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LUNG ULTRASOUND FOR THE DIAGNOSIS AND MONITORING OF PNEUMONIA IN A TUBERCULOSIS-ENDEMIC SETTING: A PROSPECTIVE STUDY

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Abstract

Lung ultrasound (LUS) has proven high diagnostic accuracy for community-acquired pneumonia (CAP) in developed countries. However, its diagnostic performance in resource-limited settings with high pulmonary tuberculosis (TB) incidence is less established. Additionally, the role of LUS in monitoring CAP progression remains underexplored.

Objectives To validate the diagnostic performance, monitoring, and prognostic utility of lung ultrasound for CAP in a high pulmonary tuberculosis incidence setting.

Design Prospective single-center cohort study

Setting Pulmonary department of a tertiary hospital in Vietnam.

Participants A total of 158 patients suspected of having CAP were enrolled, with 136 (mean age 62 years, 72.8% male) included in the final analysis.

Interventions Patients underwent LUS and chest X-ray (CXR) within 24 hours of admission, with a follow-up LUS on day 5-8.

Primary and Secondary Outcome Measures.

The primary outcome was the diagnostic accuracy of LUS and CXR compared to discharge diagnosis or CT scan results. **Secondary outcomes** assessed changes in LUS parameters—consolidation size, number, and Lung Ultrasound Score (LUSS)—and their correlation with in-hospital outcomes (mortality, ventilation, ICU admission).

Results LUS demonstrated higher sensitivity than CXR (96.0% (95%CI 90.0%-99.0%) vs. 82.8% (95%CI 73.9%-89.7%)). LUS specificity was 64.9% (95%CI 47.5%-80.0%), compared to 54.1% (95%CI 36.9%-70.5%) for CXR. The moderate specificity for LUS was due to sonographic-similar conditions, notably TB in 5.1% of patients. Consolidation size and numbers showed marginal resolution, while LUSS showed more pronounced decreases over time. The baseline LUSS poorly predicted mortality (AUC 0.65, 95%CI 0.55-0.75), while follow-up LUSS and changes in LUSS (ΔLUSS) were more predictive (AUC 0.81 (95%CI 0.71-0.89) and 0.89 (95%CI 0.80-0.95), respectively). Mortality odds increased by 70% per ΔLUSS point increase (p=0.002). An improved LUSS effectively ruled out mortality (negative predictive value 97.4%).

Conclusion Although LUS is highly sensitive for diagnosing CAP, its specificity in TB-endemic regions warrants further caution. Serial LUS assessments, particularly monitoring LUSS

changes, are valuable for tracking disease progression and prognostication, with increasing LUSS indicating potential clinical deterioration.

Keywords: diagnosis, Lung ultrasound, LUS score, monitoring, mortality, pneumonia, Tuberculosis

Article Summary

Strengths and limitations of this study

- It is among the first studies to incorporate the Lung Ultrasound Score for monitoring community-acquired pneumonia.
- Blinding between the sonographer and treating physician ensured that ultrasound findings did not influence clinical decisions, improving the objectivity of diagnostic and monitoring results.
- Only 75 patients had complete follow-up lung ultrasound data, limiting the robustness of the study's monitoring conclusions.
- The applicability of the results to outpatients is uncertain, as the study focused on inpatients whose pneumonic lesions may differ in size and resolution time.

Introduction

Community-acquired pneumonia (CAP) is the leading global infectious disease, presenting significant challenges to public health due to its high hospitalization and mortality rates [1-3]. Effective diagnosis and monitoring are crucial to improve patient outcomes and reduce the healthcare burden. Despite being frequently encountered in both outpatient and inpatient settings, pneumonia diagnosis remains complex. CAP is rarely confirmed through the gold standard of pathology. Instead, the diagnosis relies on concordant evidence of clinical symptoms, microbiological detection, and compatible imaging findings, typically new infiltrates on chest radiographs (CXR) [4]. Despite being a staple for diagnosing CAP for years, CXR may fail to detect or correctly identify pneumonic lesions [5-7].

In recent years, alternative diagnostic tools such as lung ultrasound (LUS) have emerged [8]. Besides the advantages of being radiation-free, bedside-available, and repeatable, studies have shown that LUS offers substantial diagnostic accuracy [9]. Multiple meta-analyses revealed that the LUS sensitivity for diagnosing CAP ranges from 85%-97%, with specificity between 80%-96% [10-18]. However, most of the evidence on LUS diagnostic accuracy for pneumonia was derived from developed countries. There is less emphasis on low-resource settings, where diseases such as tuberculosis (TB) and bronchiectasis can mimic pneumonia sonographically, potentially affecting diagnostic properties [17]. Furthermore, the potential of LUS in monitoring and stratifying CAP patients at risk of clinical deterioration is not well-understood. In this study, we aim to investigate the diagnostic performance of LUS in a developing country. Additionally, we seek to identify which LUS parameters can effectively monitor and prognosticate CAP.

Methods

Study design and setting

This prospective observational study was conducted at the Pulmonary Department of Cho Ray Hospital, the largest tertiary hospital in southern Vietnam, from December 2022 to June 2023. Patients provided written informed consent before enrollment. The Institutional Review Board approved the study (No.875/HĐĐĐ-DHYD).

Patient and public involvement

There were no patients or public involved in the study protocol.

Participants

Patients aged 18 years or older clinically suspected of having CAP according to the American Thoracic Society criteria [19] were eligible. This included patient presenting with fever, dyspnea, cough, sputum production, and pleuritic chest pain. Patients were excluded if hospitalized for ≥48 hours before enrollment, pregnant or lactating, or tested positive for SARS-CoV-2 via rapid antigen or RT-PCR assays.

Data collection

Upon admission to the Pulmonary Department, we collected data on anthropometry, clinical symptoms, medical history, and laboratory findings. We also retrieved clinical data regarding complications, including in-hospital mortality, the need for invasive mechanical ventilation, admission to the respiratory intensive care unit (RICU), and discharge status.

Within 24 hours of hospitalization, an initial LUS was performed by one of two experienced pulmonologists certified in sonography, both of whom were blinded to the patient's medical record data. During this period, patients also underwent CXR. A follow-up LUS was performed between day 5 and 8 by the same pulmonologist.

Lung ultrasound procedure

LUS examinations were conducted using a 2-5 MHz curved array transducer of the DP-10 (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). Patients were examined sitting when possible; otherwise, anterior regions were assessed supine and posterior regions recumbent. The procedure assessed 12 lung zones (**Figure 1**) for pleural irregularities, size and number of consolidations, the presence of air bronchograms, number and characteristics of B-lines, and pleural effusion. Consolidation size was measured in one

dimension, from the pleural line to the furthest margin. Additionally, the LUS score (LUSS), a semi-quantitative tool for lung aeration ranging from 0 to 3, was assigned to each lung zone [20, 21]. Detailed descriptions are presented in **Figure 2**, and the global LUSS was calculated as the sum of regional scores (range 0 to 36).

The finding of lung consolidation or focal interstitial syndrome (one or multiple zones involved unilaterally) was consistent with a pneumonia diagnosis [22]. In cases where bilateral interstitial syndrome was identified, additional ultrasound features such as irregular and thickened pleura, diminished lung sliding, the nonhomogeneous distribution of B-lines and subpleural consolidations were required to differentiate pneumonia from cardiogenic pulmonary edema [23, 24].

To assess inter-observer reliability, we recorded ultrasound procedures, randomly selected 30 recordings, and sent them to an expert with registered ultrasound certification to review. We then compared the interpretations of the ultrasound videos between the sonographers and the expert.

Chest radiography procedure

Every patient received a posteroanterior CXR (DRX-Ascend System, Carestream, New York, USA) within 24 hours of admission. A board-certified radiologist, blinded to the patient's clinical and LUS findings, independently reviewed these radiographs.

Diagnosis of community-acquired pneumonia

Upon discharge, the final diagnosis was confirmed by a panel of two independent pulmonologists who reviewed the patient's clinical and laboratory findings, radiology, microbiological results, and overall clinical course. The assessors were blinded to the LUS data. In case of disagreement, a third expert was consulted, with consensus from at least two experts required for the conclusion.

For patients undergoing CT scans, the result served as a secondary reference for assessing LUS diagnostic values. Scans were obtained using 128-slice Optima CT 660 (GE Healthcare, Chicago, IL, USA) and interpreted independently by a board-certified radiologist blinded to prior clinical and imaging data.

Study endpoints

The primary end-point was the diagnostic accuracy of LUS and CXR as index tests compared with the reference standards (discharge diagnosis and CT scan results). Additional end-points included changes in three LUS parameters (consolidation size, number of consolidations, and LUSS) and treatment outcomes, including in-hospital mortality, initiation of mechanical ventilation, and RICU admission.

Statistical analysis

A total sample size of 70 and 84 patients was needed to estimate a sensitivity of 85% and specificity of 93% (according to Alzahrani's meta-analysis [17]), with a precision of 10% assuming the prevalence of CAP was 70%. Normality was assessed using histograms and the Shapiro-Wilk test. Non-normal variables were described by medians and interquartile ranges, while normal variables were described by means and standard deviations. Group differences were analyzed with t-tests for normal data and Mann-Whitney U tests for non-normal data. The Wilcoxon Signed-Rank Test assessed LUS parameters over time, while the Chi-Square or Fisher's Exact Test evaluated categorical variable differences.

For diagnostic properties, sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios of LUS and CXR were calculated. McNemar's test was employed to assess statistical differences in sensitivity and specificity between LUS and CXR. The optimal LUSS cutoff was established using the Youden index. Logistic regression was used to identify associations between in-hospital outcomes and ultrasound parameters. A p-value <0.05 indicated statistical significance. Data were processed using STATA/MP 17.0 software (StataCorp, College Station, TX, USA).

Results

Characteristics of patients suspected of CAP

Between December 2022 and June 2023, 158 patients were enrolled (**Figure 3**). Exclusions for hospitalization ≥48 hours prior to admission, self-discharge, and hospital transfers left 136 patients for final analysis. The mean age was 62 ± 17 years and 72.8% were male. Demographic and clinical characteristics are presented in **Table 1**. Hospital mortality was 13.2%.

CAP was confirmed in 99 patients (72.8%) at discharge. CT scans were conducted in 93 patients, with the median time from admission to scan of 2 [IQR 1-4] days. CAP was confirmed through CT in 72/93 cases (77.4%).

Diagnostic value of LUS and CXR

LUS showed a sensitivity of 96.0% (95%CI 90.0%-99.0%) and specificity of 64.9% (95%CI 47.5%-80.0%), while CXR had a sensitivity of 82.8% (82.8%, 95%CI 73.9%-89.7%) and specificity of 54.1% (95%CI 36.9%-70.5%).

