytological manifestations of disease. No patients with benign disease had any evidence of malignancy during the follow-up period of more than 12 months [15]. Benign pleural effusion was definitively diagnosed using pathogenic microorganism isolation methods, such as those used for diagnosing tuberculosis (TB) and empyema. Tubercular pleurisy was diagnosed based on a positive mycobacterial stain/culture of pleural fluid or pleural tissue or the presence of caseous granuloma on pleural biopsy. Empyema was diagnosed if thoracentesis yielded frank pus and/or bacteria were identified by Gram staining or the culture of pleural effusion samples [16]. Parapneumonic effusion was considered exudative effusion that occurred in the presence of clinical evidence of pneumonia and the exclusion of other suspicious diagnoses. The classification of the effusion as exudate or transudate was based on Light's criteria [17].

The methods used for determining the final diagnoses are shown in Table 1. In 52/108 patients (48.15%), the definitive diagnosis of MPE was based on the pleural histocytological results. In addition, 56/108 patients (51.85%) were diagnosed with probable MPE based on clinical criteria.

Statistical analysis

All data were collected and analyzed using SPSS 17.0 (SPSS for Windows, version 17.0; SPSS, Inc., Chicago, IL, USA). For the UE and TUS data, we used paired *t*-tests and κ coefficients to determine the interobserver agreement between the two operators with different seniority levels, and the findings of the senior radiologist (BJ) were used for all subsequent analyses. Statistical analysis of the differences in diagnoses was performed using the exact binomial test. The EIs of the development set, as continuous data, were used to construct ROC curves. The AUC was used as a performance measure. We attempted to establish the optimal cut-off values for SWE-Mean and SWE-Max using Youden's index [18]. In the validation set, we tested the universality of the cut-off values for differentiating MPE from benign pleural effusion. The diagnostic efficacy (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and Youden's Index) of UE at fixed cut-off values was compared with that of traditional TUS. The 95% confidence interval (95% CI) of sensitivity, specificity, PPV, NPV, PLR and NLR was calculated by Online calculator,

available at http://vassarstats.net/clin1.html. Statistical significance was set at $p<0.05$.

Results

Baseline patient characteristics

A total of 260 consecutive patients with pleural effusion were recruited for this study. Of these patients, 244 were enrolled in the final analysis. The baseline characteristics of these patients are shown in Table 2.

Interobserver agreement of UE and TUS between two operators with different seniority levels

Good interobserver agreement was observed between the two operators when the SWE-Mean ($p=0.976$) and SWE-Max ($p=0.581$) were analyzed using paired *t*-tests. In addition, similar agreement was observed between the two operators in terms of the overall diagnosis of malignant or benign pleural effusion based on TUS (the sensitivity of the senior operator was 58.33% and that of the junior operator was 50.00%; κ coefficient=0.844, $p<0.001$). The results of the more experienced operator were used in the subsequent analysis of all results, and the results of the less experienced operator were given in supplementary materials.su

Diagnostic performance of TUS

TUS provided a correct diagnosis for 30/53 (56.60%) patients with malignant disease

and 55/61 (90.16%) patients with benign disease in the development set, and Youden's index was 46.76 (Table 3). In the validation set, the sensitivity of TUS was 60.00%, the specificity was 93.33%, and Youden's index was 53.33.

Derivation of cut-off EIs based on pleural UE for detecting MPE

The ROC curves derived from the development set that demonstrate the diagnostic capacity of UE to identify MPE based on the SWE-Mean and SWE-Max are shown in Figure 3. The diagnostic evaluation of these cut-off values is presented in Table 3. In the development set, the diagnostic performance based on SWE-Mean≥47.25 kPa showed that 88.60% of patients (101/114) were diagnosed correctly; Youden's index was 77.46. Eight patients with benign pleural effusion were misdiagnosed with MPE (6 patients with tuberculous pleurisy and 2 with empyema), and 5 MPE patients were missed. The diagnostic performance based on SWE-Max≥56.9 kPa showed that 84.21% of patients (96/114) were diagnosed correctly; Youden's index was 68.76. Eleven patients with benign pleural effusion were misdiagnosed with MPE (8 patients with tuberculous pleurisy and 3 with empyema), and 7 MPE patients were missed (see the supplementary materials).

Diagnostic performance of pleural UE

In the validation set, our data showed a sensitivity of 83.64% (46/55) and a specificity of 90.67% (68/75) for detecting MPE with the SWE-Mean (Table 3). A total of 114/130 patients (87.69%) were correctly diagnosed, and Youden's index was 74.31; 7

patients with benign pleural effusion were misdiagnosed with MPE (5 patients with tuberculous pleurisy, 1 with spontaneous bacterial pleural effusion transudate, and 1 with empyema), and 9 MPE patients were missed. In terms of SWE-Max, the analysis showed a sensitivity of 76.36% (42/55) and a specificity of 90.67% (68/75). In all, 110/130 patients (84.62%) were correctly diagnosed, and Youden's index was 67.03; 7 patients with benign pleural effusion were misdiagnosed with MPE (4 patients with tuberculous pleurisy, 1 with pleural transudate, 1 with pneumonia and 1 with empyema), and 13 MPE patients were missed. The diagnostic yield of both SWE-Mean and SWE-Max was slightly lower in the validation set than in the development set, but the differences were not significant (p=0.190; 0.053).

Comparison of diagnostic sensitivity and agreement between different techniques

In the validation set, the sensitivity of SWE-Mean was significantly higher than that of TUS (χ^2=7.591, p=0.006) (Table 3). SWE-Mean and SWE-Max both showed low agreement with TUS (κ coefficient=0.350; 0.263). There were complementary effects of TUS and UE on the diagnosis of MPE (Table 4). The combination of TUS and UE (either SWE-Mean or SWE-Max) for diagnosing MPE, where the test result is considered positive if either measure is positive, had 100% (95% CI 91.87%–100%) sensitivity, 86.67% (95% CI 76.39%-93.08%) specificity, a PLR of 7.50 (95% CI 4.21-13.36) and an NLR of 0. The AUC of SWE-Mean and SWE-Max for detecting MPE in the validation set was 0.915 (95% CI 0.862–0.968) and 0.901 (95% CI 0.841–0.960), respectively (Figure 4). The diagnostic performance of UE for detecting MPE

based on SWE-Mean compared with SWE-Max showed no significant difference (χ^2=0.258, p=0.611) and a high level of agreement (κ coefficient=0.903). Additionally, among the 108 cases of MPE among all the enrolled patients, pleural UE (SWE-Mean) detected 91.11% of the cases (41/45) missed by TUS.

Comparison of the diagnostic sensitivity of TUS and UE in different subgroups

The diagnostic sensitivity of TUS, SWE-Mean and SWE-Max was compared according to disease type (Table 5). The sensitivity of both SWE-Mean and SWE-Max was significantly higher than the sensitivity of TUS in patients with metastatic cancer (p<0.001; p<0.001), whereas SWE-Mean and SWE-Max both showed a significantly lower sensitivity than TUS for tuberculous pleurisy (p=0.027; p=0.015). There was no significant difference between definitive MPE and probable MPE diagnosed by TUS, SWE-Mean and SWE-Max (p=0.525; p=0.170; p=0.906).

Discussion

TUS is a cost-effective, noninvasive technique that is helpful for evaluating undiagnosed pleural exudate[1]. Our study demonstrates that UE had a better sensitivity for detecting MPE than TUS when the SWE-Mean was set at 47.25 kPa. UE is a novel ultrasound technique that is widely accepted for evaluating diseases of the liver, breast, and thyroid gland; UE is rapid, relatively inexpensive, and free of radiation and can be used for the diagnosis of MPE based on the assessment of the physical properties of pleura. A diagnosis of MPE made by TUS is based on pleural

morphological criteria, such as pleural thickening and the presence of nodules, but many patients do not exhibit these specific features. Pleural UE overcomes for this limitation because UE is used to diagnose MPE based on pleural stiffness. In our study, pleural UE (SWE-Mean) detected 91.11% of patients with MPE missed by TUS.

Only two previous studies have evaluated the efficacy of TUS for diagnosing suspected MPE; these studies were conducted in the UK and Portugal and reported a sensitivity of 79% and 80.3% and a specificity of 100% and 83.6%, respectively [14, 19]. Our results demonstrate that SWE-Mean had a sensitivity (83.64%) similar to that of TUS in previous studies [14, 19]. Considering the low diagnostic agreement (κ coefficient=0.350) between SWE-Mean and TUS, UE and TUS could be complementary for diagnosing MPE.

Our data revealed a specificity of 90.67% for UE, which was slightly lower than that of TUS in our study (93.33%) and in the previous study in the UK (100%)[14]. However, the two abovementioned studies[14, 19] only focused on European populations. This difference may be explained by the difference in etiology spectra of pleural effusion between European and Chinese population. The relatively high ratio of tuberculous pleurisy in our study may result in the decrease of specificity for diagnosing MPE by UE.

