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Original Article

# Lung ultrasonography in pulmonary tuberculosis: A pilot study on diagnostic accuracy in a high-risk population

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ABSTRACT

*Objectives:* The validity of lung ultrasound (LUS) in the diagnosis of interstitial or focal lung pathologies is well documented, we assessed its accuracy in the diagnosis of pulmonary tuberculosis (PTB).
*Methods:* Sonographic signs suggestive of PTB and their diagnostic accuracy were evaluated in patients admitted with clinical suspicion of PTB. Consolidations, subpleural nodules, pleural thickenings or irregularities and pleural effusion were assessed. LUS signs significantly associated with PTB in the univariate analysis ($p < .05$) were entered in a multivariate logistic regression model.
*Results:* PTB was confirmed in 51 out of 102 patients. Multiple consolidations (OR 3.54, 95%CI 1.43–8.78), apical consolidations (OR 9.65, 95%CI 3.02–30.78), superior quadrant consolidations (OR 4.01, 95%CI 1.76–9.14), and subpleural nodules (OR 5.29, 95%CI 2.27–12.33) were significantly associated with PTB diagnosis. Apical consolidation (OR 9.67, 95%CI 2.81–33.25, p 0.003) and subpleural nodules (OR 5.30, 95%CI 2.08–13.52, p 0.005) retained a significant association in a multivariate model, with an overall accuracy of 0.799.
*Conclusions:* Our data suggest a possible role of LUS in the diagnosis of PTB, a high burden pathological condition for which the delay in diagnosis still represents a critical point in the control of the disease.

## 1. Introduction

According to the World Health Organization (WHO), in 2017, 10 million individuals became ill with tuberculosis (TB) and 1.6 million died [1]. The epidemiology of TB varies substantially around the world with highest rates observed in sub-Saharan Africa, India, and the islands of Southeast Asia. Missed or late diagnosis of TB is still significant for both low- and high-income countries [2].

The most common available tests present many pitfalls and microbiologic confirmation is often lacking. Regarding pulmonary tuberculosis (PTB), smear microscopy has low sensitivity, culture methods take several weeks for the results and rapid molecular tests are not widely available although they are the recommended methods according to WHO [3].

Chest X-Ray (CXR), the mainstay for the radiological identification, is burdened by low specificity, radiation exposure and it's not promptly available in health systems with limited resources [4].

Bedside ultrasound is a safe, portable, versatile and cost-effective imaging modality [5]. The WHO has acknowledged that it should be available worldwide to assist the clinician in the diagnostic process [6]. In particular, lung ultrasonography (LUS) has been applied in the diagnosis of several lung pathologies as pneumothorax [7], interstitial lung diseases [8], pleuritis and, of course, pleural effusion [9]. Its diagnostic accuracy in recognition of pneumonia is demonstrated to be similar to computed tomography (CT) [10]. Thus, LUS is a potential useful diagnostic tool for the diagnosis of PTB, particularly in

*Abbreviations:* TB, Tuberculosis; PTB, Pulmonary tuberculosis; WHO, World Health Organization; CXR, Chest X-Ray; LUS, Lung ultrasonography; CT, Computed tomography; TST, Tuberculin Skin Test; HIV, Human immunodeficiency virus; US, Ultrasound; LR+, Likelihood ratio; LR-, Negative likelihood ratio; PPV, Positive predictive value; NPV, Negative predictive value; CI, Confidence intervals; OR, Odds ratios; ROC, Receiver-operating characteristic

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geographic areas and in situations where radiological or laboratory equipments are not readily available. [11,12]

Consolidations, subpleural nodules, pleural thickenings, fibrosis, pleural effusion and pneumothorax together with miliary pattern have been reported in descriptive studies on US in PTB [11,13,14].

Nevertheless, the diagnostic accuracy of LUS in diagnosing PTB has never been studied. Aim of this study is to assess LUS signs associated with PTB and evaluate their diagnostic accuracy.

## 2. Methods

This interventional non-pharmacologic prospective study was conducted at the Luigi Sacco Hospital, ASST Fatebenefratelli-Sacco, Milan, Italy, a university-affiliated hospital serving as a referral centre for the treatment of infectious diseases. The study is consistent with the principles of the Declaration of Helsinki on clinical research involving human subjects and according to the quality standards of Good Clinical Practice and it was approved by the Ethics Committee Milano Area 1 (project approval no. 40082/2017). Written informed consent was obtained from each patient included in the study.