CXR sensitivity was significantly lower than LUS (p=0.002), but specificities did not differ significantly (p=0.103, McNemar's test; **Table 2 and Suppplement Table 3**). Using CT as a secondary reference standard, LUS performance was quite similar to that measured against discharge diagnosis as a reference standard, achieving a sensitivity of 95.8% and a specificity of 52.4%.

LUS missed lesions not reaching the pleura in two cases, subsequently confirmed by CT scans. In two other false negative cases without CT scans, CAP was confirmed by experts based on clinical signs, elevated inflammatory markers, CXR-detected lesions, and positive responses to antibiotics.

On the other hand, LUS incorrectly identified CAP in 13 patients due to tuberculosis (n=6), lung cancer (n=2), heart failure (n=2), bronchiectasis (n=1), COPD with fibrosis (n=1), and interstitial lung disease (n=1).

Sonographic characteristics of CAP at baseline and monitoring

The time to perform the LUS was under 10 minutes (median 9 minutes 38 seconds). The inter-rater variability was low, with Cohen’s kappa value of 0.89 (p<0.001) for pneumonia diagnosis and 0.85 (p<0.001) for LUSS assessment.

Sonographic characteristics of cases where LUS detected and confirmed CAP upon discharge are detailed in **Supplement Table 1**. In six cases with bilateral interstitial patterns, findings such as irregular and thickened pleura, reduced lung sliding, and subpleural consolidations helped distinguish pneumonia from cardiogenic pulmonary edema. Echocardiography performed in these six cases also confirmed the findings.

Follow-up LUS was performed on 98 out of 136 patients (72.1%), including 75 pneumonia cases and 23 non-pneumonia cases. Among the pneumonia cases, only a slight reduction in the size and number of consolidations was noted after 5-8 days. LUSS showed a more significant reduction (**Table 3**).

The prognostic value of LUS

The association of LUS parameters with patient-centered outcomes is detailed in **Table 4**. Consolidation size or count were not associated with mortality risk. The global LUSS was associated with mortality (unadjusted OR = 1.09, 95% CI 1.01–1.16, p = 0.021). The baseline LUSS had an AUC of 0.65 (95% CI 0.55-0.75) for predicting mortality, with an optimal cut-point of 17 (52.9% sensitivity, 73.1% specificity). At the second evaluation, the LUSS predictive accuracy improved, with an AUC of 0.81 (95% CI 0.71–0.89) and an optimal cut-point of 21 (66.7% sensitivity, 87.9% specificity) and the unadjusted OR was 1.19 (95% CI 1.06–1.34, p=0.004).

All mortality cases had worsening LUSS. Changes in Lung Ultrasound Score (ΔLUSS) over time were also analyzed. For each LUS point increase in the follow-up compared to the initial, the odds of in-hospital death increased by 70% (OR 1.70, 95%CI 1.22–2.38, p=0.002). ΔLUSS had a predictive AUC of 0.89 (95% CI 0.80–0.95) for in-hospital mortality. Patients with no improvement in monitoring LUS (ΔLUSS ≥0) demonstrated a sensitivity of 88.9%, specificity of 57.6%, NPV of 97.4%, and PPV of 22.2% in predicting mortality (**Table 5**).

For other outcomes, including ventilation and RICU admission, sonographic parameters had a similar prognostic value. Univariate analysis showed no link between outcomes and the size or number of lung consolidations, except for the LUSS, with predictive value improving in the second assessment and for ΔLUSS.

Discussion

This study confirmed that LUS has a higher sensitivity than CXR for diagnosing CAP, although it yielded moderate specificity due to its inability to differentiate between pneumonia and tuberculosis lesions. To the best of our knowledge, this is one of the first study to incorporate LUSS for monitoring CAP. The changes in LUSS during monitoring provided valuable prognostic insights, helping to identify disease progression and stratify patients with lower mortality risk.

Previous studies have shown that LUS has a high sensitivity for detecting pneumonia [14-17]. Our study aligns with these findings, demonstrating greater sensitivity than CXR. These results reaffirm LUS as a reliable tool for ruling out pneumonia. However, if LUS is negative but other pneumonia signs persist, further investigation and close monitoring after antibiotic treatment are necessary for a definitive diagnosis. Despite showing great sensitivity, LUS specificity falls below those in previous reports [14-17]. The low specificity may be explained by the presence of respiratory disorders with LUS appearances resembling pneumonia, notably TB. On ultrasound, TB patients were also presented with consolidation with or without surrounding B-lines. In our study, we classified pulmonary tuberculosis as false positive rather than a type of CAP. This decision was based on the rationale that the diagnosis determines subsequent antibiotic strategies, which differ between the two conditions. Among 136 patients, *Mycobacterium tuberculosis* was detected in respiratory specimens of 7 individuals (6 as false positives and 1 as true positive, as the patient had *Pseudomonas aeruginosa* detected in sputum culture, making it CAP with *M. tuberculosis* co-infection). To our understanding, our study has identified the highest number of TB cases to date, compared to other diagnostic LUS studies in CAP. Previous research primarily focused on countries where tuberculosis is less commonly reported. Two studies in TB-endemic regions, Liu [25] in China and Amatya [26] in Nepal, found zero and one TB case, respectively. In addition to the already high incidence of TB due to the geographic factor, the timing of the study, following the COVID-19 pandemic, likely contributed to an increase in TB isolates. The pandemic has notably disrupted global TB control efforts, with newly detected cases dropping from 7.1 million in 2019 to 5.8 million in 2020 [27]. Our study may coincide with a period of tuberculosis resurgence as a consequence of diminished surveillance during the pandemic.

Besides evaluating the diagnostic properties, our study aimed to observe sonographic changes in CAP over time and assess if these changes could aid in monitoring and predicting clinical outcomes. We focused on three ultrasound parameters: consolidation size, number of consolidations, and LUSS. Previous studies in both pediatric [28-30] and adult populations [31] have examined lesion sizes and numbers, suggesting that disease remission could be observed through the resolution of these parameters. However, our findings indicate that changes in the size and overall number of consolidations during follow-up assessments were relatively small. These marginal changes may not be readily apparent to clinicians, making it less ideal to utilize these parameters for monitoring purposes. The difference in pneumonic lesion resolution between our study and that reported in the adult population by Reissig [31] may stem from variations in measurement methods and sample selection. We used a one-dimensional measure for the largest consolidation, whereas Reissig et al. employed a two-dimensional measure in cm^2. Additionally, for comparisons of lesion size at two time points, our initial assessment only included subjects available for a follow-up ultrasound, in contrast to Reissig's approach, which involved measuring pneumonic size in all patients, regardless of follow-up availability [31].

The LUSS has recently emerged as a useful tool for assessing severity and the baseline score is closely related to adverse outcomes in COVID-19 patients [32]. Our analysis showed that the baseline score has limited predictive value for CAP outcomes. Instead, the dynamic changes in the LUSS during follow-up provided a more accurate prognosis for adverse events. Since the LUSS incorporates both consolidation and interstitial components and given that changes in consolidation measurements were small, this suggests that changes in the interstitial pattern occur earlier and are more predictive of the clinical course of CAP than consolidative changes. From the clinical practice perspective, LUSS progression should alert physicians about a deteriorating clinical course. A ΔLUSS cut-off of 0 is clinically applicable as it allows for the simple categorization of patients into groups with improved or unimproved LUSS over time. An unimproved LUSS at follow-up (ΔLUSS ≥0) demonstrated high sensitivity and high NPV for mortality. This allows clinicians to be less likely to miss patients at risk and confidently rule out the potential for future deterioration if the LUSS shows improvement. Utilizing LUSS for stratification may lead to a more efficient allocation of medical resources, ensuring that attention and care are prioritized for patients with a higher risk of mortality.

This study has several limitations. First, due to ethical reasons, CT scan was not performed on all patients, leaving the possibility of missing or misidentifying pneumonic lesions. However, in those who did receive a CT scan, the performance of LUS was found to be similar when compared to both discharge diagnosis and CT imaging, indicating the former's reliability. Second, the study was designed for the inpatient setting. It is less certain whether the results can be applicable to outpatients, whose lesions are presumably smaller and may resolve more quickly. Third, the consolidation size was recorded in a single dimension, which does not fully capture the lesion's three-dimensional volume. However, measurements in one dimension have been shown to effectively represent overall lesion volume [29]. Finally, ultrasound is an operator-dependent tool, and its interpretation is subjective to sonographer's experience. Nevertheless, our study demonstrated high reliability between performers.

Conclusion

LUS serves as a non-invasive, rapid, and bedside-accessible modality with high sensitivity for detecting CAP. However, the sonographic similarities between pneumonia and other respiratory conditions, such as TB, particularly in regions where TB is endemic, require careful interpretation during evaluations. Monitoring with LUS revealed that consolidation size and total lesion resolved slowly. In contrast, changes in the LUSS were more notable. An increasing LUSS was strongly predictive of in-hospital mortality and adverse outcomes, making it a valuable tool for monitoring disease progression and stratifying patients at risk.

Abbreviation

AUC: Area Under the Curve

CAP: Community-Acquired Pneumonia

COPD: Chronic Obstructive Pulmonary Disease

CT: Computed Tomography

CXR: Chest X-Ray

ΔLUSS: Change in Lung Ultrasound Score

LUS: Lung Ultrasound

LUSS: Lung Ultrasound Score

NPV: Negative Predictive Value

OR: Odds Ratio

PPV: Positive Predictive Value

RICU: Respiratory Intensive Care Unit

RT-PCR: Reverse Transcription Polymerase Chain Reaction

TB: Tuberculosis

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Author contributions

QKTL, NVH, and VLT conceptualized the study and designed the data collection instruments with input from TTT, KND, NTN, PTHN, and LP. Lung ultrasound training and support were provided by LP. QKTL and TTT coordinated and supervised data collection at the study sites, with KND and NTN supervising their respective sites. Data acquisition and management were carried out by QKTL, NDM, LNH, and NTN. QKTL, TTT, and PTHN analyzed and interpreted the data. QKTL and TTT wrote the manuscript with critical input from LP and VLT. All authors collaboratively reviewed and approved the final manuscript.