In mesothelioma cases, UE (9/9) performed as well as TUS (8/9) (p=1.000). Marked heterogeneity exists in the incidence of malignant mesothelioma among countries. The crude incidence of mesothelioma in some European countries ranges from 10-30

cases per million [20], with the highest annual incidence (29 cases per million in 2009) in the UK [21]; this is in sharp contrast to the low incidence of mesothelioma in Asian countries (2-9 cases per million) [20]. In particular, Qureshi et al. performed a study in a tertiary pleural center, and their cohort had a high proportion of mesothelioma cases (14/33)[14].

Tuberculous pleurisy is the second most common extrapulmonary manifestation of TB [22], and its most common sequela is residual pleural thickening. Pleural thickening (more than 2 mm) has been reported to occur in approximately 50% of cases [23]. False-positive results due to tuberculous pleurisy are a common problem in UE and TUS examinations. In our study, there were 4 false-positive results based on TUS and 12 false-positive results based on SWE-Mean in 45 patients with tuberculous pleurisy, which is consistent with this phenomenon. Only 2 patients with tuberculous pleurisy were reported out of a total of 52 patients in the study by Qureshi et al.[14], which is consistent with the low incidence of TB in the UK. However, in our study, 45 out of a total of 244 patients had tuberculous pleurisy, which is consistent with the high burden of TB in China and may have reduced the specificity of UE in this study. In low-income developing countries, TB remains an important cause of disease burden and may interfere with the use of TUS and UE for detecting MPE.

Additionally, in a subgroup of patients with empyema, TUS and UE (SWE-Mean) detected only 3 and 2 cases, respectively, out of the 5 cases of empyema (non-tubercular pleuritis). The low diagnostic yield of UE and TUS in patients with

empyema may be due to severe irritation of the pleura leading to thickening [24] and changes in elasticity [25].

TUS and UE (SWE-Mean) correctly detected 93.62% (44/47) and 97.87% (46/47) of patients with benign effusion in the transudate subgroup, respectively. Such a high diagnostic yield is important for elderly patients with pleural effusion in whom the differential diagnoses include both malignant and benign diseases that can cause transudate. In particular, for elderly patients for whom further examinations (such as thoracentesis) are risky due to complex underlying diseases or poor health conditions, ultrasound technology, which is harmless and highly specific, may be useful to help clinicians determine whether further examinations for malignant diseases should be performed, thereby helping patients avoid unnecessary radiological or invasive examinations. Due to its easy accessibility and high sensitivity, UE can be used as an initial tool for screening patients with pleural effusion of an unknown etiology.

Several limitations exist in our study. First, the sample size of this single-center study was relatively small, which may have affected the determination of the cut-off EIs for UE. Thus, further exploration should be conducted in a larger population of outpatients, and comparisons of the diagnostic yield of UE should be performed by radiologists and others to simplify diagnostic procedures. As pulmonologists can master techniques such as endobronchial ultrasound-guided transbronchial needle aspiration and rapid on-site evaluation of transbronchial needle aspiration (TBNA) specimens after receiving training [26], we believe that pulmonologists can also use UE after training. The use of UE to evaluate the liver is more complicated than its use

to evaluate the pleura due to the complex anatomy of the liver, and it has been reported that a one-year learning curve, or the equivalent of 130 examinations, is needed to master using UE to evaluate the liver [27]. Thus, we believe that the learning curve for examining the pleura by UE would be shorter than that for examining the liver by UE. However, the exact learning curve that would be needed for a pulmonologist to master the use of UE for pleural examination remains to be explored. Second, 6 cases were excluded from the data analysis due to the lack of a definitive diagnosis, which may have affected the accuracy of our results. Third, we enrolled the entire development set first and then the entire validation set, which may have resulted in the observers gaining experience and skill during development set data acquisition that could have resulted in improved performance during validation set data acquisition, thus leading to bias. Fourth, we did not perform UE-guided pleural biopsy, although this technique better illustrates the value of UE for diagnosing MPE. Thus, a prospective multicenter study with an adequate sample size should be conducted in the future.

Conclusion

With SWE-Mean at 47.25 kPa, pleural UE may be a better technique than TUS for differentiating MPE from benign pleural disease, especially in countries with a high tuberculosis burden.

Acknowledgments

For their continuous support and assistance with patient screening, we appreciate the help of Wei Wang, Jiang-wei Ma, and Zan-feng Wang (Department of Respiratory and Critical Care Medicine), Xue-jun Hu and Xiao-nan Wang (Department of Geriatrics), Yun-peng Liu, Ying Chen, Ping Yu, Bo Jin and Ming-fang Zhao (Department of Medical Oncology), Chun-wei Wu (Department of Cardiology), Lin-lin Liu and Yi Fan (Department of Nephrology), Jing Tong (Department of Gastroenterology), and Bao-cheng Deng (Department of Infectious Disease) of the First Hospital of China Medical University. No funding sources were involved. The authors declare no conflicts of interest.

References

1. Hooper C, Lee YC, Maskell N, Group BTSPG. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* 2010: 65 Suppl 2: ii4-17.
2. Bibby AC, Dorn P, Psallidas I, Porcel JM, Janssen J, Froudarakis M, Subotic D, Astoul P, Licht P, Schmid R, Scherpereel A, Rahman NM, Cardillo G, Maskell NA. ERS/EACTS statement on the management of malignant pleural effusions. *The European respiratory journal* 2018: 52(1).
3. Lin X, Chang C, Wu C, Chen Q, Peng Y, Luo B, Tang L, Li J, Zheng J, Zhou R, Cui G, Li A, Wang X, Qian L, Zhang J, Wen C, Gay J, Zhang H, Li A, Chen Y. Confirmed value of shear wave elastography for ultrasound characterization of breast masses using a conservative approach in Chinese women: a large-size prospective multicenter trial. *Cancer management and research* 2018: 10: 4447-4458.
4. Rago T, Scutari M, Loiacono V, Santini F, Tonacchera M, Torregrossa L, Giannini R, Borrelli N, Proietti A, Basolo F, Miccoli P, Piaggi P, Latrofa F, Vitti P. Low Elasticity of Thyroid Nodules on Ultrasound Elastography Is Correlated with Malignancy, Degree of Fibrosis, and High Expression of Galectin-3 and Fibronectin-1. *Thyroid : official journal of the American Thyroid Association* 2017: 27(1): 103-110.
5. Tian WS, Lin MX, Zhou LY, Pan FS, Huang GL, Wang W, Lu MD, Xie XY. Maximum Value Measured by 2-D Shear Wave Elastography Helps in Differentiating Malignancy from Benign Focal Liver Lesions. *Ultrasound in medicine & biology* 2016: 42(9): 2156-2166.
6. Marasco G, Colecchia A, Colli A, Ravaioli F, Casazza G, Bacchi Reggiani ML, Cucchetti A, Cescon M, Festi D. Role of liver and spleen stiffness in predicting the recurrence of hepatocellular carcinoma after resection. *Journal of hepatology* 2018.
7. Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample

size calculation for sensitivity and specificity. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 1996: 3(9): 895-900.

8. Diacon AH, Theron J, Bolliger CT. Transthoracic ultrasound for the pulmonologist. *Current opinion in pulmonary medicine* 2005: 11(4): 307-312.

9. Koenig SJ, Narasimhan M, Mayo PH. Thoracic ultrasonography for the pulmonary specialist. *Chest* 2011: 140(5): 1332-1341.

10. Gorg C, Restrepo I, Schwerk WB. Sonography of malignant pleural effusion. *European radiology* 1997: 7(8): 1195-1198.

11. Brandenburg JE, Eby SF, Song P, Zhao H, Brault JS, Chen S, An KN. Ultrasound elastography: the new frontier in direct measurement of muscle stiffness. *Archives of physical medicine and rehabilitation* 2014: 95(11): 2207-2219.

12. Lacourpaille L, Hug F, Bouillard K, Hogrel JY, Nordez A. Supersonic shear imaging provides a reliable measurement of resting muscle shear elastic modulus. *Physiological measurement* 2012: 33(3): N19-28.

13. Azizi G, Keller JM, Mayo ML, Piper K, Puett D, Earp KM, Malchoff CD. Thyroid Nodules and Shear Wave Elastography: A New Tool in Thyroid Cancer Detection. *Ultrasound in medicine & biology* 2015: 41(11): 2855-2865.

14. Qureshi NR, Rahman NM, Gleeson FV. Thoracic ultrasound in the diagnosis of malignant pleural effusion. *Thorax* 2009: 64(2): 139-143.

15. Venekamp LN, Velkeniers B, Noppen M. Does 'idiopathic pleuritis' exist? Natural history of non-specific pleuritis diagnosed after thoracoscopy. *Respiration; international review of thoracic diseases* 2005: 72(1): 74-78.

16. Davies CW, Gleeson FV, Davies RJ, Pleural Diseases Group SoCCBTS. BTS guidelines for the management of pleural infection. *Thorax* 2003: 58 Suppl 2: ii18-28.