All consecutive patients admitted to the Department of Infectious Diseases presenting with clinical suspicion of PTB in a 15-months period were included. According to international guidelines suspicion of PTB was defined by the presence of at least one of the following clinical scenarios: 1) any patients with a cough of ≥ 2–3 weeks duration with at least one additional symptom including fever, night sweats, weight loss or hemoptysis; 2) any patient at high risk for TB with unexplained illness including respiratory symptoms of ≥ 2–3 weeks duration; 3) any patient with HIV infection and unexplained cough and fever; 4) any patient at high risk for TB with a diagnosis of community acquired pneumonia who has not improved after seven days of treatment; 5) any patient at high risk for TB with incidental finding on CXR suggestive of TB even if symptoms are minimal or absent [15]. CXR was considered suggestive of PTB in case of infiltrates with or without cavitation in the upper lobes or involving the superior segments of the lower lobes [16]. Risk factors for TB were: any known contact or family member affected by TB, history of previous TB or any TB treatment or positive TST results, high risk congregate settings, substance abuse, country of birth, immunosuppressive therapy and immunodeficiency-associated diseases with particular attention to HIV status.

We considered exclusion criteria a previously known interstitial lung disease, active PTB diagnosed before the admission to the hospital, LUS contraindications (subcutaneous emphysema, burns localized on the thorax or skin diseases that interfere with the methodology) or refusal of consent. Primary assessment of the enrolled patients consisted in routine evaluation with medical history and physical examination.

According to WHO [17], PTB refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB and patients with both PTB and extrapulmonary TB were classified as case of PTB. A bacteriologically confirmed PTB case is one from whom sputum/broncho-alveolar lavage had a positive smear microscopy, culture or nucleic acid amplification tests for *M. tuberculosis*. Samples were sent to the Microbiology Laboratory of L. Sacco Hospital and examined for acid-fast bacilli using the Ziehl-Neelsen method. The presence of *M. tuberculosis* complex was determined also by real-time polymerase chain reaction (PCR), after DNA extraction, using Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA). Mycobacterial cultures were performed on both solid and liquid media, using Lowenstein-Jensen medium and BACTEC MGIT (Mycobacteria Growth Indicator Tube; BD, Sparks, MD, USA), respectively. In clinically diagnosed PTB bacteriological confirmation was not obtained but the physician diagnosed active PTB on clinical/radiological basis and treated the patient with a full course anti-TB chemotherapy.

Patients underwent LUS within 3 days after admission to the ward. The examination was performed by a physician of the Internal Medicine Department experienced in clinical ultrasonography, blinded to the patient clinical information and radiological examinations. Sonography was conducted using a portable US device Sonosite M-Turbo (Fujifilm SonoSite, Inc., USA) with a 5–2 MHz convex probe. Patients were studied in the supine position for evaluation of the anterior thorax and in seated position for evaluation of posterior and lateral thorax. If the patient was not able to maintain the seated position the exam was performed in the supine position and lateral decubitus to assess the posterior areas. Patients were examined by longitudinal and oblique scans. During the exam of the posterior regions, the patients were asked to raise the arms above the head in order to displace the shoulder blade and uncover the area of the lung which is usually masked by the bone. The examination of the lung apexes was performed by applying the probe vertically between the clavicle and the trapezius muscle anteriorly (Fig. 1) and directly on the cranial part of the trapezius muscle on the back. The whole surface of the chest was sistematically analized. To describe and record echographic signs each hemithorax was divided following anatomical lines in 6 areas (4 anterior and 2 posterior areas) as illustrated in Fig. 2.