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Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Consent obtained directly from patient(s). Ethics approval

Data statement

Please send any requests for access to the datasets to khanhtlq@ump.edu.vn

References

1. World Health Organization. Disease burden and mortality estimates, 2000 - 2016. https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html. Date last updated: December 9 2020. Date last accessed: January 25 2023.
2. Ferreira-Coimbra J, Sarda C, Rello J. Burden of Community-Acquired Pneumonia and Unmet Clinical Needs. Advances in therapy. 2020;37(4):1302-18.
3. Almirall J, Serra-Prat M, Bolíbar I, *et al.* Risk Factors for Community-Acquired Pneumonia in Adults: A Systematic Review of Observational Studies. Respiration; international review of thoracic diseases. 2017;94(3):299-311.
4. Waterer G. What is pneumonia? Breathe (Sheff). 2021;17(3):210087.
5. Claessens YE, Debray MP, Tubach F, *et al.* Early Chest Computed Tomography Scan to Assist Diagnosis and Guide Treatment Decision for Suspected Community-acquired Pneumonia. American journal of respiratory and critical care medicine. 2015;192(8):974-82.
6. Self WH, Courtney DM, McNaughton CD, *et al.* High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. The American journal of emergency medicine. 2013;31(2):401-5.
7. Upchurch CP, Grijalva CG, Wunderink RG, *et al.* Community-Acquired Pneumonia Visualized on CT Scans but Not Chest Radiographs: Pathogens, Severity, and Clinical Outcomes. Chest. 2018;153(3):601-10.
8. Jones BP, Tay ET, Elikashvili I, *et al.* Feasibility and Safety of Substituting Lung Ultrasonography for Chest Radiography When Diagnosing Pneumonia in Children: A Randomized Controlled Trial. Chest. 2016;150(1):131-8.
9. Mathis G. Pneumonia. In: Laursen CB RN, Volpicelli G, eds. Thoracic Ultrasound (ERS Monograph). Sheffield: European Respiratory Society; 2018. pp. 87–101.
10. Chavez MA, Shams N, Ellington LE, *et al.* Lung ultrasound for the diagnosis of pneumonia in adults: a systematic review and meta-analysis. Respiratory research. 2014;15(1):50.
11. Hu QJ, Shen YC, Jia LQ, *et al.* Diagnostic performance of lung ultrasound in the diagnosis of pneumonia: a bivariate meta-analysis. International journal of clinical and experimental medicine. 2014;7(1):115-21.
12. Ye X, Xiao H, Chen B, *et al.* Accuracy of Lung Ultrasonography versus Chest Radiography for the Diagnosis of Adult Community-Acquired Pneumonia: Review of the Literature and Meta-Analysis. PloS one. 2015;10(6):e0130066.
13. Berlet T. Thoracic ultrasound for the diagnosis of pneumonia in adults: a meta-analysis. Respiratory research. 2015;16(1):89.
14. Xia Y, Ying Y, Wang S, *et al.* Effectiveness of lung ultrasonography for diagnosis of pneumonia in adults: a systematic review and meta-analysis. Journal of thoracic disease. 2016;8(10):2822-31.
15. Llamas-Álvarez AM, Tenza-Lozano EM, Latour-Pérez J. Accuracy of Lung Ultrasonography in the Diagnosis of Pneumonia in Adults: Systematic Review and Meta-Analysis. Chest. 2017;151(2):374-82.
16. Long L, Zhao HT, Zhang ZY, *et al.* Lung ultrasound for the diagnosis of pneumonia in adults: A meta-analysis. Medicine. 2017;96(3):e5713.
17. Alzahrani SA, Al-Salamah MA, Al-Madani WH, *et al.* Systematic review and meta-analysis for the use of ultrasound versus radiology in diagnosing of pneumonia. Critical ultrasound journal. 2017;9(1):6.
18. Orso D, Guglielmo N, Copetti R. Lung ultrasound in diagnosing pneumonia in the emergency department: a systematic review and meta-analysis. European journal of emergency medicine : official journal of the European Society for Emergency Medicine. 2018;25(5):312-21.
19. Niederman MS, Mandell LA, Anzueto A, *et al.* Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. American journal of respiratory and critical care medicine. 2001;163(7):1730-54.

20. Bouhemad B, Brisson H, Le-Guen M*, et al.* Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. American journal of respiratory and critical care medicine. 2011;183(3):341-7.
21. Mongodi S, Bouhemad B, Orlando A*, et al.* Modified Lung Ultrasound Score for Assessing and Monitoring Pulmonary Aeration. Ultraschall in der Medizin (Stuttgart, Germany : 1980). 2017;38(5):530-7.
22. Volpicelli G, Elbarbary M, Blaivas M*, et al.* International evidence-based recommendations for point-of-care lung ultrasound. Intensive care medicine. 2012;38(4):577-91.
23. Copetti R, Soldati G, Copetti P. Chest sonography: a useful tool to differentiate acute cardiogenic pulmonary edema from acute respiratory distress syndrome. Cardiovascular ultrasound. 2008;6:16.
24. Soldati G, Demi M. The use of lung ultrasound images for the differential diagnosis of pulmonary and cardiac interstitial pathology. Journal of ultrasound. 2017;20(2):91-6.
25. Liu XL, Lian R, Tao YK*, et al.* Lung ultrasonography: an effective way to diagnose community-acquired pneumonia. Emergency medicine journal : EMJ. 2015;32(6):433-8.
26. Amatya Y, Rupp J, Russell FM*, et al.* Diagnostic use of lung ultrasound compared to chest radiograph for suspected pneumonia in a resource-limited setting. International journal of emergency medicine. 2018;11(1):8.
27. Bagcchi S. WHO's Global Tuberculosis Report 2022. The Lancet Microbe. 2023;4(1):e20.
28. Omran A, Eesai S, Ibrahim M*, et al.* Lung ultrasound in diagnosis and follow up of community acquired pneumonia in infants younger than 1-year old. The clinical respiratory journal. 2018;12(7):2204-11.
29. Urbankowska E, Krenke K, Drobczyński Ł*, et al.* Lung ultrasound in the diagnosis and monitoring of community acquired pneumonia in children. Respiratory medicine. 2015;109(9):1207-12.
30. Berce V, Tomazin M, Gorenjak M*, et al.* The Usefulness of Lung Ultrasound for the Aetiological Diagnosis of Community-Acquired Pneumonia in Children. Scientific reports. 2019;9(1):17957.
31. Reissig A, Copetti R, Mathis G*, et al.* Lung ultrasound in the diagnosis and follow-up of community-acquired pneumonia: a prospective, multicenter, diagnostic accuracy study. Chest. 2012;142(4):965-72.
32. Song G, Qiao W, Wang X*, et al.* Association of Lung Ultrasound Score with Mortality and Severity of COVID-19: A Meta-Analysis and Trial Sequential Analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2021;108:603-9.

Table 1. Demographic and clinical characteristics of patients with and without pneumonia

	Overall (n=136)	Patients with pneumonia (n=99)	Patients without pneumonia (n=37)	p
Age, years (M ± SD)	62.35 ± 17.03	61.30 ± 17.83	65.14 ± 14.52	0.244
Male sex (n, %)	99 (72.8%)	73 (73.7%)	26 (70.3%)	0.686
Symptoms (n, %)				
Fever	68 (50.0)	59 (59.6)	9 (24.3)	**<0.001**
Dyspnea	108 (79.4)	79 (79.8)	29 (78.4)	0.855
Cough	107 (78.7)	78 (78.8)	29 (78.4)	0.959
Purulent expectoration	57 (41.9)	44 (44.4)	13 (35.1)	0.328
Chest pain	45 (33.1)	30 (30.3)	15 (40.5)	0.259
Risk factors (n, %)				
Nicotine abuse	49 (36.0)	35 (35.4)	14 (37.8)	0.788
Alcohol abuse	8 (5.9)	7 (7.1)	1 (2.7)	0.447
Prolonged corticoid treatment	28 (20.6)	22 (22.2)	6 (16.2)	0.441
Comorbidities (n, %)				
Diabetes mellitus	33 (24.3)	26 (26.3)	7 (18.9)	0.374
Hypertension	59 (43.4)	42 (42.4)	17 (45.9)	0.712
Coronary artery disease	15 (11.0)	9 (9.1)	6 (16.2)	0.238
COPD	22 (16.2)	10 (10.1)	12 (32.4)	**0.002**
Asthma	9 (6.6)	3 (3.0)	6 (16.2)	**0.013**
History of tuberculosis	12 (8.8)	10 (10.1)	2 (5.4)	0.390
Clinical signs upon admission (n, %)				
Temperature > 37.5°C	22 (16.2)	17 (17.2)	5 (13.5)	0.606
Hypoxemia	94 (69.1)	73 (73.7)	21 (56.8)	0.056
MAP < 65 mmHg	7 (5.2)	6 (6.1)	1 (2.7)	0.675
Pulse > 100 l/min	57 (41.9)	46 (46.5)	11 (29.7)	0.078
Laboratory findings				
White blood cell (G/L) (Median [IQR])	11.37 [8.37 – 16.14]	11.60 [9.10 – 17. 27]	9.60 [7.49 – 14.19]	0.073
Neutrophil (G/L) (Median [IQR])	9.50 [6.05 – 14.17]	10.03 [6.90 – 15.78]	6.91 [5.25 – 11.87]	**0.021**
Lymphocyte (G/L) (Median – [IQR])	0.93 [0.62 – 1.51]	0.91 [0.58 – 1.45]	1.26 [0.73 – 2.05]	0.114
Neutrophil/Lymphocyte Ratio (Median [IQR])	8.90 [4.38 –19.08]	9.05 [5.14– 20.64]	7.53 [2.14 –13.49]	**0.021**
Hemoglobin (g/L) (M ± SD)	120.76 ± 22.59	118.03 ± 22.62	127.87 ± 20.86	**0.023**
Platelet (G/L) (Median [IQR])	247.0 [188.0– 313.0]	251.5 [179.3 – 316.0]	241.0 [209.0–293.0]	0.636
CRP (mg/L) (n=104) (Median [IQR])	95.60 [40.38 – 131.75]	107.20 [59.95 – 137.00]	58.90 [8.60 – 120.90]	**0.021**
Creatinine (mg/dl) (Median [IQR])	0.84 [0.66 – 1.09]	0.83 [0.65 – 1.09]	0.85 [0.70 – 1.10]	0.441
BUN (mg/dl) (Median [IQR])	17.00 [12.00 – 22.75]	17.00 [13.00 – 23.00]	16.00 [10.00 – 22.00]	0.415
AST (U/L) (n =132) (Median [IQR])	37.00 [26.00 – 54.75]	38.0 [26.50 – 56.50]	30.00 [23.00 – 51.00]	0.125