17. Light RW, Macgregor MI, Luchsinger PC, Ball WC, Jr. Pleural effusions: the diagnostic separation of transudates and exudates. *Annals of internal medicine* 1972: 77(4): 507-513.

18. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950: 3(1): 32-35.

19. Bugalho A, Ferreira D, Dias SS, Schuhmann M, Branco JC, Marques Gomes MJ, Eberhardt R. The diagnostic value of transthoracic ultrasonographic features in predicting malignancy in undiagnosed pleural effusions: a prospective observational study. *Respiration; international review of thoracic diseases* 2014: 87(4): 270-278.

20. Bianchi C, Bianchi T. Malignant mesothelioma: global incidence and relationship with asbestos. *Industrial health* 2007: 45(3): 379-387.

21. Robinson BM. Malignant pleural mesothelioma: an epidemiological perspective. *Annals of cardiothoracic surgery* 2012: 1(4): 491-496.

22. Shaw JA, Irusen EM, Diacon AH, Koegelenberg CF. Pleural tuberculosis: A concise clinical review. *The clinical respiratory journal* 2018: 12(5): 1779-1786.

23. Ryan H, Yoo J, Darsini P. Corticosteroids for tuberculous pleurisy. *The Cochrane database of systematic reviews* 2017: 3: CD001876.

24. Malhotra P, Aggarwal AN, Agarwal R, Ray P, Gupta D, Jindal SK. Clinical characteristics and outcomes of empyema thoracis in 117 patients: a comparative analysis of tuberculous vs. non-tuberculous aetiologies. *Respiratory medicine* 2007: 101(3): 423-430.

25. Mutsaers SE, Prele CM, Brody AR, Idell S. Pathogenesis of pleural fibrosis. *Respirology* 2004: 9(4): 428-440.

26. Bonifazi M, Sediari M, Ferretti M, Poidomani G, Tramacere I, Mei F, Zuccatosta L, Gasparini S. The role of the pulmonologist in rapid on-site cytologic evaluation of transbronchial needle aspiration: a prospective study. *Chest* 2014: 145(1): 60-65.
27. Fraquelli M, Baccarin A, Casazza G, Conti CB, Giunta M, Massironi S, Invernizzi F, Donato MF, Maggioni M, Aghemo A, Conte D, Colombo M. Liver stiffness measurement reliability and main determinants of point shear-wave elastography in patients with chronic liver disease. *Alimentary pharmacology & therapeutics* 2016: 44(4): 356-365.

Table 1. Methods used for the final diagnosis of malignant pleural effusions.

Diagnostic method	Number of patients
Malignant disease	
Definitive diagnosis	52
Thoracoscopic biopsy	39
Percutaneous pleural biopsy	4
Pleural fluid cytology	9
Probable diagnosis*	56
Histocytological evidence of primary tumor and clinical follow-up (>6 months)	49
Clinical follow-up (>6 months) and repeated radiography	7

* There were no etiologies other than cancer that could explain these cases of pleural effusion according to clinical criteria.

Table 2. Summary of baseline patient characteristics and final diagnoses.

	All patients (n=244)	Development set (n=114)	Validation set (n=130)	*p**
Age (years)	56.15±14.76 (median, 58; range, 16-94)	55.93±15.18 (median, 57.5; range, 16-87)	56.34±14.44 (median, 58; range, 21-94)	0.830
Sex (male/female)	150/94	68/46	82/48	0.583
Diagnosis				0.512
Malignant	108 (44.26%)	53 (46.49%)	55 (42.31%)	
Benign	136 (55.74%)	61 (53.51%)	75 (57.69%)	
Final diagnosis				
Malignant**	108 (44.26%)	53 (46.49%)	55 (42.31%)	
Definitive diagnosis	52 (48.15%)	33 (62.26%)	19 (34.55%)	
Probable diagnosis	56 (51.85%)	20 (37.74%)	36 (65.45%)	
Benign	136 (55.74%)	61 (53.51%)	75 (57.69%)	
Pneumonia	44 (18.03%)	22 (19.30%)	22 (16.92%)	
Tuberculous pleurisy	45 (18.44%)	33 (28.95%)	12 (9.23%)***	
Congestive heart failure	11 (4.51%)	2 (1.75%)	9 (6.92%)	
Hepatic disease	22 (9.02%)	3 (2.63%)	19 (14.62%)	
Renal failure	8 (3.28%)	0 (0)	8 (6.15%)	
Other benign disease****	6 (2.46%)	1 (0.88%)	5 (3.85%)	

* Comparison of the development set with the validation set.

** "Malignant" refers to lung cancer (40 cases), mesothelioma (5 cases), thymic tumor (1 case), breast cancer (1 case), gastrointestinal cancer (1 case) and unclassified malignancy (5 cases) in the development set, and refers to lung cancer (34 cases), mesothelioma (4 cases), thymic tumor (3 case), breast cancer (6 case), gastrointestinal cancer (4 case) and unclassified malignancy (4 cases) in the validation set.

*** One patient suffered from tuberculous pleurisy and empyema and was listed only once, under tuberculous pleurisy.

**** "Other benign diseases" refers to Sjogren syndrome (1 case) in the development set and systemic sclerosis (1 case), systemic lupus erythematosus (3 cases) and Sjogren syndrome (1 case) in the validation set.

Table 3. Diagnostic evaluation of TUS and the cut-off mean and maximal EIs of UE.

		TUS	SWE-Mean[a]	χ^2 and p[b]	SWE-Max[c]	χ^2 and p[d]
Diagnostic cut-off value (kPa)		-	47.25		56.9	
Development set	Yield (%)	74.56	88.60		84.21	
	Sensitivity (% (95% CI))	56.60 (42.36-69.90)	90.57 (78.58-96.47)		86.79 (74.05-94.09)	
	Specificity (% (95% CI))	90.16 (79.15-95.94)	86.89 (75.23-93.77)		81.97 (69.60-90.24)	
	PPV (% (95% CI))	83.33 (66.53-93.04)	85.71 (73.22-93.20)	χ^2=15.725, p <0.001	80.70 (67.68-89.53)	χ^2=11.902, p=0.001
	NPV (% (95% CI))	70.51 (58.96-80.03)	91.38 (80.28-96.78)		87.72 (75.71-94.51)	
	PLR (95% CI)	5.75 (2.60-12.75)	6.91 (3.60-13.25)		4.81 (2.79-8.30)	
	NLR (95% CI)	0.48 (0.35-0.66)	0.11 (0.05-0.25)		0.16 (0.08-0.32)	
Validation set	Yield (%)	79.23	87.69		84.62	
	Sensitivity (% (95% CI))	60.00 (45.92-72.68)	83.64 (70.70-91.80)		76.36 (62.67-86.35)	
	Specificity (% (95% CI))	93.33 (84.47-97.52)	90.67 (81.15-95.85)		90.67 (81.15-95.85)	
	PPV (% (95% CI))	86.84 (71.12-95.05)	86.79 (74.05-94.09)	χ^2=7.591, p=0.006	85.71 (72.14-93.59)	χ^2=3.394, p=0.065
	NPV (% (95% CI))	76.09 (65.85-84.10)	88.31 (78.48-94.19)		83.95 (73.75-90.85)	
	PLR (95% CI)	9.00 (3.76-21.57)	8.96 (4.38-18.32)		8.18 (3.98-16.82)	
	NLR (95% CI)	0.43 (0.31-0.59)	0.18 (0.10-0.33)		0.26 (0.16-0.42)	

TUS, traditional thoracic ultrasound; EI, elasticity index; UE, ultrasound elastography; SWE, shear wave elastography; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; 95% CI, 95% confidence interval.

a: SWE-Mean indicates the mean SWE EI.

b: Comparison of sensitivity between traditional TUS and SWE-Mean.

c: SWE-Max indicates the maximum SWE EI.

d: Comparison of sensitivity between traditional TUS and SWE-Max.

Table 4. The complementary effects of TUS and the cut-off mean and maximal EIs of UE for diagnosing malignant pleural effusions.

Development set		TUS		
SWE-Mean[a]/ SWE-Max[b]		+	-	Total
	+	29/28	19/18	48/46
	-	1/2	4/5	5/7
	total	30	23	53
Validation set		TUS		
SWE-Mean[a]/ SWE-Max[b]		+	-	Total
	+	24/20	22/22	46/42
	-	9/13	0/0	9/13
	total	33	22	55
All patients		TUS		
SWE-Mean[a]/ SWE-Max[b]		+	-	Total
	+	53/48	41/40	94/88
	-	10/15	4/5	14/20
	total	63	45	108

TUS, traditional thoracic ultrasound; EI, elasticity index; UE, ultrasound elastography; SWE, shear wave elastography.

a: SWE-Mean indicates the mean SWE EI.

b: SWE-Max indicates the maximum SWE EI.

Table 5. Diagnostic sensitivity of TUS and the cut-off mean and maximal EIs of UE in different subgroups.