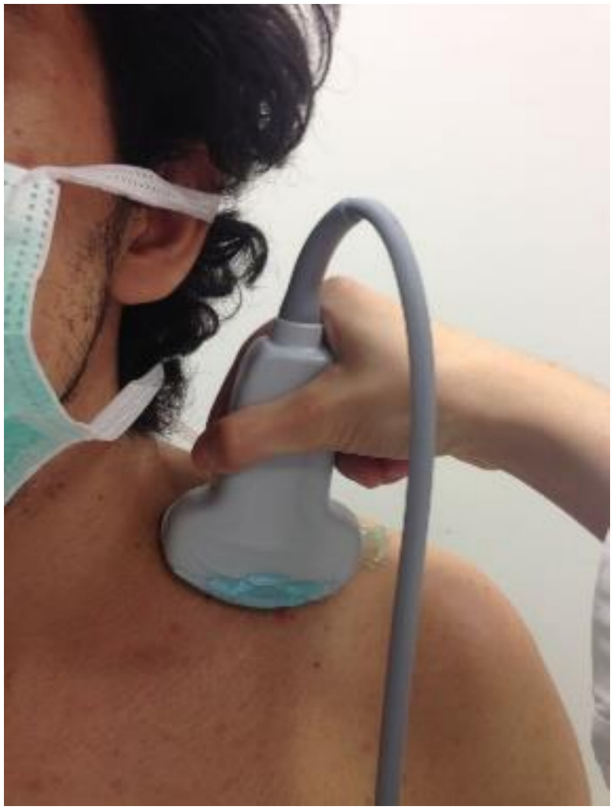

**Fig. 1.** Convex probe placed coronally on the supraclavicular region for visualization of the lung apex.

Taking into consideration the descriptive studies [11,13,14], the following US findings were considered and recorded: consolidation (single or multiple); subpleural nodules (circular or ellipsoidal hypoechoic subpleural lesions < 15 mm (measured as extension on the pleural line and as depth)); irregularities or focal thickenings of the pleura; presence of pleural effusion. Apical consolidations were defined as visible by scanning the supraclavicular region or within the first two intercostal spaces or the body of the first thoracic vertebra posteriorly.

In the first half of enrolled populations patients with cavitations at CXR/CT images underwent a second non-blind US evaluation to identify possible US characteristics of cavitated lesions. Thus, in the second half, we blindly searched for recurrent US characteristics associated with cavitated consolidations.

Electronic images of each examination were acquired and stored. At

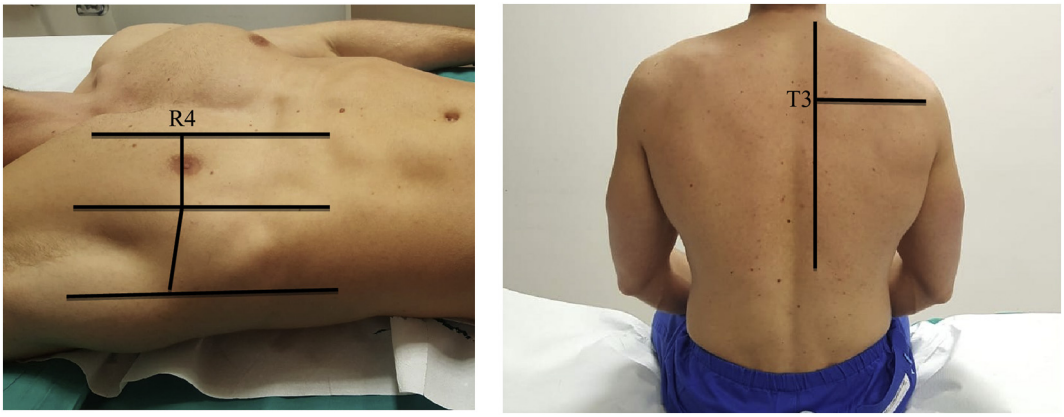


**Fig. 2.** Anatomical Lines identifying superior and inferior areas anteriorly (left panel) and posteriorly (right panel).
R4: fourth rib.
T3: third thoracic vertebra.

the end of each exam, the physician was required to fill a predefined form where an accurate description and localization of the pathological findings were outlined.

## 3. Calculations

Continuous variables were reported as mean (standard deviation) or median (range), as appropriate. Categorical data were expressed as counts (percentages). For group comparison, the Student's *t*-test or Mann-Whitney test were used for continuous variables, as appropriate, and the Fisher exact test was used for categorical variables.

Diagnostic accuracy of each echographic sign was assessed and sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), positive predictive value (PPV) and negative predictive value (NPV), with their 95% confidence intervals (95% CI), were calculated. Then a logistic regression approach was adopted to find the combination of echographic signs with the best diagnostic accuracy. First, univariate logistic models were fitted to assess the association between each of the sign and PTB diagnosis. Then, a multivariate analysis was performed by considering only the signs significantly associated with PTB diagnosis at univariate analysis and adopting a stepwise strategy in order to find the best model. Results of logistic regression analysis were reported as odds ratios (OR) with 95% CI. The c-statistic, which can be interpreted as the area under the receiver-operating characteristic (ROC) curve, was used to assess the overall accuracy of univariate and multivariate models. Finally, in order to translate the results of the models into clinical practice, diagnostic accuracy was assessed considering only the echographic signs that were found to be statistically significant at the multivariate analysis. Sensitivity and specificity were calculated for combinations of signs, according to the following two scenarios: positive patients are all those with a positive result in at least one of the signs; positive patients are all those with positive results in all the signs.