ALT (U/L) (n =132) (Median [IQR])	34.0 [22.0 – 60.0]	28.0 [21.0 – 62.0]	35.0 [22.6 – 60.0]	0.504
In-hospital Outcomes (n,%)				
Ventilation	19 (14.0)	16 (16.2)	3 (8.1)	0.278
Shock	19 (14.0)	18 (18.2)	1 (2.7)	**0.024**
RICU	25 (18.4)	22 (22.2)	3 (8.1)	0.081
In-hospital mortality	18 (13.2)	17 (17.2)	1 (2.7)	**0.025**
Length of stay (days) (Median [IQR]	8.0 [6.0 -10.0]	8.0 [6.0 – 11.0]	6.0 [4.0 – 8.0]	**<0.001**

Table 2. Diagnostic performance of lung ultrasound and chest X-ray with reference to discharge diagnosis and CT scan

Reference test	Discharge diagnosis		CT scan	
	Lung ultrasound	Chest X-ray	Lung ultrasound	Chest X-ray
Sensitivity (%)	96.0 (90.0 – 99.0)	82.8 (73.9 – 89.7)	95.8 (88.3 – 99.1)	77.8 (66.4 – 86.7)
Specificity (%)	64.9 (47.5 – 80.0)	54.1 (36.9 – 70.5)	52.4 (29.8 – 74.3)	42.9 (21.8 – 66.0)
Positive predictive value (%)	88.0 (82.5 – 91.9)	82.8 (77.1 – 87.4)	87.3 (78.0 – 93.8)	82.4 (71.2 – 90.5)
Negative predictive value (%)	85.7 (69.1 – 94.2)	54.1 (41.0 – 66.5)	78.6 (49.2 – 95.3)	36.0 (18.0 – 57.5)
Likelihood ratio (+)	2.73 (1.76 – 5.24)	1.80 (1.26 – 2.59)	2.01 (1.28 – 3.16)	1.36 (0.92 – 2.01)
Likelihood ratio (-)	0.06 (0.02 – 0.17)	0.32 (0.19 – 0.54)	0.08 (0.02 – 0.26)	0.52 (0.27 – 1.00)
Accuracy (%)	87.5 (80.7 – 92.6)	75.0 (66.7 – 82.0)	86.0 (77.3 – 92.3)	69.9 (59.5 – 79.0)
AUC	0.80 (0.72 – 0.88)	0.68 (0.56 – 0.79)	0.74 (0.63 – 0.85)	0.60 (0.48 – 0.72)

Table 3. Comparison of ultrasound findings between initial (LUS 1) and follow-up (LUS 2) assessments

	LUS 1	LUS 2	p
Largest consolidation size (cm) (n=66)	3.68 [2.50 – 6.86]	3.13 [1.64 – 6.27]	0.009
Number of consolidations (n=66)	2 [1 – 3]	2 [1 – 2]	0.017
LUS score (n=75)	13 [9 – 17]	11 [6 – 18]	0.002

Table 4. Association of lung ultrasound parameters with in-hospital outcomes in patients with community-acquired pneumonia

	Mortality				Ventilation				RICU admission			
	Yes	No	OR (95% CI)	p	Yes	No	OR (95% CI)	p	Yes	No	OR (95% CI)	p
Largest consolidation size (cm) (n=84)	6.24 [3.46 – 7.69]	3.36 [1.72 – 6.86]	1.10 (0.96 – 1.29)	0.174	5.77 [2.62 – 6.78]	3.57 [2.07 – 6.98]	1.01 (0.85 – 1.18)	0.950	4.57 [2.37– 6.78]	3.36 [1.78 – 6.98]	1.05 (0.91 – 1.20)	0.539
Number of consolidations (n=84)	2 [1 – 4]	2 [1 – 3]	1.38 (0.99 – 1.94)	0.055	2 [1 – 4]	2 [1 – 3]	1.38 (0.99 – 19.93)	0.059	2 [1 – 3]	2 [1 – 3]	1.34 (0.97 – 1.85)	0.078
LUS 1 (n=95)	17 [10 – 23]	12 [6 – 17]	1.09 (1.01 – 1.16)	0.021	13 [9 – 25]	12 [7 – 17]	1.08 (1.01 – 1.16)	0.034	13.5 [10 – 23]	12 [6 – 17]	1.07 (1.01–1.14)	0.034
LUS 2 (n=75)	22 [12 – 24]	10 [5 – 16]	1.19 (1.06 – 1.34)	0.004	21 [12 – 23]	10 [5 – 16]	1.16 (1.04 – 1.29)	0.008	16 [11 – 23]	10 [6 – 16]	1.09 (1.01 – 1.19)	0.026
Δ LUS (LUS2-LUS1) (n=75)	4 [1 – 6]	-1 [-4 – 0]	1.70 (1.22 – 2.38)	0.002	3 [0 – 6]	-1 [-3 – 0]	1.38 (1.10 – 1.72)	0.005	-1 [-3 – 0]	-1.5 [-1 – 5]	1.10 (1.07 – 1.53)	0.007

Table 5. Cutoff points of ΔLUS in predicting in-hospital mortality

Δ LUS cutoff	Sensitivity (%)	Specificity (%)	LR (+)	LR (-)	PPV	NPV
≥ -1	100.0 (63.1 – 100)	45.5 (34.0 – 58.9)	1.83 (1.49 – 2.32)	-	18.2 (8.19 – 32.7)	100 (88.9 – 100)
≥ 0	88.9 (51.8 – 99.7)	57.6 (44.8 - 69.7)	2.10 (1.46 - 3.01)	0.19 (0.03 - 1.24)	22.2 (10.1 – 39.2)	97.4 (86.5 – 99.9)
≥ 1	77.8 (40.0 - 97.2)	86.4 (75.7 – 93.6)	5.70 (2.83 - 11.5)	0.26 (0.08 - 0.88)	43.8 (19.8 - 70.1)	96.6 (88.3 - 99.6)

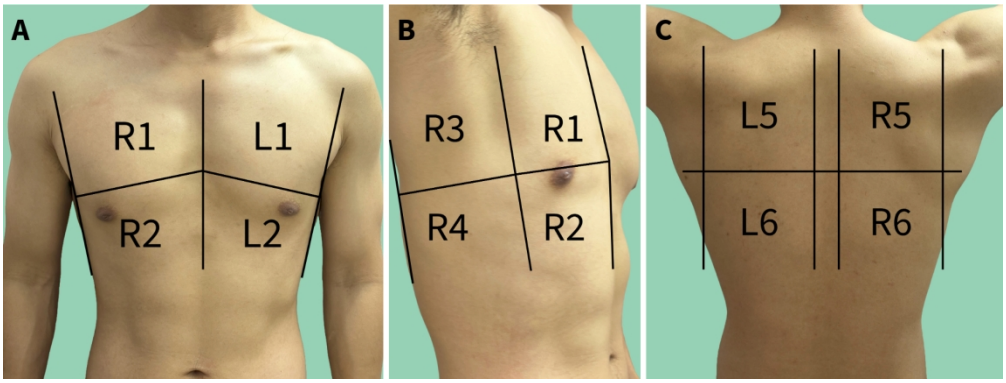
AUC = 0.89 (95% CI 0.80 - 0.95)

Figure legends

Figure 1. Division of 12 lung zones, with six zones allocated to each hemithorax. The zones are divided as follows: each hemithorax is segmented into anterior, lateral, and posterior chest areas, demarcated by the anterior and posterior axillary lines. Each area on either side is further divided into an upper and a lower half: A) Anterior Chest Area: The right hemithorax is divided into an upper zone (R1) and a lower zone (R2); the left hemithorax is divided into an upper zone (L1) and a lower zone (L2). B) Lateral Chest Area (Right Side): Features an upper lateral zone (R3) and a lower lateral zone (R4). The left lateral view is not shown. C) Posterior Chest Area: Illustrates the right upper (R5) and lower (R6) zones, and the left upper (L5) and lower (L6) zones.

Figure 2. **Lung Ultrasound Scores (LUSS) for assessing lung aeration, ranging from 0 to 3**. A) demonstrates LUSS 0, characterized by the presence of A-lines, indicative of normal lung aeration. B) LUSS 1, where there are more than three B-lines per intercostal space, accompanied by irregular or thickened pleura. C) LUSS 2, displaying confluent B-lines, with or without sub-pleural consolidations. D) LUSS 3, featuring large consolidations with a height greater than 1 cm.

Figure 3. Flowchart of patient enrollment and outcomes in the study



Division of 12 lung zones, with six zones allocated to each hemithorax. The zones are divided as follows: each hemithorax is segmented into anterior, lateral, and posterior chest areas, demarcated by the anterior and posterior axillary lines. Each area on either side is further divided into an upper and a lower half: A) Anterior Chest Area: The right hemithorax is divided into an upper zone (R1) and a lower zone (R2); the left hemithorax is divided into an upper zone (L1) and a lower zone (L2). B) Lateral Chest Area (Right Side): Features an upper lateral zone (R3) and a lower lateral zone (R4). The left lateral view is not shown. C) Posterior Chest Area: Illustrates the right upper (R5) and lower (R6) zones, and the left upper (L5) and lower (L6) zones.