Subgroup	TUS	SWE-Mean[a]		SWE-Max[b]	
	Sensitivity, % (n/N)	Sensitivity, % (n/N)	*p* value[c]	Sensitivity, % (n/N)	*p* value[d]
Malignant disease					
Mesothelioma	88.89% (8/9)	100% (9/9)	1	100% (9/9)	1
Metastatic cancer	55.56% (55/99)	85.86% (85/99)	<0.001	79.80% (79/99)	<0.001
Definitive MPE	55.77% (29/52)	92.31% (48/52)	<0.001	82.69% (43/52)	0.003
Benign disease					
Tuberculous pleurisy*	91.11% (41/45)	73.33% (33/45)	0.027	71.11% (32/45)	0.015
Empyema	66.67% (4/6)	50% (3/6)	1	33.33% (2/6)	0.567
Transudate	93.62% (44/47)	97.87% (46/47)	0.617	97.87% (46/47)	0.617
Parapneumonic effusion#	94.87% (37/39)	100% (39/39)	0.494	97.44% (38/39)	1

TUS, traditional thoracic ultrasound; EI, elasticity index; UE, ultrasound elastography; SWE, shear wave elastography; MPE, malignant pleural effusion.

* One patient had both tuberculosis pleurisy and empyema.

Excluding empyema.

a: SWE-Mean indicates the mean SWE EI.

b: SWE-Max indicates the maximum SWE EI.

c: Comparison of sensitivity between TUS and SWE-Mean.

d: Comparison of sensitivity between TUS and SWE-Max.

Figure legends

Figure 1 Flow chart of patient enrollment.

Figure 2 Ultrasound features of pleural nodules and focal pleural thickening and measurements of pleural stiffness by shear wave elastography.

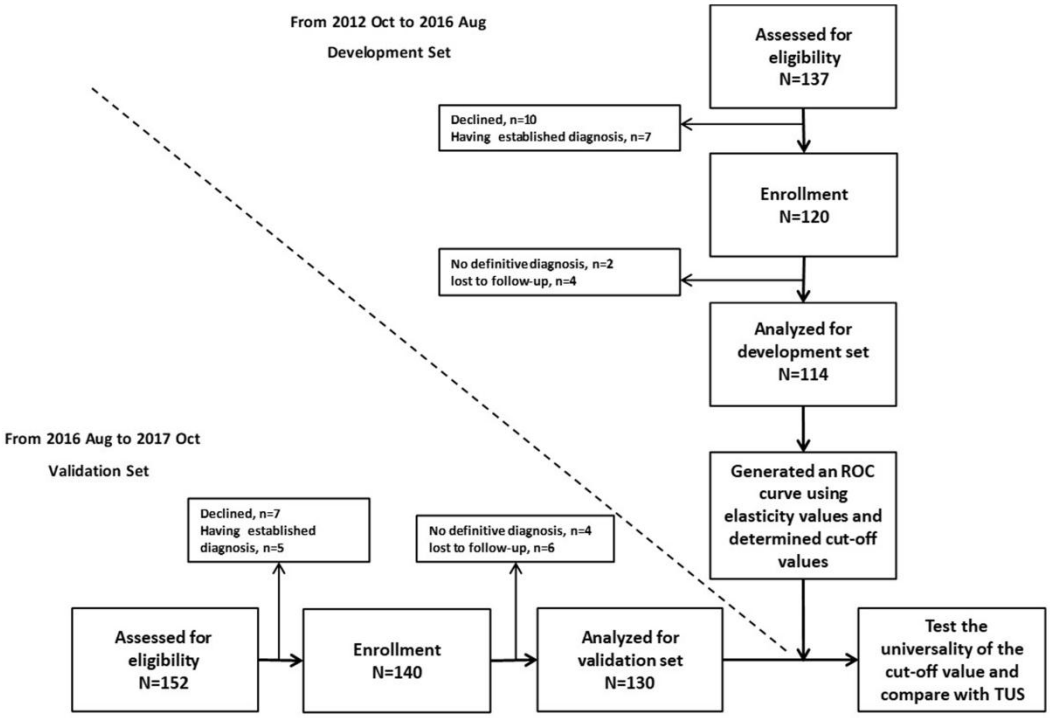
Pleural nodules appeared as hypoechoic nodular lesions with defined margins located in the parietal or visceral pleura (a), while focal pleural thickening was identified as an echogenic area of increased thickness in the parietal pleura with poorly defined margins (b). Images of pleural thickening or nodules are displayed together with the grayscale ultrasound images. After placing a box (frame) over the pleura, a colored image appeared, revealing blue and red areas on an elastogram. Dark blue areas correspond to soft tissues, whereas red areas correspond to stiff tissues (c).

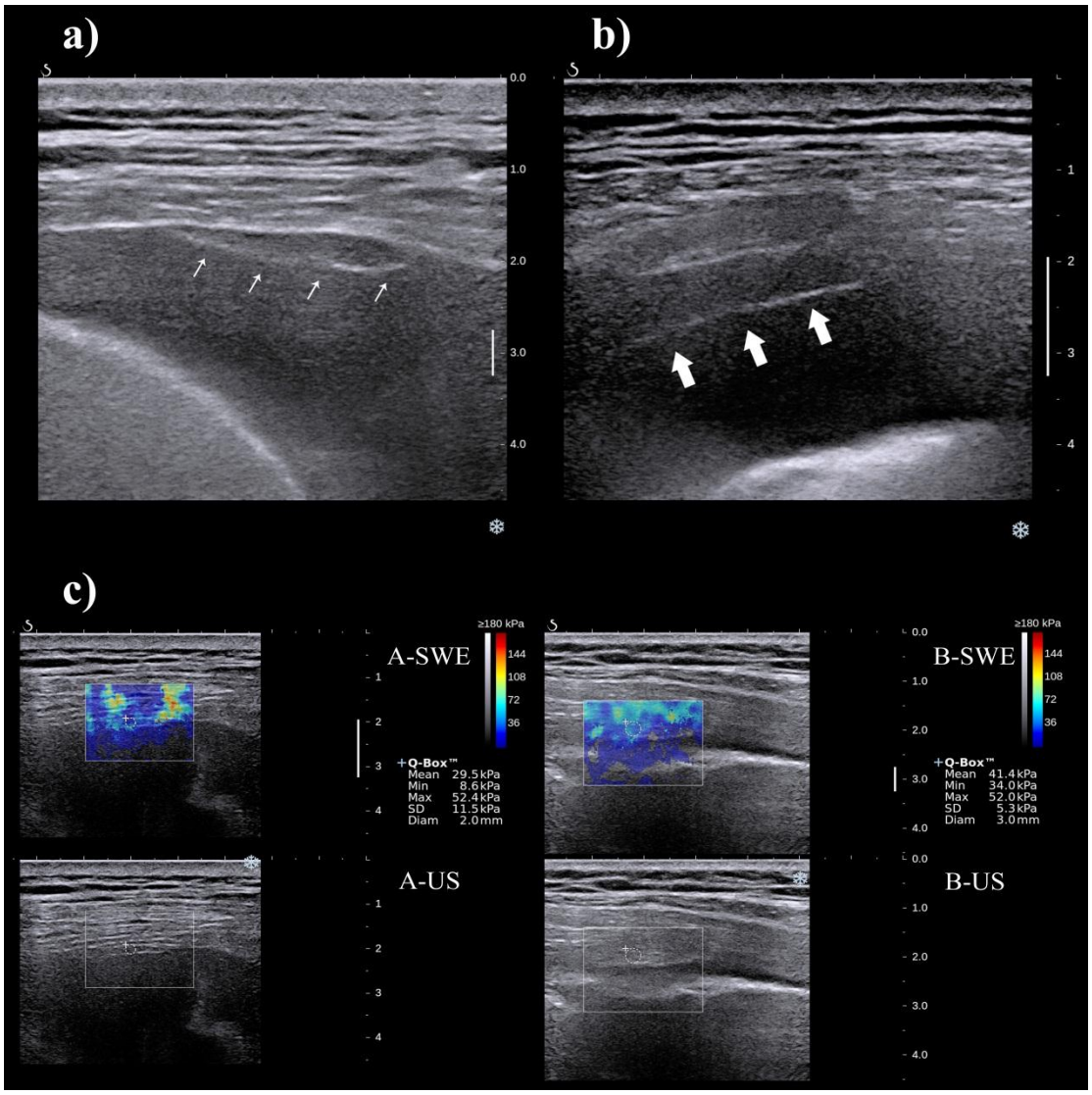
Figure 3 Receiver operating characteristic curve analysis of the mean and maximal elasticity indexes (EIs) of pleural ultrasound elastography for diagnosing malignant pleural effusion in the development set.