*P* values < .05, two sided, were considered statistically significant. All the statistical analyses were performed using SAS statistical software (release 9.4).

### 3.1. Sample size

We were interested in the assessment of the ability of echographic signs in ruling-out PTB. We expected that the sign with the highest sensitivity would have 80% sensitivity. Assuming a PTB prevalence of 45%, the inclusion of at least 100 consecutive patients (45 with PTB) would have provided an estimate of the anticipated sensitivity with 95% CI from 65% to 90%, that can be considered sufficiently precise.

## 4. Results

One hundred-ten consecutive patients with clinical suspicion of PTB were enrolled. Eight patients have been excluded: 2 of them had a known interstitial lung disease while in 6 patients the diagnosis of PTB predated the day of admission. One hundred-two patients were thus included and completed the study. PTB was confirmed in 51 (44 by culture and 7 on clinical basis) with a disease prevalence of 50% in our population.

Study population characteristics are reported in Table 1. Ninety-six (94.1%) of the patients had at least one risk factor for TB. PTB patients were younger, more frequently foreign born and living in overcrowded conditions (homelessness, incarceration, refugee camp). We observed longer duration of symptoms in the PTB patients and a lower white blood cells count. Out of the overall population, 28 patients (27%) tested HIV positive, of which 11 have been diagnosed with PTB. Discharge diagnosis are shown in Table 2. The most frequent non-PTB diagnosis was bacterial pneumonia, followed by pulmonary neoplasia, pneumocystosis and aspergillosis. In 10 patients no definite diagnosis was obtained, TB was nonetheless excluded.

Univariate analysis of LUS findings showed significant association with PTB diagnosis for multiple consolidations, apical consolidations, superior quadrant involvement and subpleural nodules. These variables were then included in the multivariate model where apical consolidation (OR 9.67, 95%CI 2.81–33.25, p 0.003) and subpleural nodules (OR 5.30, 95%CI 2.08–13.52, p 0.005) were found to be independently correlated with the diagnosis of PTB (Table 3, Fig. 3). Calculation of sensitivity and specificity were performed for each echographic sign (Table 4) and for the model constructed by using the two variables significantly correlated with PTB in the multivariate analysis (apical consolidation and subpleural nodules) (Table 5). We observed a specificity of 96% when the apical consolidations and subpleural nodules were found in the same patient, with sensitivity of 31%. Sensitivity of 86% and specificity of 63% were attained when the test was considered positive with the detection of at least one of those signs. The c-statistic for the model with two variables was 0.799.

We analysed the characteristics of subpleural nodules. Maximal pleural extension and depth measured 8 ± 3 mm (range 3–15) x 8 ± 2 (range 3–14) in TB patients and 7 ± 3 mm (range 4–14) x 6 ± 2 mm (range 3–11) in non-TB. Eighteen out of 37 TB patients presenting subpleural nodules had bilateral involvement. In twenty-one patients nodules were confined to superior quadrants, while 14 patients presented diffuse nodules (superior and inferior quadrants). In only two PTB patients (5%) subpleural nodules were limited to inferior quadrants. Five out of the 17 patients without TB (29%) presented nodules just in the inferior quadrant while in 11 the superior quadrants were