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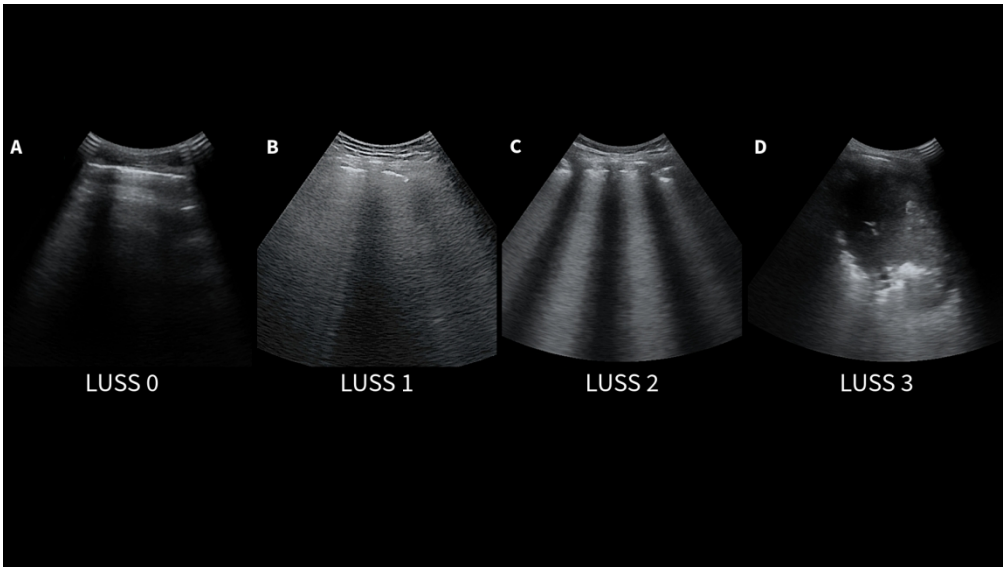
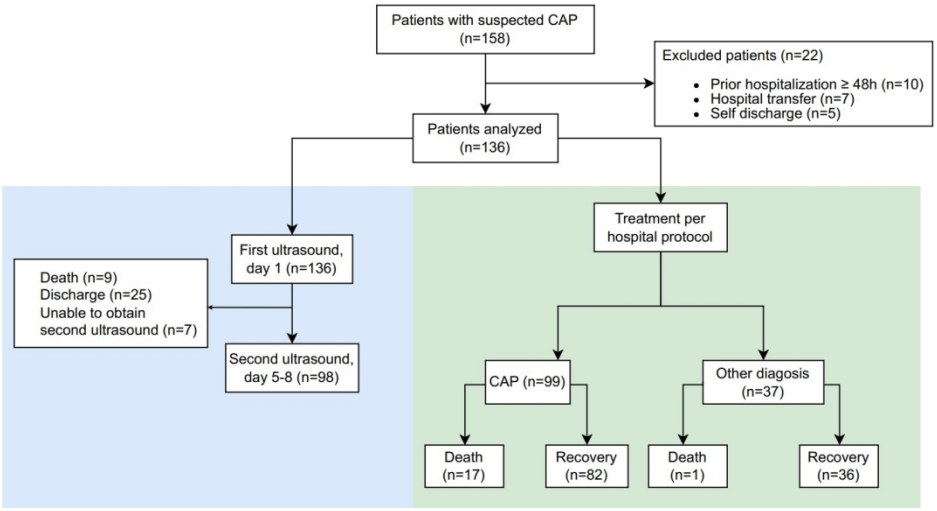


Lung Ultrasound Scores (LUSS) for assessing lung aeration, ranging from 0 to 3. A) demonstrates LUSS 0, characterized by the presence of A-lines, indicative of normal lung aeration. B) LUSS 1, where there are more than three B-lines per intercostal space, accompanied by irregular or thickened pleura. C) LUSS 2, displaying confluent B-lines, with or without sub-pleural consolidations. D) LUSS 3, featuring large consolidations with a height greater than 1 cm.

677x381mm (72 x 72 DPI)



Flowchart of patient enrollment and outcomes in the study

280x145mm (144 x 144 DPI)

Supplement Table 1. Ultrasound findings in confirmed CAP case with positive LUS (n=95)

	n (%)
Consolidation + / – interstitial syndrome	84 (88.4)
On left side only	11 (13.1)
On right side only	21 (25.0)
On both side	52 (61.9)
Number of consolidations	2 [1 – 3]
Largest consolidation size (cm)	3.67 [2.14 – 6.92]
Air bronchogram	56 (66.7)
Dynamic air bronchogram	46 (54.8)
Static air bronchogram	10 (11.9)
Interstitial syndrome	11 (11.6)
Focal	5 (45.4)
Bilateral	6 (54.6)
Pleural effusion	48 (50.5)
On left side only	9 (9.5)
On right side only	18 (18.9)
On both side	21 (22.1)
LUS score	12 [8-18]

Supplement Table 2. Ultrasound findings from the first and second examinations

	First ultrasound				Second ultrasound			
	Overall (n=136)	Pneumonia (n=99)	No pneumonia (n=37)	p	Overall (n=98)	Pneumonia (n=78)	No pneumonia (n=20)	p
Consolidation + / – interstitial syndrome	95 (69.9)	84 (84.8)	12 (32.4)	**<0.001**	69 (70.4)	61 (78.2)	8(40.0)	**0.001**
On left side only	11 (8.1)	11 (13.1)	0 (0.0)	0.349	14 (14.3)	13 (16.7)	1 (5.0)	0.288
On right side only	23 (16.9)	21 (25.0)	2 (16.7)	0.725	19 (19.4)	16 (20.5)	3 (15.0)	0.756
On both side	61 (44.9)	52 (61.9)	10 (83.3)	0.203	36 (36.7)	32 (41.0)	4 (20.0)	0.118
Number of consolidations	2 [1 – 3]	2 [1 – 3]	2 [1 – 4]	0.421	2 [1 – 2]	2 [1 – 2]	1 [1 – 3.5]	0.589
Largest consolidation size (cm)	3.73 [2.21 – 7.52]	3.67 [2.10 – 6.95]	5.87 [2.28 – 9.54]	0.283	3.46 [1.92 – 7.35]	3.76 [1.83 – 7.37]	2.98 [2.08 – 8.04]	0.918
Air bronchogram	64 (67.7)	56 (66.7)	8 (66.7)	1.000	55 (79.7)	48 (78.7)	7 (87.5)	1.000
Dynamic air bronchogram	50 (52.6)	46 (54.8)	4 (33.3)	0.221	36	35 (77.4)	1 (12.5)	**0.024**
Static air bronchogram	14 (14.7)	10 (11.9)	4 (33.3)	0.071	19	13 (21.3)	6 (75.0)	**0.004**
Interstitial syndrome	21 (15.4)	12 (12.1)	9 (24.3)	0.080	15 (15.3)	12 (15.4)	3 (15.0)	1.000
Focal	10 (7.4)	5 (5.1)	5 (13.5)	0.092	8 (8.2)	7 (9.0)	1 (5.0)	1.000
Bilateral	11 (8.8)	7 (7.1)	4 (10.8)	0.477	7 (7.1)	5 (6.4)	2 (10.0)	0.629
Pleural effusion	57 (41.9)	50 (50.5)	7 (18.9)	**0.001**	43 (43.9)	39 (50.0)	4 (20.0)	**0.022**

On left side only	11 (8.1)	10 (10.1)	1 (2.7)	0.288	9 (9.2)	8 (13.3)	1 (5.0)	0.681
On right side only	20 (14.7)	18 (18.2)	2 (5.4)	0.100	16 (16.3)	15 (25.2)	1 (5.0)	0.180
On both side	26 (19.1)	22 (22.2)	4 (10.8)	0.150	18 (18.4)	16 (26.5)	2 (10.0)	0.516
Pleural effusion volume (ml)	378.0 [171.0 – 564.0]	356.0 [167.0 – 493.0]	654.0 [474.0 – 766.0]	**0.011**	440.0 [240.0 – 678.0]	410.0 [240.0 – 650.0]	643.0 [560.0 – 714.0]	0.109
LUS score	13 [7.0 – 18.0]	12 [8 – 18]	15 [4 – 22]	0.935	9 [3 – 17]	11 [5 – 17]	4 [0 – 10]	**0.003**

Supplement table 3. Results of lung ultrasound and chest X-ray compare to confirm CAP cases at discharge

	Pneumonia (n= 99)	No pneumonia (n=37)
Lung ultrasound		
Positive	95	13
Negative	4	24
Chest X-ray		
Positive	82	17
Negative	17	20

Supplement table 4. Results of lung ultrasound and chest X-ray compare to CT scan

	CT positive (n= 72)	CT negative (n = 21)
Lung ultrasound		
Positive	69	10
Negative	3	11
Chest X-ray		
Positive	56	12
Negative	16	9

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LUNG ULTRASOUND FOR THE DIAGNOSIS AND MONITORING OF PNEUMONIA IN A TUBERCULOSIS-ENDEMIC SETTING: A PROSPECTIVE STUDY

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Word count: 3396 words

Abstract

Lung ultrasound (LUS) has proven high diagnostic accuracy for community-acquired pneumonia (CAP) in developed countries. However, its diagnostic performance in resource-limited settings with high pulmonary tuberculosis (TB) incidence is less established. Additionally, the role of LUS in monitoring CAP progression remains underexplored.

Objectives To validate the diagnostic performance, monitoring, and prognostic utility of lung ultrasound for CAP in a high pulmonary tuberculosis incidence setting.

Design Prospective single-center cohort study

Setting Pulmonary department of a tertiary hospital in Vietnam.

Participants A total of 158 patients suspected of having CAP were enrolled, with 136 (mean age 62 years, 72.8% male) included in the final analysis.

Interventions Patients underwent LUS and chest X-ray (CXR) within 24 hours of admission, with a follow-up LUS on day 5-8.

Primary and Secondary Outcome Measures.

The primary outcome was the diagnostic accuracy of LUS and CXR compared to discharge diagnosis. **Secondary outcomes** included the accuracy compared to CT scan results, changes in LUS parameters—consolidation size, number, and Lung Ultrasound Score (LUSS)—and their association with in-hospital mortality.

Results LUS demonstrated higher sensitivity than CXR (96.0% (95%CI 90.0%-99.0%) vs. 82.8% (95%CI 73.9%-89.7%)). LUS specificity was 64.9% (95%CI 47.5%-80.0%), compared to 54.1% (95%CI 36.9%-70.5%) for CXR. The moderate specificity for LUS was due to sonographic-similar conditions, notably TB in 5.1% of patients. Consolidation size and numbers showed marginal resolution, while LUSS showed more pronounced decreases over time. The baseline LUSS showed limited discriminative ability for predicting mortality (AUC 0.65, 95%CI 0.55-0.75), while follow-up LUSS and changes in LUSS (ΔLUSS) demonstrated higher levels of discrimination (AUC 0.81 (95%CI 0.71-0.89) and 0.89 (95%CI 0.80-0.95), respectively). For each one-point increase in ΔLUSS, the likelihood of mortality went up by 70% (p=0.002). An improved LUSS effectively ruled out mortality (negative predictive value 97.4%).

Conclusion Although LUS is highly sensitive for diagnosing CAP, its specificity in TB-endemic regions warrants further caution. Serial LUS assessments, particularly monitoring LUSS

changes, are valuable for tracking disease progression and prognostication, with increasing LUSS indicating potential clinical deterioration.

Keywords: diagnosis, Lung ultrasound, LUS score, monitoring, mortality, pneumonia, Tuberculosis

Article Summary

Strengths and limitations of this study

- Diagnostic accuracy was validated against comprehensive reference standards, including discharge diagnoses and CT scan results, enhancing the reliability of the findings.
- Blinding between the sonographer and treating physician ensured that ultrasound findings did not influence clinical decisions, improving the objectivity of diagnostic and monitoring results.
- Recorded ultrasound procedures were independently reviewed by a certified expert to assess inter-observer agreement and ensure reproducible ultrasound measurements.
- The applicability of the results to outpatients is uncertain, as the study focused on inpatients whose pneumonic lesions may differ in size and resolution time.