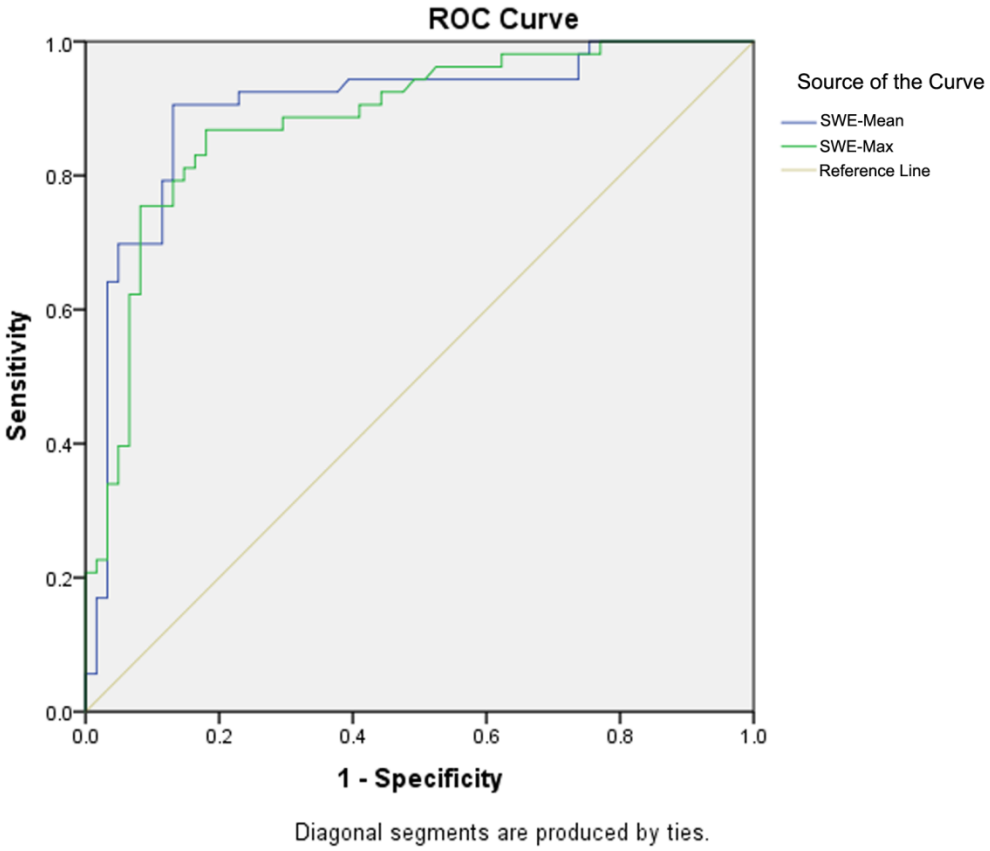
SWE-Mean indicates the mean shear wave elastography (SWE) EI; SWE-Max indicates the maximal SWE EI.

Figure 4 Receiver operating characteristic curve analysis of the mean and maximal elasticity indexes (EIs) of pleural ultrasound elastography for diagnosing malignant pleural effusion in the validation set.

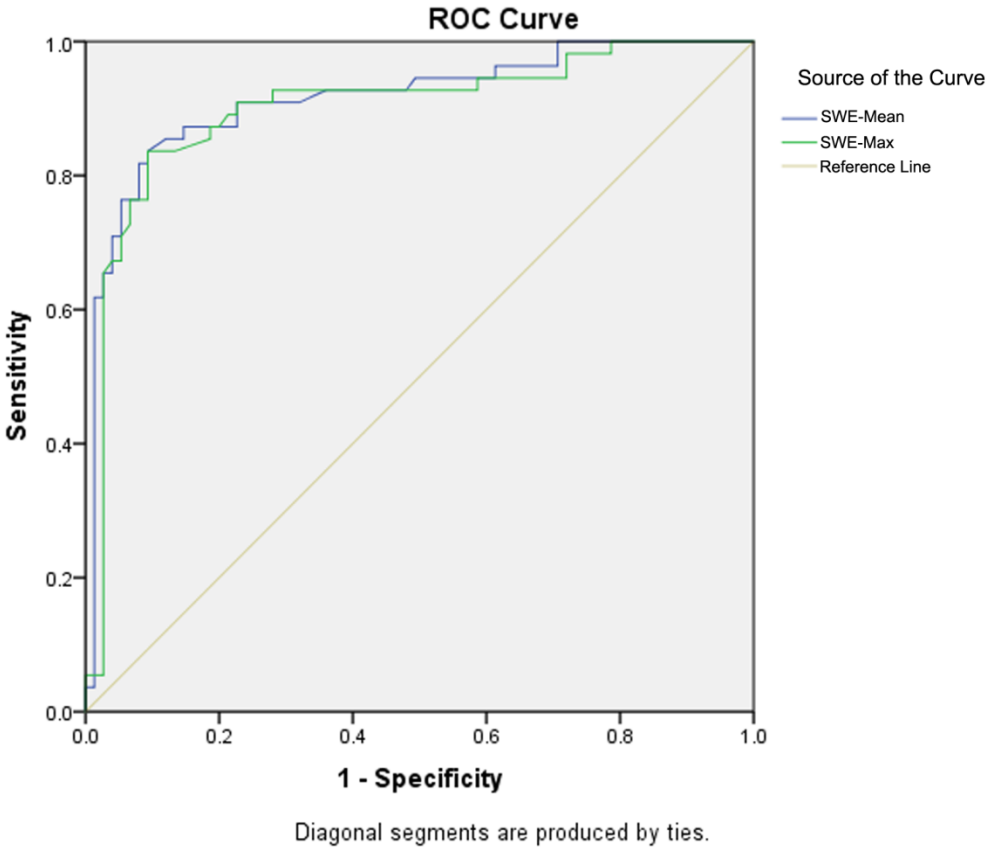
SWE-Mean indicates the mean shear wave elastography (SWE) EI; SWE-Max indicates the maximum SWE EI.


From 2012 Oct to 2016 Aug
Development Set
Assessed for eligibility N=137
Declined, n=10
Having established diagnosis, n=7
Enrollment N=120
No definitive diagnosis, n=2
lost to follow-up, n=4
Analyzed for development set N=114
Generated an ROC curve using elasticity values and determined cut-off values
From 2016 Aug to 2017 Oct
Validation Set
Declined, n=7
Having established diagnosis, n=5
No definitive diagnosis, n=4
lost to follow-up, n=6
Assessed for eligibility N=152
Enrollment N=140
Analyzed for validation set N=130
Test the universality of the cut-off value and compare with TUS


a)
b)
c)
A-SWE
≥180 kPa
144
108
72
36
+Q-Box™
Mean 29.5 kPa
Min 8.6 kPa
Max 52.4 kPa
SD 11.5 kPa
Diam 2.0 mm
A-US
B-SWE
≥180 kPa
144
108
72
36
+Q-Box™
Mean 41.4 kPa
Min 34.0 kPa
Max 52.0 kPa
SD 5.3 kPa
Diam 3.0 mm
B-US



Diagonal segments are produced by ties.



Diagonal segments are produced by ties.

Figure legends of supplemental figures

S1. True-positive case: malignant pleural mesothelioma.

The patient's pleural effusion was not extensive or turbid. No separation was observed, but the parietal pleura was diffuse and obviously thickened, and the elasticity value of the thickened pleura was significantly increased (98.6 kPa). The increased elasticity value and diffuse thickness of the pleura were helpful for diagnosing malignant pleural mesothelioma.

S2. True-positive case: non-small cell lung cancer (adenocarcinoma).

A moderate amount of slightly turbid pleural effusion was noted. The parietal pleura was focally thickened, and the elasticity value of the pleural nodule was 98.2 kPa, which was beyond the cut-off value. A focally thickened pleura with an increased elasticity value indicates a diagnosis of malignant pleural effusion.

S3. True-negative case: tubercular pleurisy.

A moderate amount of clear pleural effusion with a small amount of separation was noted. The thickness of the pleura was normal. The elasticity value of the pleura was 19.2 kPa, which was below the cut-off value. A pleura with a normal thickness and elasticity value indicates benign pleural effusion.

S4. True-negative case: nephrotic syndrome.

The moderate amount of pleural effusion was not turbid. Slight separation was

observed in the pleural cavity. The pleura was not significantly thick, and the pleural elasticity value was 29.5 kPa.

A pleura with a normal thickness and elasticity value indicates benign pleural effusion.

S5. False-positive case: tubercular pleurisy.

A large amount of pleural effusion with obvious separation was noted. The parietal pleura was thickened, and the elasticity value (73.5 kPa) was higher than the cut-off value. Assessments based on the elasticity value of the pleura alone will result in a mistaken diagnosis of benign pleural effusion because chronic tubercular pleurisy or empyema can cause fibrothorax and an increased pleural elasticity value. Evaluating the presence of characteristics of fibrothorax or empyema by conventional transthoracic ultrasound is helpful in the differential diagnosis of benign pleural effusion.

S6. False-negative case: non-small cell lung cancer (adenocarcinoma).