**Table 1**
Baseline population characteristics.

| | PTB | non PTB | p Value |
|---|---|---|---|
| | n = 51 | n = 51 | |
| Sex M, No. (%) | 37 (72) | 30 (59) | 0,2105 |
| Age, years, Median (IQR) | 34 (24–49) | 49 (39–60) | **0,0001** |
| **Origin, No. (%)** | | | |
| Italy | 9 (18) | 29 (57) | |
| Others | 42 (82) | 22 (43) | < **0,0001** |
| **Risk factors** | | | |
| HIV +, No. (%) | 11 (22) | 17 (33) | 0,2672 |
| CD4+ cell/mm3, Median (IQR) | 150 (74–279) | 255 (158–749) | 0,0776 |
| Smoke, No. (%) | 21 (41) | 24 (47) | 0,8417 |
| Type II Diabetes Mellitus, No. (%) | 6 (12) | 4 (8) | 0,7409 |
| Alcohol abuse, No. (%) | 15 (30) | 11 (22) | 0,496 |
| Active IV abuse, No. (%) | 4 (8) | 8 (16) | 0,3573 |
| Malnutrition, No. (%) | 3 (6) | 0 (0) | 0,2426 |
| High risk congregate settings, No. (%) | 14 (28) | 3 (6) | **0,0065** |
| Chronic kidney disease, No. (%) | 1 (2) | 0 (0) | 0,9999 |
| Immunosuppressive therapy, No. (%) | 1 (2) | 4 (8) | 0,3624 |
| Active cancer, No. (%) | 0 (0) | 5 (10) | 0,0564 |
| Previous Tuberculosis, No. (%) | 7 (14) | 14 (27) | 0,1406 |
| **Symtoms, No. (%)** | | | |
| Fever | 34 (66) | 35 (69) | 0,9999 |
| Cough | 37 (72) | 35 (69) | 0,8282 |
| Sputum production | 19 (37) | 16 (31) | 0,6769 |
| Haemoptysis | 13 (25) | 15 (29) | 0,8247 |
| Generalized weakness | 19 (37) | 18 (35) | 0,9999 |
| Weight loss | 13 (25) | 10 (20) | 0,6362 |
| Night sweats | 12 (24) | 10 (20) | 0,8102 |
| Thoracic pain | 16 (32) | 17 (33) | 0,9999 |
| Pharyngodynia | 2 (4) | 1 (2) | 0,9999 |
| Lynphadenopathy | 4 (8) | 1 (2) | 0,3624 |
| No symptoms | 1 (2) | 2 (4) | 0,577 |
| **Duration of symptoms, Median (IQR)** | 30 (14–62) | 15 (5–45) | **0,009** |
| **Positive lung physical examination, No. (%)** | 30 (59) | 26 (51) | 0,5508 |
| **Laboratory findings** | | | |
| CRP, mg/dL, Median (IQR) | 49 (21–99) | 38 (8–102) | 0,4257 |
| Leukocytes, cell/mm3, Median (IQR) | 7700 (5730–9530) | 9710 (7700–11,660) | **0,0092** |
| Hb, g/dL, Mean (SD) | 12,0 (2) | 12,3 (1,8) | 0,2896 |
| LDH, UI/l, Median (IQR) | 216,5 (178,5–257) | 207 | 0,8127 |

PTB: Pulmonary Tuberculosis; IV: Intravenous; CRP: C reactive protein; Hb: Hemoglobin; LDH: Lactate dehydrogenase; IQR: interquartile range; SD: standard deviation.

**Table 2**
Discharge diagnosis.

| | *n (%)* |
|---|---|
| Pulmonary Tuberculosis | *51 (50)* |
| Pneumonia | *19 (18,6)* |
| Lung lesions of unknown origin | *10 (9,8)* |
| Pneumocystosis | *3 (2,9)* |
| Lung cancer | *3 (2,9)* |
| Aspergillosis | *3 (2,9)* |
| Bronchiectasis | *2 (1,9)* |
| Upper respiratory infections | *2 (1,9)* |
| Hematologic malignancy | *2 (1,9)* |
| Atypical mycobacterial diseases | *2 (1,9)* |
| Pleural disease other than TB | *2 (1,9)* |
| Extrapulmonary TB | *1 (0,9)* |
| Miscellaneous | *2 (1,9)* |

TB: Tuberculosis.

involved. Five of these latter presented a previous PTB diagnosis. In non-TB patients nodules were frequently found in the context of diffuse pleural irregularities. A diffuse interstitial pattern and multiple subpleural nodules were identified in the two cases presenting miliary TB.

On chest US pleural effusion was inversely associated with PTB and mainly represented in patients with a different discharge diagnosis (e.g. pneumonia, lung cancer). Pleural fluid characteristics did not differ between TB and non-TB patients: in 5 out of 10 TB patients and in 5 out of 13 non-TB patients' pleural fluid presented septations and loculations.