Introduction

Community-acquired pneumonia (CAP) is the leading global infectious disease, presenting significant challenges to public health due to its high hospitalization and mortality rates [1-3]. Effective diagnosis and monitoring are crucial to improve patient outcomes and reduce the healthcare burden. Despite being frequently encountered in both outpatient and inpatient settings, pneumonia diagnosis remains complex. CAP is rarely confirmed through the gold standard of pathology. Instead, the diagnosis relies on concordant evidence of clinical symptoms, microbiological detection, and compatible imaging findings, typically new infiltrates on chest radiographs (CXR) [4]. Despite being a staple for diagnosing CAP for years, CXR may fail to detect or correctly identify pneumonic lesions [5-7].

In recent years, alternative diagnostic tools such as lung ultrasound (LUS) have emerged [8]. Besides the advantages of being radiation-free, bedside-available, and repeatable, studies have shown that LUS offers substantial diagnostic accuracy [9]. Multiple meta-analyses revealed that the LUS sensitivity for diagnosing CAP ranges from 85%-97%, with specificity between 80%-96% [10-18]. However, most of the evidence on LUS diagnostic accuracy for pneumonia was derived from developed countries. There is less emphasis on low-resource settings, where diseases such as tuberculosis (TB) and bronchiectasis can mimic pneumonia sonographically, potentially affecting diagnostic properties [17]. Furthermore, the potential of LUS in monitoring and stratifying CAP patients at risk of clinical deterioration is not well-understood. In this study, we aim to investigate the diagnostic performance of LUS in a developing country. Additionally, we seek to identify which LUS parameters can effectively monitor and prognosticate CAP.

Methods

Study design and setting

This prospective observational study was conducted at the Pulmonary Department of Cho Ray Hospital, the largest tertiary hospital in southern Vietnam, from December 2022 to June 2023. Patients or their legally authorized representatives provided written informed consent before enrollment. Ethical approval for this study was obtained from the Ethical Committee for Biomedical Research (No. 875/HĐĐĐ-DHYD). The study was conducted in accordance with the Declaration of Helsinki.

Patient and public involvement

There were no patients or public involved in the study protocol.

Participants

Patients aged 18 years or older clinically suspected of having CAP according to the American Thoracic Society criteria [19] were eligible. This included patient presenting with fever, dyspnea, cough, sputum production, and pleuritic chest pain. Patients were excluded if hospitalized for ≥48 hours before enrollment, pregnant or lactating, or tested positive for SARS-CoV-2 via rapid antigen or RT-PCR assays.

Data collection

Eligible patients were systematically identified by a pulmonologist overseeing admissions and recruited consecutively. Enrollment occurred promptly upon admission, after which data were collected and the sonographer was notified to perform the ultrasound within 24 hours of hospitalization. Patient data collected included anthropometric measurements, clinical symptoms, medical history, and laboratory findings. Information on clinical complications, including in-hospital mortality, need for invasive mechanical ventilation, admission to the respiratory intensive care unit (RICU), and discharge status, was also recorded.

An initial LUS was performed by one of two pulmonologists, each with medical sonographer certification and experience in over 50 lung ultrasounds. They were blinded to the patients' medical records. During this period, patients also underwent CXR. A follow-up LUS was performed between day 5 and 8 by the same pulmonologist. This timeframe was chosen based on the assumption that LUS can detect pulmonary changes with sensitivity comparable

to CXR and provide similar benefits [20]. Additionally, Reissig [21] demonstrated that a 5–8 day timeframe effectively detects sonographic changes in pneumonia.

Lung ultrasound procedure

LUS examinations were conducted using a 2-5 MHz curved array transducer of the DP-10 (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). Patients were examined sitting when possible; otherwise, anterior regions were assessed supine and posterior regions recumbent. The procedure assessed 12 lung zones (**Figure 1**) for pleural irregularities, size and number of consolidations, the presence of air bronchograms, number and characteristics of B-lines, and pleural effusion. Consolidation size was measured in one dimension, from the pleural line to the furthest margin. Additionally, the LUS score (LUSS), a semi-quantitative tool for lung aeration ranging from 0 to 3, was assigned to each lung zone [22]. Detailed descriptions are presented in **Figure 2**, and the global LUSS was calculated as the sum of regional scores (range 0 to 36).

The finding of lung consolidation or focal interstitial syndrome (one or multiple zones involved unilaterally) was consistent with a pneumonia diagnosis [23]. In cases where bilateral interstitial syndrome was identified, additional ultrasound features such as irregular and thickened pleura, diminished lung sliding, the nonhomogeneous distribution of B-lines and subpleural consolidations were required to differentiate pneumonia from cardiogenic pulmonary edema [24, 25].

To assess inter-observer reliability, we recorded ultrasound procedures, randomly selected 30 recordings, and sent them to an expert with registered ultrasound certification to review. We then compared the interpretations of the ultrasound videos between the sonographers and the expert.

Chest radiography procedure

Every patient received a posteroanterior CXR (DRX-Ascend System, Carestream, New York, USA) within 24 hours of admission. A board-certified radiologist, blinded to the patient's clinical and LUS findings, independently reviewed these radiographs.

Diagnosis of community-acquired pneumonia

Upon discharge, the final diagnosis was confirmed by a panel of two independent pulmonologists who reviewed the patient's clinical and laboratory findings, radiology, microbiological results, and overall clinical course. The assessors were blinded to the LUS

data. In case of disagreement, a third expert was consulted, with consensus from at least two experts required for the conclusion.

For patients undergoing CT scans, the result served as a secondary reference for assessing LUS diagnostic values. Scans were obtained using 128-slice Optima CT 660 (GE Healthcare, Chicago, IL, USA) and interpreted independently by a board-certified radiologist blinded to prior clinical and imaging data.

Diagnosis of pulmonary tuberculosis

All pneumonia-suspected patients underwent acid-fast bacilli (AFB) staining of at least two sputum samples per the national guideline due to high TB prevalence, supplemented by GeneXpert MTB/RIF and TB culture when indicated. Gastric aspiration or bronchoalveolar lavage for TB workup was performed on a case-by-case basis. Active pulmonary TB diagnosis required compatible symptoms, radiographic findings, and microbiological confirmation (positive AFB stain, GeneXpert MTB/RIF, or *M. tuberculosis* culture). Patients with a history of previous treatment for TB but no active disease were excluded.

Study endpoints

The primary end-point was the diagnostic accuracy of LUS and CXR as index tests compared with the discharge diagnosis. Additional end-points included diagnostic accuracy compared with CT scan results, changes in three LUS parameters (consolidation size, number of consolidations, and LUSS) and their association with in-hospital mortality.

Statistical analysis

A total sample size of 70 and 84 patients was needed to estimate a sensitivity of 85% and specificity of 93% (according to Alzahrani's meta-analysis [17]), with a precision of 10% assuming the prevalence of CAP was 70%. Normality was assessed using histograms and the Shapiro-Wilk test. Non-normal variables were described by medians and interquartile ranges, while normal variables were described by means and standard deviations. Group differences were analyzed with t-tests for normal data and Mann-Whitney U tests for non-normal data. The Wilcoxon Signed-Rank Test assessed LUS parameters over time, while the Chi-Square or Fisher's Exact Test evaluated categorical variable differences.

For diagnostic properties, sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios of LUS and CXR were calculated. McNemar's test was employed to assess statistical differences in sensitivity and specificity between LUS and CXR. The optimal

LUSS cutoff was established using the Youden index. Logistic regression identified associations between mortality and ultrasound parameters but was limited to univariable analysis due to the small number of events. A p-value <0.05 indicated statistical significance. Data were processed using STATA/MP 17.0 software (StataCorp, College Station, TX, USA).

Results

Characteristics of patients suspected of CAP

Between December 2022 and June 2023, 158 patients were enrolled (**Figure 3**). Exclusions for hospitalization ≥48 hours prior to admission, self-discharge, and hospital transfers left 136 patients for final analysis. The mean age was 62 ± 17 years and 72.8% were male. Demographic and clinical characteristics are presented in **Table 1**. Hospital mortality was 13.2%.

CAP was confirmed in 99 patients (72.8%) at discharge. CT scans were conducted in 93 patients, with the median time from admission to scan of 2 [IQR 1-4] days. CAP was confirmed through CT in 72/93 cases (77.4%).

Diagnostic value of LUS and CXR

LUS showed a sensitivity of 96.0% (95%CI 90.0%-99.0%) and specificity of 64.9% (95%CI 47.5%-80.0%), while CXR had a sensitivity of 82.8% (82.8%, 95%CI 73.9%-89.7%) and specificity of 54.1% (95%CI 36.9%-70.5%).

CXR sensitivity was significantly lower than LUS (p=0.002), but specificities did not differ significantly (p=0.103, McNemar's test; **Table 2 and Supplement Table 1**). Using CT as a secondary reference standard, the performance of LUS showed a sensitivity of 95.8%, comparable to its sensitivity measured against discharge diagnosis as the reference standard. However, specificity was lower at 52.4% (95% CI 29.8-74.3%). Results of lung ultrasound and chest X-ray compared to CT scan are shown **in Supplementary Table 2.**

LUS missed lesions not reaching the pleura in two cases, subsequently confirmed by CT scans. In two other false negative cases without CT scans, CAP was confirmed by experts based on clinical signs, elevated inflammatory markers, CXR-detected lesions, and positive responses to antibiotics. On the other hand, LUS incorrectly identified pneumonia in 13 patients due to tuberculosis (n=6), lung cancer (n=2), heart failure (n=2), bronchiectasis (n=1), COPD with fibrosis (n=1), and interstitial lung disease (n=1).

Among 136 patients, *Mycobacterium tuberculosis* was detected in respiratory specimens of 7 individuals (6 false positives and 1 true positive, as the patient had *Pseudomonas aeruginosa* in sputum culture, making it CAP with *M. tuberculosis* co-infection). The 6 tuberculosis cases were older adults (median age 60 [59–64] years) presenting with a short symptom duration (≤2 weeks). Laboratory tests revealed elevated inflammatory markers: white blood cell count

13.25 [9.8-15.8] G/L, neutrophil predominance (85.5% [82.5-96.4%]), and elevated CRP (134.7 [115.0-178.1] mg/L), resembling non-TB CAP. CT scans showed consolidations in all 6 patients, with 5 exhibiting abscesses or cavitation; other findings included bronchiectasis, multiple small nodules, and pleural effusion. While LUS detected the consolidations, it could not visualize the cavitary lesions in these patients.