A small amount of pleural effusion without separation was noted. The thickness of the parietal pleura was 0.4 cm, and the elasticity value of the pleura was lower than the cut-off value (41.4 kPa). If the amount of pleural effusion is not substantial, separation is not obvious, and the elasticity value is not high, then making a positive judgment is difficult

S7. Receiver operating characteristic curve analysis of the mean and maximal elasticity indexes (EIs) of pleural ultrasound elastography for diagnosing malignant pleural effusion in the development set based on data determined by the junior operator.

SWE-Mean indicates the mean shear wave elastography (SWE) EI; SWE-Max indicates the maximal SWE EI.

S8. Receiver operating characteristic curve analysis of the mean and maximal elasticity indexes (EIs) of pleural ultrasound elastography for diagnosing malignant pleural effusion in the validation set based on data determined by the junior operator.

SWE-Mean indicates the mean shear wave elastography (SWE) EI; SWE-Max indicates the maximum SWE EI.

Supplemental table

S-table 1. Diagnostic evaluation of traditional thoracic ultrasound and the cut-off mean and maximal elasticity indexes of ultrasound elastography based on data determined by the junior operator.

		TUS	SWE-Mean[a]	χ^2 and p[b]	SWE-Max[c]	χ^2 and p[d]
Diagnostic cut-off value (kPa)		-	46.85		69.1	
Development set	Yield (%)	71.05	85.96		84.21	
	Sensitivity (% (95% CI))	52.83 (38.77-66.48)	88.68 (76.28-95.31)		83.02 (69.70-91.48)	
	Specificity (% (95% CI))	86.88 (75.23-93.77)	83.61 (71.45-91.45)		85.25 (73.33-92.62)	
	PPV (% (95% CI))	77.78 (60.41-89.27)	82.46 (69.64-90.83)	χ^2=16.458, p<0.001	83.02 (69.70-91.48)	χ^2=11.085, p=0.001
	NPV (% (95% CI))	67.95 (56.30-77.81)	89.47 (77.81-95.65)		85.25 (73.33-92.62)	
	PLR (95% CI)	4.03 (2.01-8.07)	5.41 (3.04-9.61)		5.63 (3.04-10.41)	
	NLR (95% CI)	0.54 (0.41-0.73)	0.14 (0.06-0.29)		0.20 (0.11-0.36)	
Validation set	Yield (%)	70.00	85.38		86.15	
	Sensitivity (% (95% CI))	47.27 (33.86-61.07)	83.64 (70.70-91.80)		76.36 (62.67-86.35)	
	Specificity (% (95% CI))	86.67 (76.39-93.08)	86.67 (76.39-93.08)		93.33 (84.47-97.52)	
	PPV (% (95% CI))	72.22 (54.57-85.21)	82.14 (69.15-90.66)	χ^2=16.082, p<0.001	89.36 (76.11-96.02)	χ^2=9.860, p=0.002
	NPV (% (95% CI))	69.15 (58.66-78.05)	87.84 (77.67-93.95)		84.34 (74.34-91.07)	
	PLR (95% CI)	3.55 (1.87-6.73)	6.27 (3.48-11.30)		11.45 (4.85-27.05)	

	NLR (95% CI)	0.61 (0.47-0.78)	0.19 (0.10-0.34)		0.25 (0.16-0.41)

TUS, traditional thoracic ultrasound; EI, elasticity index; UE, ultrasound elastography; SWE, shear wave elastography; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; 95% CI, 95% confidence interval.

a: SWE-Mean indicates the mean SWE EI.

b: Comparison of sensitivity between traditional TUS and SWE-Mean.

c: SWE-Max indicates the maximum SWE EI.

d: Comparison of sensitivity between traditional TUS and SWE-Max.

S-table 2. The operating characteristic data of traditional thoracic ultrasound and ultrasound elastography in isolation and combined in the validation set

		Final diagnosis		Yield (%)	Sensitivity (%)	Specificity (%)	PLR	NLR
		MPE	BPE					
TUS	MPE	33	5	79.23	60.00	93.33	9.00	0.43
	BPE	22	70					
SWE-Mean[a]	MPE	46	7	87.69	83.64	90.67	8.96	0.18
	BPE	9	68					
SWE-Max[b]	MPE	42	7	84.62	76.36	90.67	8.18	0.26
	BPE	13	68					
SWE-Mean+TUS[c]	MPE	55	10	92.31	100	86.67	7.50	0
	BPE	0	65					
SWE-Max+TUS[d]	MPE	55	10	92.31	100	86.67	7.50	0
	BPE	0	65					

TUS, traditional thoracic ultrasound; UE, ultrasound elastography; SWE, shear wave elastography; MPE, malignant pleural effusion; BPE, benign pleural effusion; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

a: SWE-Mean indicates the mean SWE elasticity index.

b: SWE-Max indicates the maximum SWE elasticity index.

c: SWE-Mean+TUS indicates the combination of SWE-Mean and TUS, which means a SWE-Mean+TUS-based diagnosis of MPE would be recorded when either SWE-Mean≥47.25 kPa or a TUS-based diagnosis of MPE was recorded.

D: SWE-Max+TUS indicates the combination of SWE-Mean and TUS, which means a SWE-Max+TUS-based diagnosis of MPE would be recorded when either SWE-Mean≥47.25 kPa or a TUS-based diagnosis of MPE was recorded.

Methods

Ultrasound details

Gray scale ultrasound was performed with an Aixplorer ultrasound scanning system (SuperSonic Imagine, Aixen Provence, France) with a bandwidth between 4 and 15 MHz and a 55-mm-long linear-array transducer, as described in previous studies[1-3]. To detect the presence of pleural effusion, scanning was performed using the intercostal spaces one by one from top to bottom as acoustic windows, with the patient in a seated position with the arms raised above the head to widen the intercostal space and facilitate scanning. The normal pleura is characterized by a smooth echogenic surface and a hypoechoic subpleural line. The normal pleura has a thickness of only 0.2 mm and reaches the limit of sonographic depiction. However, with high-resolution scanning, the visceral and parietal pleurae can be displayed as two distinct echogenic lines. Thickening pleura can be detected and measured in B mode. The pleural nodules were hypoechoic nodular lesions with defined margins located in the parietal or visceral pleura, while focal pleural thickenings were echogenic areas of increased thickness in the parietal pleura that had poorly defined margins. A diagnosis of malignant disease was recorded when the following three characteristics were founded: diaphragmatic and parietal pleural nodule or nodules, pleural thickening > 1 cm, and hepatic metastasis.

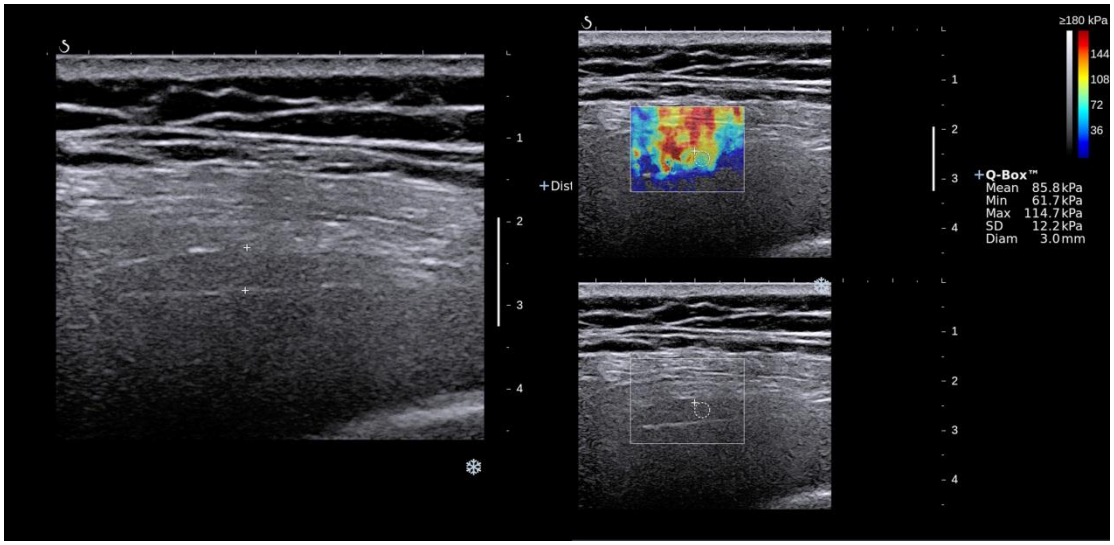
Following the physical exam measurements, pleural stiffness was measured using shear wave elastography (SWE)[4, 5]. An Aixplorer ultrasonic scanner (SuperSonic Imagine, Aix-en-Provence, France) with a linear array transducer (SL15-4; SuperSonic Imagine, Aix-en-Provence, France) was used. With musculoskeletal presettings, the ultrasound probe generates transient shear waves in the pleura by transmitting ultrasound push beams, the speed of which can be used to calculate Young's modulus. Young's modulus is the output of the Aixplorer.