In the first half of population we performed a second non-blind ultrasonography in 13 patients with cavitations at CXR/CT. Six of them had markedly hypoechogenic or anechogenic areas inside a consolidation, without bronchograms or signs of vascularization at color Doppler. In the second half of population we checked the suspicion of cavitations in all 58 patients. The presence of hypoechogenic or anechogenic areas inside a consolidation, without bronchograms or signs of vascularization at color Doppler was identified in 12 cases. Two of them were not confirmed by CT scan. Radiology found cavitations in 24 patients out of 52, 18 by CRX and 6 more by CT. Out of these 24, 15 were TB patients and 9 non-TB.

## 5. Discussion

To our knowledge this is the first study dealing with the diagnostic accuracy of LUS in the diagnosis of PTB in adults. We assessed the echographic signs associated with PTB showing that apical consolidation and subpleural nodules were independently correlated with the diagnosis of PTB. They had a good sensitivity when considered individually and an excellent specificity when present simultaneously.

Ultrasound is a potent tool for the diagnosis, screening, and monitoring of treatment response for a broad and still expanding range of infectious diseases [18]. In areas with high prevalence of TB the detection of echographic signs may suffice to initiate a treatment for extrapulmonary TB without histologic confirmation [19]. Point-of-care ultrasonography is increasingly used in resource-limited settings because of its diagnostic accuracy associated with non-invasiveness, repeatability and easy transportability. LUS has emerged as a pivotal part of point of care ultrasound: its sonographic signs are simple to learn and analysis of artefacts and morphologic images allows accurate diagnosis in many lung pathologies [9]. The WHO states that plain radiography and ultrasonography, singly or in combination, meet up to 90% of all imaging needs in developing countries [20].

A screening test with accuracy in the order of CXR for TB abnormalities but without the need for CXR equipment would be an highly desirable asset to facilitate TB screening and a way to improve TB case detection [4] which is a key component of the End TB Strategy [21].

In the literature, with the exception of case reports [11,13,22] and a paediatric study [23], there is only one study describing the echographic picture of PTB in adult patients already diagnosed with the disease [14]. The authors showed that subpleural nodules were the most frequent echographic sign in patients with active PTB in Sub-Saharan Africa, being often bilateral and randomly distributed. In the same study consolidations identified by LUS were described as irregular consolidations of relatively homogeneous texture, indistinguishable from bacterial pneumonia [14].

In our study apical consolidations and subpleural nodules were the two echographic signs independently correlated with the diagnosis of PTB. The association of LUS finding of subpleural nodules with PTB is of particular interest because, as previously described [14], subpleural nodules are often missed by CXR. Among our 17 patients with subpleural nodules but no PTB diagnosis, 7 had a previous TB infection and 6 were immunodepressed. Furthermore 7 of them had pulmonary disease detected on CT scan such as emphysema with bronchiectasis, pulmonary fibrosis, pulmonary neoplasm and aspergillosis. Distribution

**Table 3**
Diagnostic accuracy of LUS signs.

| | | | | Univariate | | | Multivariate[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | n (%) | PTB (%) | non PTB (%) | OR (95% CI) | *p*-value | c-statistic | OR (95% CI) | p-value | c-statistic |
| Consolidations | 73 (72) | 40 (77) | 33 (64) | 1,98 (0,82-4,78) | 0,1274 | 0,569 | | | 0,799 |
| Multiple consolidations | 31 (30) | 22 (43) | 9 (18) | 3,54 (1,43-8,78) | 0,0064 | 0,627 | | | |
| Apical consolidation | 27 (26) | 23 (45) | 4 (8) | 9,65 (3,02-30,78) | < 0,0001 | 0.686 | 9,67 (2,81-33,25) | 0,003 | |
| Superior consolidation | 53 (52) | 35 (69) | 18 (35) | 4,01 (1,76-9,14) | 0,001 | 0,667 | | | |
| Subpleural nodules | 54 (53) | 37 (73) | 17 (33) | 5,29 (2,27-12,33) | < 0,0001 | 0,696 | 5,30 (2,08-13,52) | 0,005 | |
| Pleural irregularities | 70 (69) | 37 (73) | 33 (65) | 1,44 (0,62-3,34) | 0,3943 | 0.539 | | | |
| Pleural effusion | 23 (23) | 10 (20) | 13 (25) | 0,71 (0,28-1,82) | 0.4782 | 0.529 | | | |
| Cavitations ($n$ = 58 PTB = 30) | 12 (21) | 9 (30) | 3 (11) | 3,57 (8,85-14,92) | 0,081 | 0,596 | | | |

PTB: Pulmonary Tuberculosis; OR: Odds ratio; CI: Confidence Interval; AUC: Area Under Curve.
[a] Only the variables found to be statistically significant after stepwise strategy are reported in the table.