Sonographic characteristics of CAP at baseline and monitoring

The time to perform the LUS was under 10 minutes (median 9 minutes 38 seconds). The inter-rater variability was low, with Cohen's kappa value of 0.89 ($p<0.001$) for pneumonia diagnosis and 0.85 ($p<0.001$) for LUSS assessment.

Sonographic characteristics of cases where LUS detected and confirmed CAP upon discharge are detailed in **Supplement Table 3**. In six cases with bilateral interstitial patterns, findings such as irregular and thickened pleura, reduced lung sliding, and subpleural consolidations helped distinguish pneumonia from cardiogenic pulmonary edema. Echocardiography performed in these six cases also confirmed the findings.

Follow-up LUS was performed in 98 out of 136 patients (72.1%), including 75 with pneumonia and 23 without. The median time between admission and the follow-up ultrasound was 5 [IQR 5–6] days. At the time of the second ultrasound, 24 patients had been discharged (15 pneumonia patients and 9 non-pneumonia patients), while 10 had died, including 9 with pneumonia. Among those still hospitalized, two pneumonia patients required mechanical ventilation, and six were in RICU (**Supplement Table 4**). In pneumonia patients, follow-up scans showed only a slight reduction in the size and number of consolidations after 5–8 days, whereas the LUSS demonstrated a more significant reduction (**Table 3**).

The prognostic value of lung ultrasound

The association of LUS parameters with in-hospital mortality is detailed in **Table 4**. Consolidation size or count were not associated with mortality risk. The global LUSS was associated with mortality (unadjusted OR=1.09, 95%CI 1.01-1.16, p=0.021). The baseline LUSS had an AUC of 0.65 (95% CI 0.55-0.75), indicating modest discrimination for predicting mortality, with an optimal cut-point of 17 (52.9% sensitivity, 73.1% specificity). At the second evaluation, the LUSS demonstrated an improved discrimination, with an AUC of 0.81 (95%CI 0.71-0.89) and an optimal cut-point of 21 (66.7% sensitivity, 87.9% specificity) and the unadjusted OR was 1.19 (95%CI 1.06–1.34, p=0.004).

All mortality cases had worsening LUSS. Changes in Lung Ultrasound Score (ΔLUSS) over time were also analyzed.). Patients whose LUSS increased from the initial to the follow-up examination were more likely to die in the hospital. Specifically, each one-point rise in LUSS between the two scans was associated with a 70% increase in the odds of in-hospital death (OR 1.70, 95%CI 1.22–2.38, p=0.002). ΔLUSS had a predictive AUC of 0.89 (95% CI 0.80-0.95) for in-hospital mortality. Patients with no improvement in monitoring LUS (ΔLUSS≥0) demonstrated a sensitivity of 88.9%, specificity of 57.6%, NPV of 97.4%, and PPV of 22.2% in predicting mortality (**Table 5**).

Discussion

This study confirmed that LUS has a higher sensitivity than CXR for diagnosing community-acquired pneumonia. However, its moderate specificity may be influenced by the difficulty in differentiating pneumonia from other respiratory conditions, particularly tuberculosis. To our knowledge, this is one of the first studies to incorporate lung ultrasound score for monitoring CAP. Our findings indicate that LUSS changes over time may offer preliminary prognostic insights, potentially aiding in the identification of disease progression and mortality risk stratification.

Previous studies have shown that LUS has a high sensitivity for detecting pneumonia [14-17]. Our study aligns with these findings, demonstrating greater sensitivity than CXR. These results reaffirm LUS as a reliable tool for ruling out pneumonia. However, if ultrasound is negative but other pneumonia signs persist, further investigation and close monitoring after antibiotic treatment are necessary for a definitive diagnosis. Despite showing great sensitivity, LUS specificity was lower than in prior reports [14-17] and varied depending on the reference standard used. The lower specificity observed with CT as the standard, compared to a clinical panel combining clinical features and CXR, reflects CT's superior ability to detect detailed pulmonary changes. Studies have also shown that clinical features and CXR frequently lead to misdiagnosis of CAP compared to CT [5]. While LUS is more sensitive than CXR in detecting interstitial abnormalities and consolidations, it shares similar limitations, such as difficulty distinguishing acute from chronic changes and less detailed lung pattern analysis compared to CT. For example, B-lines on LUS may indicate acute infections or chronic fibrotic processes, and hypoechoic lesions may also signify various pathologies, including pneumonia, atelectasis, lung cancer, pulmonary embolism, or nodular scarring.

Our findings indicate that LUS has difficulty in differentiating pneumonia from other respiratory diseases, with TB being the most frequently misdiagnosed. In this study, we classified pulmonary tuberculosis as false positive rather than a type of CAP. This decision was based on the rationale that the diagnosis determines subsequent antibiotic strategies, which differ between the two conditions. While some sonographic findings (e.g., subpleural nodules, pleural effusion, consolidation with fluid collections) may suggest TB, the modality is inherently limited in detecting cavity lesions, which is a consistent radiologic feature in our TB patients, due to air within cavities preventing ultrasound penetration. This is particularly relevant in our setting, which reported the highest number of tuberculosis cases among LUS

studies on CAP. In contrast, previous research, primarily conducted in low-TB-prevalence settings, found no TB cases, while studies in endemic areas such as Liu [26] in China and Amatya [27] in Nepal, reported zero and one case, respectively. Our findings highlight the diagnostic challenges of LUS for pneumonia in TB-endemic regions, where sonographic presentations of TB and pneumonia often overlap. Given these challenges, larger, targeted studies are needed to better characterize ultrasound findings in TB. Clinically, when consolidations appear (with or without complementary features such as pleural effusion or subpleural nodules) and align with clinical suspicion of TB, further evaluation with CT scans and specific TB workup is indispensable.

Besides evaluating the diagnostic properties, our study aimed to observe sonographic changes in CAP over time and assess whether these changes could aid in monitoring and predicting clinical outcomes. We focused on three ultrasound parameters: consolidation size, number of consolidations, and LUSS. Previous studies in both pediatric [28-30] and adult populations [21] suggest disease remission can be observed through the resolution of lesion sizes and numbers. However, our findings indicate that changes in the size and overall number of consolidations during follow-up assessments were relatively small. These marginal changes may not be readily apparent to clinicians, making it less ideal to utilize these parameters for monitoring purposes. The difference in pneumonic lesion resolution between our study and that reported in the adult population by Reissig [21] may stem from variations in measurement methods and sample selection. We used a one-dimensional measure for the largest consolidation, whereas Reissig et al. employed a two-dimensional measure in cm^2. Additionally, for comparisons of lesion size at two time points, our initial assessment only included subjects available for a follow-up ultrasound, in contrast to Reissig's approach, which involved measuring pneumonic size in all patients, regardless of follow-up availability [21].

The LUSS has recently emerged as a useful tool for assessing severity and the baseline score is closely related to adverse outcomes in COVID-19 patients [31]. Our analysis showed that the baseline score has limited predictive value for in-hospital mortality. Instead, the dynamic changes in the LUSS during follow-up may offer a more reliable indication of mortality. Hypothetically, since the Lung Ultrasound score incorporates both consolidation and interstitial components, and considering that changes in consolidation measurements were small, it is possible that changes in the interstitial pattern occur earlier and are more predictive of the clinical course of CAP than consolidative changes. From the clinical practice perspective, LUSS progression should alert physicians about a deteriorating clinical course. A

ΔLUSS cut-off of 0 is clinically applicable as it allows for the simple categorization of patients into groups with improved or unimproved LUSS over time. Patients with no improvement in monitoring LUS (ΔLUSS ≥0) demonstrated a sensitivity of 88.9%, specificity of 57.6%, NPV of 97.4%, and PPV of 22.2% in predicting mortality. While the high sensitivity and NPV suggest that a ΔLUSS≥0 is effective in identifying patients at risk of mortality, the moderate specificity and PPV indicate that ΔLUSS should be used in conjunction with other clinical indicators. Utilizing LUSS for stratification may lead to a more efficient allocation of medical resources, ensuring that attention and care are prioritized for patients with a higher risk of mortality. Timely interventions, such as escalating antibiotics, advanced imaging, microbiology workup, and complication investigation, can potentially help prevent progression to critical illness and ultimately educe mortality. However, as our observations are based on a limited sample size, further studies focusing on sonographic pneumonic lesion evolution and their impact on clinical outcomes are needed to validate these findings.

This study has several limitations. First, due to ethical reasons, CT scan was not performed on all patients, leaving the possibility of missing or misidentifying pneumonic lesions. However, in those who did receive a CT scan, the performance of LUS was found to be to be comparable to both discharge diagnosis and CT imaging, indicating the former's reliability. Second, the study was designed for the inpatient setting. It is less certain whether the results can be applicable to outpatients, whose lesions are presumably smaller and may resolve more quickly. Additionally, some patients were discharged before the second planned ultrasound, leading to follow-up data potentially skewed away from those with milder disease. However, similar to CXR, follow-up ultrasounds may be unnecessary for patients showing early recovery, as their clinical symptoms suggest resolution without additional imaging. For patients who died early before the second ultrasound, it is plausible they had greater pneumonic lesion progression, potentially amplifying our findings. Future studies should consider shorter follow-up intervals to evaluate the prognostic role of earlier follow-up LUS in severely ill patients. Third, the consolidation size was recorded in a single dimension, which does not fully capture the lesion's three-dimensional volume. However, measurements in one dimension have been shown to effectively represent overall lesion volume [29]. Finally, ultrasound is an operator-dependent tool, and its interpretation is subjective to sonographer's experience. Nevertheless, our study demonstrated high reliability between performers.

Conclusion

LUS serves as a non-invasive, rapid, and bedside-accessible modality with high sensitivity for detecting CAP. However, the sonographic similarities between pneumonia and other respiratory conditions, such as TB, particularly endemic region, require careful interpretation and consideration of the clinical scenario, as well as further workup, to ensure accurate diagnosis. Monitoring with LUS revealed that consolidation size and total lesion resolved slowly. In contrast, changes in the LUSS were more notable. An increasing LUSS was strongly predictive of in-hospital mortality, making it a valuable tool for monitoring disease progression and stratifying patients at risk.