2D-SWE was performed for each of the cases, and images of pleural thickening or nodules were displayed along with the grayscale US picture. After a box (frame) is placed over the pleura, a colored image appears, revealing blue and red areas on an elastogram. Dark-blue areas correspond to soft tissues, whereas red areas correspond

to stiff tissues. With the aid of the device's software, a circular region of interest was placed inside the pleural elastogram, and the diameter of the circle was increased as much as possible to between 1 and 8 mm, taking care not to surpass the limits of the analyzed pleura. The default setting for the pleural 2D-SWE scale was used (range 0 to ≥100 kPa). The summary quantitative stiffness data were automatically displayed. The following parameters for the elasticity index (EI), expressed in kPa, were provided by the system: the mean value of the EI (SWE-Mean), the maximum value of the EI (SWE-Max), the minimum value of the EI (SWE-Min), and the standard deviation of the EI (SWE-SD)[6].

References:

1. Diacon AH, Theron J, Bolliger CT. Transthoracic ultrasound for the pulmonologist. *Current opinion in pulmonary medicine* 2005: 11(4): 307-312.
2. Koenig SJ, Narasimhan M, Mayo PH. Thoracic ultrasonography for the pulmonary specialist. *Chest* 2011: 140(5): 1332-1341.
3. Gorg C, Restrepo I, Schwerk WB. Sonography of malignant pleural effusion. *European radiology* 1997: 7(8): 1195-1198.
4. Brandenburg JE, Eby SF, Song P, Zhao H, Brault JS, Chen S, An KN. Ultrasound elastography: the new frontier in direct measurement of muscle stiffness. *Archives of physical medicine and rehabilitation* 2014: 95(11): 2207-2219.
5. Lacourpaille L, Hug F, Bouillard K, Hogrel JY, Nordez A. Supersonic shear imaging provides a reliable measurement of resting muscle shear elastic modulus. *Physiological measurement* 2012: 33(3): N19-28.
6. Azizi G, Keller JM, Mayo ML, Piper K, Puett D, Earp KM, Malchoff CD. Thyroid Nodules and Shear Wave Elastography: A New Tool in Thyroid Cancer Detection. *Ultrasound in medicine & biology* 2015: 41(11): 2855-2865.