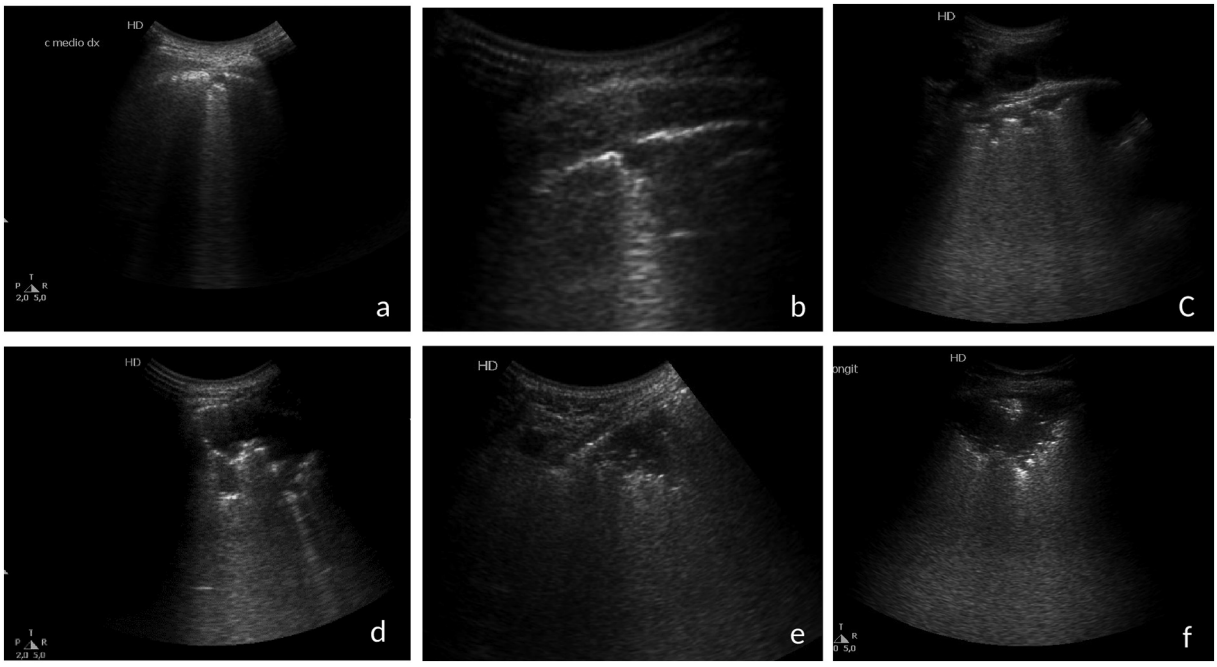


**Fig. 3.** (a,b) Single subpleural nodule (c) multiple subpleural nodules (d,e,f) apical consolidations.

**Table 4**
Diagnostic accuracy of LUS signs.

| | SE | CI 95% | SP | CI 95% | LR+ | | LH- | | PPV | CI 95% | NPV | CI 95% |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Consolidations | 78,4 | 64,7-88,7 | 35,3 | 22,4-49,9 | 1212 | 0,945-1554 | 0,611 | 0,322-1661 | 54,8 | 42,7-66,5 | 62,1 | 42,3-79,3 |
| Multiple consolidations | 43,1 | 29,3-57,8 | 82,4 | 69,1-91,6 | 2444 | 1249-4784 | 0,69 | 0,527-0,905 | 71 | 52–85,8 | 59,2 | 46,8-70,7 |
| Apical consolidation | 45,1 | 31,1-59,7 | 92,2 | 81,1-97,8 | 5,75 | 2,14-15,449 | 0,596 | 0,459–0,774 | 85,2 | 66,3-95,8 | 62,7 | 50,7-73,6 |
| Superior consolidation | 68,6 | 54,1-80,9 | 64,7 | 50,1-77,6 | 1944 | 1284-2946 | 0,485 | 0,308-0,763 | 66 | 51,7-78,5 | 67,3 | 52,5-80,1 |
| Subpleural nodules | 72,5 | 58,3-84,1 | 66,7 | 52,1-79,2 | 2176 | 1425-3323 | 0,412 | 0,253-0,67 | 68,5 | 54,4-80,5 | 70,8 | 55,9–83 |
| Pleural irregularities | 72,5 | 58,3-84,1 | 35,3 | 22,4-49,9 | 1121 | 0,861-1460 | 0,778 | 0,435-1390 | 52,9 | 40,6-64,9 | 56,3 | 37,7-73,6 |
| Pleural effusion | 19,6 | 9,8-33,1 | 74,5 | 60,4-85,7 | 0,769 | 0,372-1592 | 1079 | 0,874-1331 | 43,5 | 23,2-65,5 | 48,1 | 36,7-59,6 |

SE: Sensitivity; CI: Confidence interval; SP: Specificity; LR: Likelihood ratio; PPV: Positive predictive value; NPV: Negative predictive value.