≥180 kPa
144
108
72
36
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Min 61.7 kPa
Max 114.7 kPa
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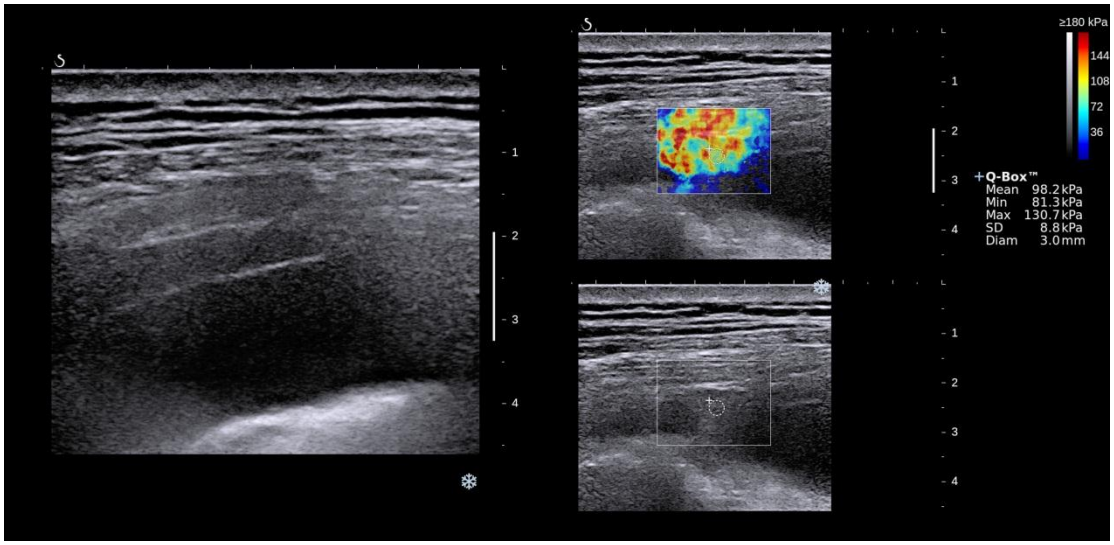
Diam 3.0 mm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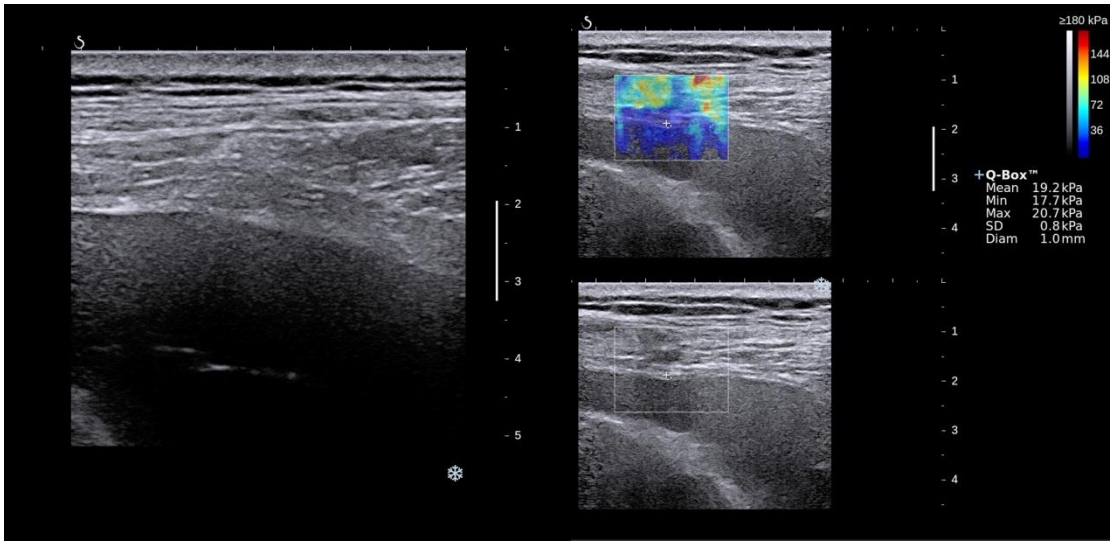
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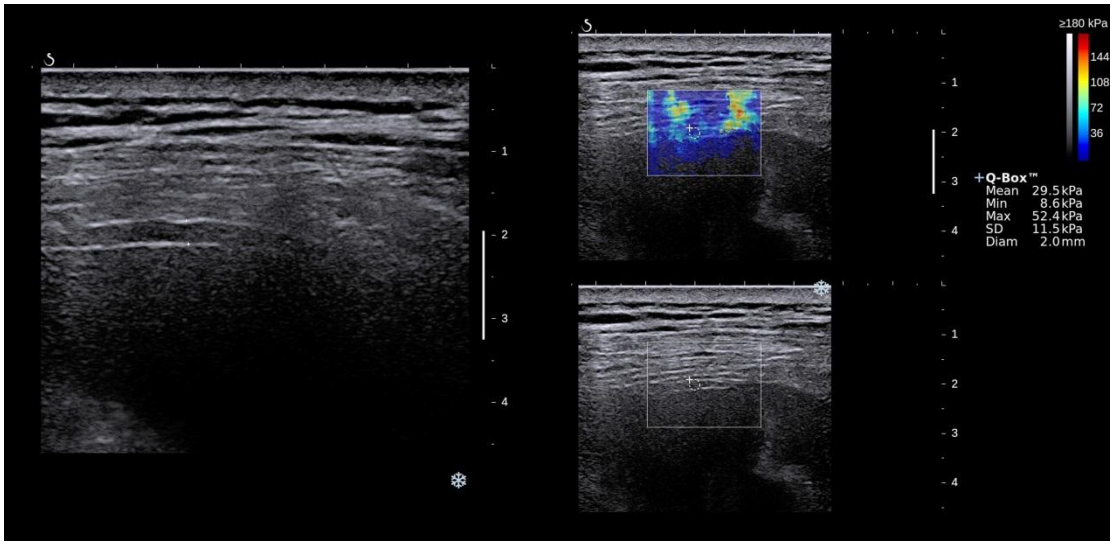
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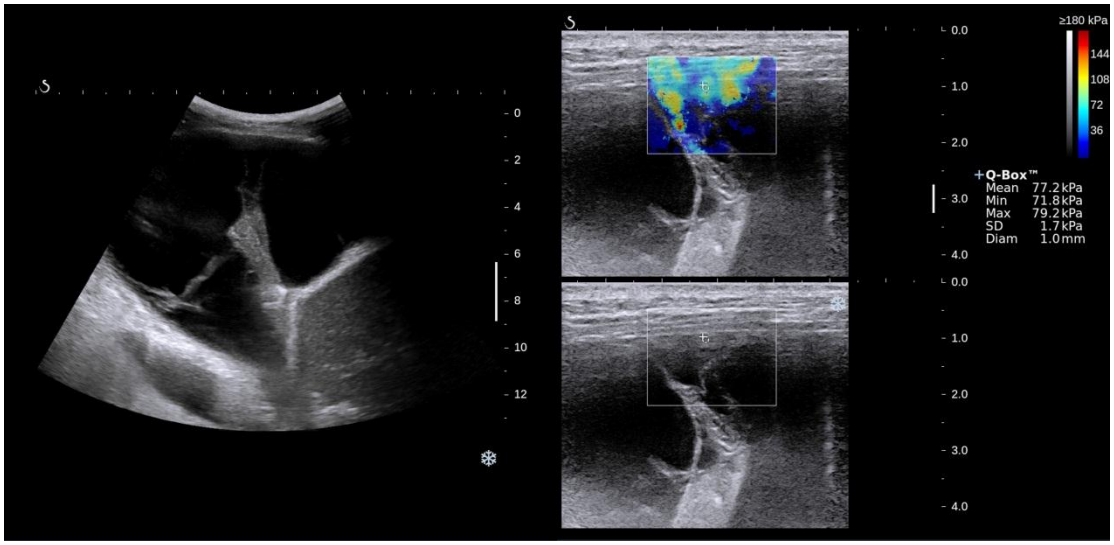
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2
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12
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Max 79.2 kPa
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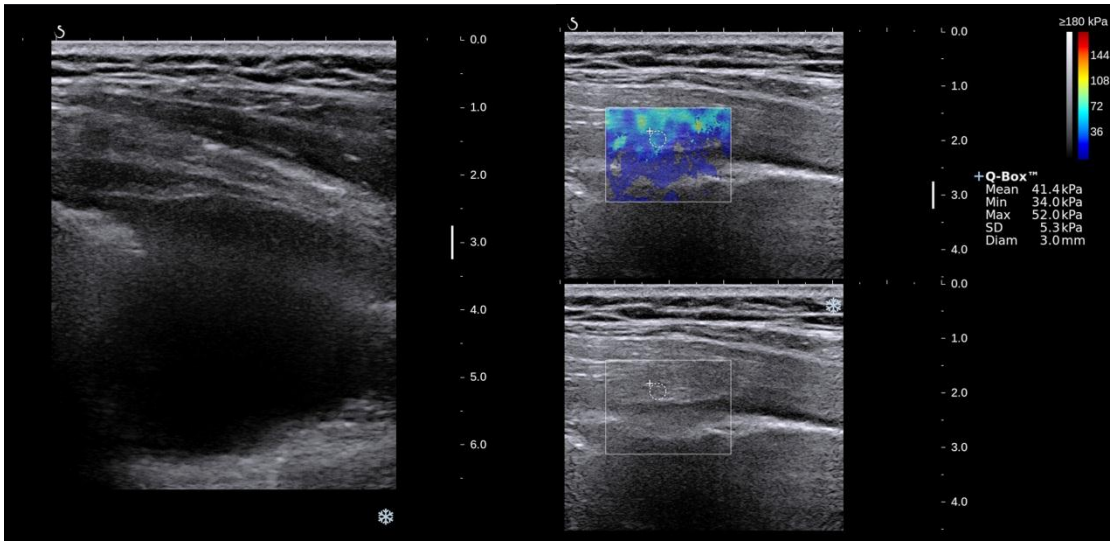
Diam 1.0 mm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≥180 kPa
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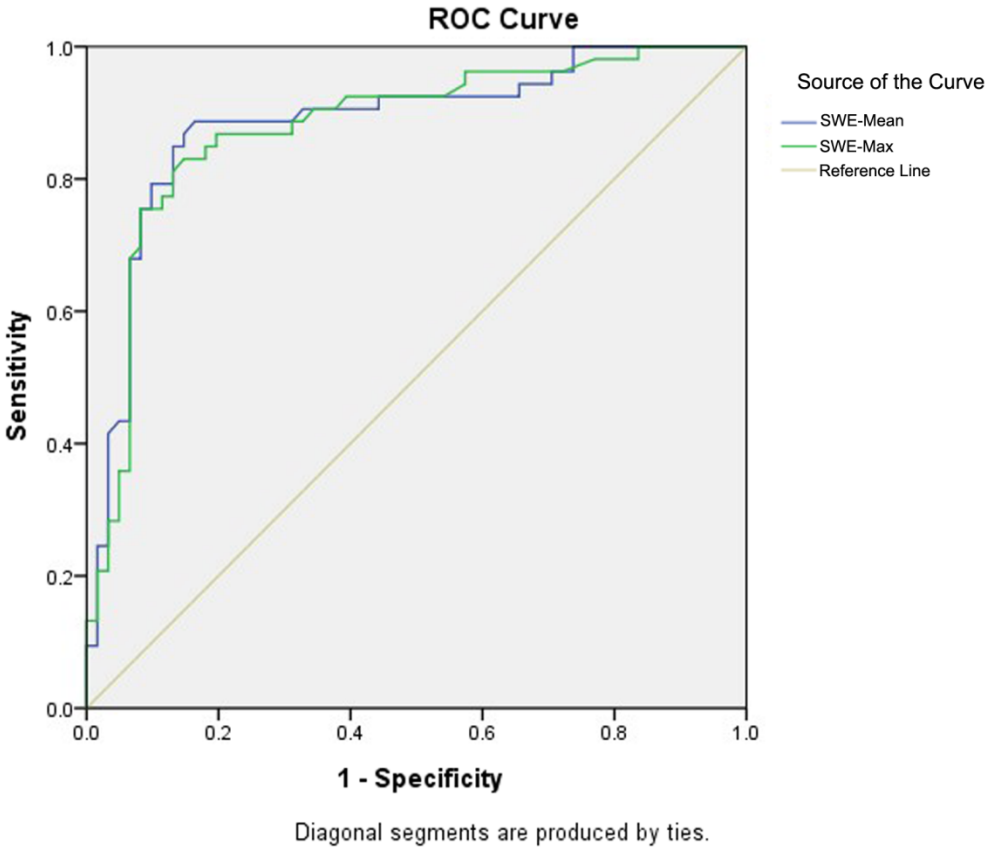
ROC Curve
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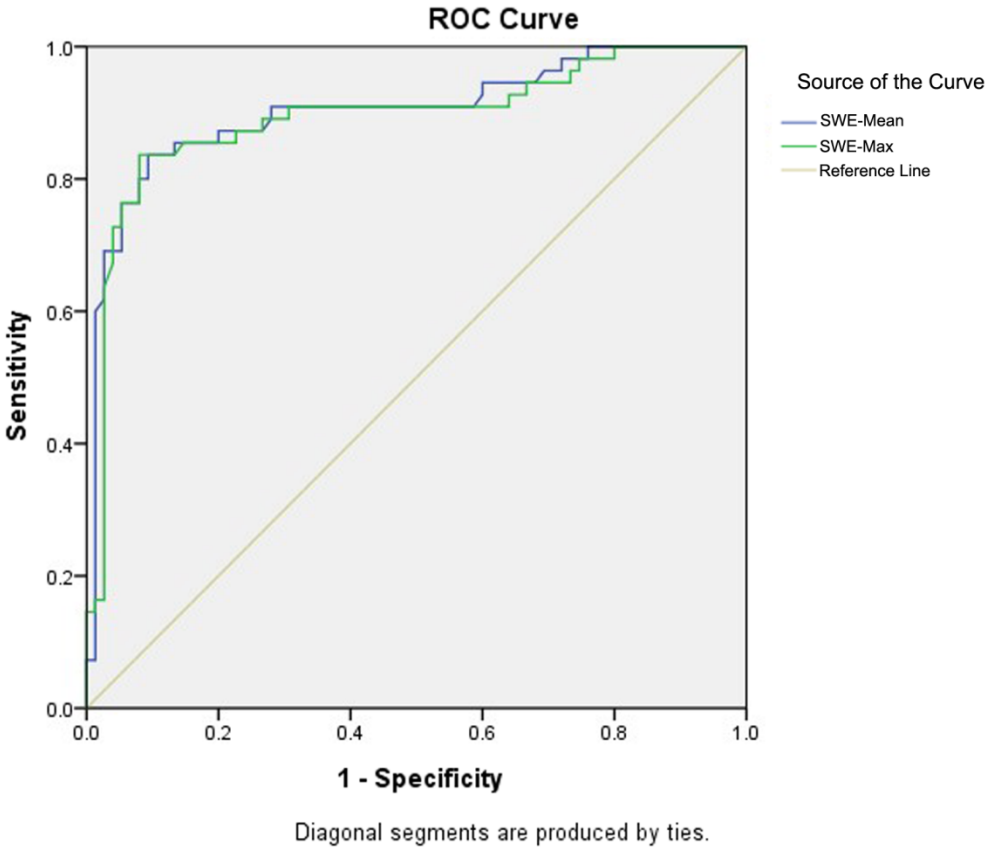
0.2
0.4
0.6
0.8
1.0
Source of the Curve
SWE-Mean
SWE-Max
Reference Line
Diagonal segments are produced by ties.



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