**Table 5**
Diagnostic accuracy of the model based on LUS signs.

| | TP | FP | FN | TN | SE | CI 95% | SP | CI 95% | LR+ | CI 95% | LR- | CI 95% | PPV | CI 95% | NPV | CI 95% |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Apical consolidation OR subpleural nodules | 44 | 19 | 7 | 32 | 86 | 74–94 | 63 | 48–76 | 2,32 | 1,6-3,36 | 0,22 | 0,11-0,45 | 69,80% | 57–80,8% | 82,10% | 66,5-92,5% |
| Apical consolidation AND subpleural nodules | 16 | 2 | 35 | 49 | 31 | 19–46 | 96 | 87–100 | 8 | 1,94-33,03 | 0,71 | 0,59-0,87 | 88,89% | 65,3-98,6% | 58,30% | 47,1–69% |

TP: True positive; FP: False positive; FN: False negative; TN: True negative; SE: Sensitivity; SP: Specificity; LR: Likelihood ratio; PPV: Positive predictive value; NPV: Negative predictive value.

of the nodules seems to be different in the PTB and non PTB population. The superior quadrant involvement of the subpleural nodules seems to be associated with active PTB or history of TB disease in our population. In previous studies subpleural nodules were also described in cryptococcosis, aspergillosis, sarcoidosis, cytomegalovirus and pneumocystis pneumonia [24]. It is possible to hypothesize that in patients with symptoms compatible with PTB and without the confounding presence of chronic pulmonary disease the detection of subpleural nodules with superior involvement may narrow the differential diagnosis and increase the pre-test probability of PTB diagnosis.

Apical consolidations reached a high specificity with a lower sensitivity. We systematically visualized the lung apexes by performing a specific US projection usually described only in US-guided procedures on brachial plexus. The only three false positives cases showed particular conditions: one was diagnosed with pneumonia with multiple consolidations in Hodgkin's lymphoma; one patient had residual scar tissue from a spontaneous pneumothorax; the third one was a HIV positive patient with multiple supraclavicular lymphadenopathies in myeloproliferative disease.

The high specificity of apical consolidation was further increased by the concomitant presence of subpleural nodules, indicating LUS as a useful rule-in test in these cases.

In our study LUS had a reliable sensitivity for PTB diagnosis when considering the presence of at least one between apical consolidation and subpleural nodules. Moreover, it should be emphasized that no patient with PTB had completely negative ultrasound examination. Considering the 7 patients who did not show either apical consolidation or subpleural nodules, 4 of them had pleural effusion, 5 had pleural irregularities, 3 had multiple consolidations.

These data suggest that the implementation of other sonographic signs besides apical consolidation and subpleural nodules may further increase the rule-out value of LUS.

As previously shown [14] hypoechogenic or anechogenic areas inside a consolidation, without bronchograms or signs of vascularisation were the US findings more frequently associated with cavitations. However these signs does not appear to be enough sensitive probably due to the high number of lesions not reaching the pleura and the presence of air in cavitation.

## 6. Conclusions

Low cost, easy to use and to transport, rapid learning curve, absence of radiation exposure and repeatability are recognized advantages of ultrasonography making it a useful point of care diagnostic and monitoring tool.

Our data suggest that chest ultrasonography may be a promising tool to support clinical, radiological and microbiological data in the diagnosis of PTB, a high burden pathological condition for which the delay in diagnosis represents a critical point in the control of the disease.

Future studies are warranted to assess a possible role of LUS as a triage/screening test in high burden countries. Furthermore the use of LUS as a follow-up examination to monitor therapy efficacy may be another attractive application to be investigated.

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## Declaration of Competing Interest

The authors have no conflict of interest to disclose. On behalf of all authors, the corresponding author states that there is no conflict of interest.

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