Abbreviation

AFB: acid-fast bacilli

AUC: Area Under the Curve

CAP: Community-Acquired Pneumonia

COPD: Chronic Obstructive Pulmonary Disease

CT: Computed Tomography

CXR: Chest X-Ray

ΔLUSS: Change in Lung Ultrasound Score

LUS: Lung Ultrasound

LUSS: Lung Ultrasound Score

NPV: Negative Predictive Value

OR: Odds Ratio

PPV: Positive Predictive Value

RICU: Respiratory Intensive Care Unit

RT-PCR: Reverse Transcription Polymerase Chain Reaction

TB: Tuberculosis

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Author contributions

QKTL, NVH, and VLT conceptualized the study and designed the data collection instruments with input from TTT, KND, NTN, PTHN, and LP. Lung ultrasound training and support were provided by LP. QKTL and TTT coordinated and supervised data collection at the study sites, with KND and NTN supervising their respective sites. Data acquisition and management were carried out by QKTL, NDM, LNH, and NTN. QKTL, TTT, and PTHN analyzed and interpreted the data. QKTL and TTT wrote the manuscript with critical input from LP and VLT. All authors collaboratively reviewed and approved the final manuscript. Quoc-Khanh Tran-Le is the guarantor of the study.

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Competing interests

None declared**.**

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research**.**

Patient consent for publication

Consent obtained directly from patient(s). Ethics approval

Data statement

Please send any requests for access to the datasets to khanhtlq@ump.edu.vn

References

1. World Health Organization. Disease burden and mortality estimates, 2000 - 2016. https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html. Date last updated: December 9 2020. Date last accessed: January 25 2023.
2. Ferreira-Coimbra J, Sarda C, Rello J. Burden of Community-Acquired Pneumonia and Unmet Clinical Needs. Advances in therapy. 2020;37(4):1302-18.
3. Almirall J, Serra-Prat M, Bolíbar I, *et al.* Risk Factors for Community-Acquired Pneumonia in Adults: A Systematic Review of Observational Studies. Respiration; international review of thoracic diseases. 2017;94(3):299-311.
4. Waterer G. What is pneumonia? Breathe (Sheffield, England). 2021;17(3):210087.
5. Claessens YE, Debray MP, Tubach F, *et al.* Early Chest Computed Tomography Scan to Assist Diagnosis and Guide Treatment Decision for Suspected Community-acquired Pneumonia. American journal of respiratory and critical care medicine. 2015;192(8):974-82.
6. Self WH, Courtney DM, McNaughton CD, *et al.* High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. The American journal of emergency medicine. 2013;31(2):401-5.
7. Upchurch CP, Grijalva CG, Wunderink RG, *et al.* Community-Acquired Pneumonia Visualized on CT Scans but Not Chest Radiographs: Pathogens, Severity, and Clinical Outcomes. Chest. 2018;153(3):601-10.
8. Jones BP, Tay ET, Elikashvili I, *et al.* Feasibility and Safety of Substituting Lung Ultrasonography for Chest Radiography When Diagnosing Pneumonia in Children: A Randomized Controlled Trial. Chest. 2016;150(1):131-8.
9. Mathis G. Pneumonia. In: Laursen CB RN, Volpicelli G, eds. Thoracic Ultrasound (ERS Monograph). Sheffield: European Respiratory Society; 2018. pp. 87–101.
10. Chavez MA, Shams N, Ellington LE, *et al.* Lung ultrasound for the diagnosis of pneumonia in adults: a systematic review and meta-analysis. Respiratory research. 2014;15(1):50.
11. Hu QJ, Shen YC, Jia LQ, *et al.* Diagnostic performance of lung ultrasound in the diagnosis of pneumonia: a bivariate meta-analysis. International journal of clinical and experimental medicine. 2014;7(1):115-21.
12. Ye X, Xiao H, Chen B, *et al.* Accuracy of Lung Ultrasonography versus Chest Radiography for the Diagnosis of Adult Community-Acquired Pneumonia: Review of the Literature and Meta-Analysis. PloS one. 2015;10(6):e0130066.
13. Berlet T. Thoracic ultrasound for the diagnosis of pneumonia in adults: a meta-analysis. Respiratory research. 2015;16(1):89.
14. Xia Y, Ying Y, Wang S, *et al.* Effectiveness of lung ultrasonography for diagnosis of pneumonia in adults: a systematic review and meta-analysis. Journal of thoracic disease. 2016;8(10):2822-31.
15. Llamas-Álvarez AM, Tenza-Lozano EM, Latour-Pérez J. Accuracy of Lung Ultrasonography in the Diagnosis of Pneumonia in Adults: Systematic Review and Meta-Analysis. Chest. 2017;151(2):374-82.
16. Long L, Zhao HT, Zhang ZY, *et al.* Lung ultrasound for the diagnosis of pneumonia in adults: A meta-analysis. Medicine. 2017;96(3):e5713.
17. Alzahrani SA, Al-Salamah MA, Al-Madani WH, *et al.* Systematic review and meta-analysis for the use of ultrasound versus radiology in diagnosing of pneumonia. Critical ultrasound journal. 2017;9(1):6.
18. Orso D, Guglielmo N, Copetti R. Lung ultrasound in diagnosing pneumonia in the emergency department: a systematic review and meta-analysis. European journal of emergency medicine : official journal of the European Society for Emergency Medicine. 2018;25(5):312-21.
19. Niederman MS, Mandell LA, Anzueto A, *et al.* Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. American journal of respiratory and critical care medicine. 2001;163(7):1730-54.
20. Metlay JP, Waterer GW, Long AC, *et al.* Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. American journal of respiratory and critical care medicine. 2019;200(7):e45-e67.

21. Reissig A, Copetti R, Mathis G*, et al.* Lung ultrasound in the diagnosis and follow-up of community-acquired pneumonia: a prospective, multicenter, diagnostic accuracy study. Chest. 2012;142(4):965-72.
22. Via G, Storti E, Gulati G*, et al.* Lung ultrasound in the ICU: from diagnostic instrument to respiratory monitoring tool. Minerva anestesiologica. 2012;78(11):1282-96.
23. Volpicelli G, Elbarbary M, Blaivas M*, et al.* International evidence-based recommendations for point-of-care lung ultrasound. Intensive care medicine. 2012;38(4):577-91.
24. Copetti R, Soldati G, Copetti P. Chest sonography: a useful tool to differentiate acute cardiogenic pulmonary edema from acute respiratory distress syndrome. Cardiovascular ultrasound. 2008;6:16.
25. Soldati G, Demi M. The use of lung ultrasound images for the differential diagnosis of pulmonary and cardiac interstitial pathology. Journal of ultrasound. 2017;20(2):91-6.
26. Liu XL, Lian R, Tao YK*, et al.* Lung ultrasonography: an effective way to diagnose community-acquired pneumonia. Emergency medicine journal : EMJ. 2015;32(6):433-8.
27. Amatya Y, Rupp J, Russell FM*, et al.* Diagnostic use of lung ultrasound compared to chest radiograph for suspected pneumonia in a resource-limited setting. International journal of emergency medicine. 2018;11(1):8.
28. Omran A, Eesai S, Ibrahim M*, et al.* Lung ultrasound in diagnosis and follow up of community acquired pneumonia in infants younger than 1-year old. The clinical respiratory journal. 2018;12(7):2204-11.
29. Urbankowska E, Krenke K, Drobczyński Ł*, et al.* Lung ultrasound in the diagnosis and monitoring of community acquired pneumonia in children. Respiratory medicine. 2015;109(9):1207-12.
30. Berce V, Tomazin M, Gorenjak M*, et al.* The Usefulness of Lung Ultrasound for the Aetiological Diagnosis of Community-Acquired Pneumonia in Children. Scientific reports. 2019;9(1):17957.
31. Song G, Qiao W, Wang X*, et al.* Association of Lung Ultrasound Score with Mortality and Severity of COVID-19: A Meta-Analysis and Trial Sequential Analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2021;108:603-9.

Table 1. Demographic and clinical characteristics of patients with and without pneumonia

	Overall (n=136)	Patients with pneumonia (n=99)	Patients without pneumonia (n=37)
Age, years (M ± SD)	62.35 ± 17.03	61.30 ± 17.83	65.14 ± 14.52
Male sex (n, %)	99 (72.8%)	73 (73.7%)	26 (70.3%)
Symptoms (n, %)			
Fever	68 (50.0)	59 (59.6)	9 (24.3)
Dyspnea	108 (79.4)	79 (79.8)	29 (78.4)
Cough	107 (78.7)	78 (78.8)	29 (78.4)
Purulent expectoration	57 (41.9)	44 (44.4)	13 (35.1)
Chest pain	45 (33.1)	30 (30.3)	15 (40.5)
Risk factors (n, %)			
Nicotine abuse	49 (36.0)	35 (35.4)	14 (37.8)
Alcohol abuse	8 (5.9)	7 (7.1)	1 (2.7)
Comorbidities (n, %)			
Diabetes mellitus	33 (24.3)	26 (26.3)	7 (18.9)
Hypertension[+]	59 (43.4)	42 (42.4)	17 (45.9)
Coronary artery disease	15 (11.0)	9 (9.1)	6 (16.2)
COPD	22 (16.2)	10 (10.1)	12 (32.4)
Asthma	9 (6.6)	3 (3.0)	6 (16.2)
History of tuberculosis	12 (8.8)	10 (10.1)	2 (5.4)
Clinical signs upon admission (n, %)			
Temperature > 37.5°C	22 (16.2)	17 (17.2)	5 (13.5)
Hypoxemia	94 (69.1)	73 (73.7)	21 (56.8)
MAP < 65 mmHg	7 (5.2)	6 (6.1)	1 (2.7)
Pulse > 100 l/min	57 (41.9)	46 (46.5)	11 (29.7)
Laboratory findings			
White blood cell (G/L) (Median [IQR])	11.37 [8.37 – 16.14]	11.60 [9.10 – 17. 27]	9.60 [7.49 – 14.19]
Neutrophil (G/L) (Median [IQR])	9.50 [6.05 – 14.17]	10.03 [6.90 – 15.78]	6.91 [5.25 – 11.87]
Lymphocyte (G/L) (Median – [IQR])	0.93 [0.62 – 1.51]	0.91 [0.58 – 1.45]	1.26 [0.73 – 2.05]
Neutrophil/Lymphocyte Ratio (Median [IQR])	8.90 [4.38 –19.08]	9.05 [5.14– 20.64]	7.53 [2.14 –13.49]
Hemoglobin (g/L) (M ± SD)	120.76 ± 22.59	118.03 ± 22.62	127.87 ± 20.86
Platelet (G/L) (Median [IQR])	247.0 [188.0– 313.0]	251.5 [179.3 – 316.0]	241.0 [209.0–293.0]
CRP (mg/L) (n=104) (Median [IQR])	95.60 [40.38 – 131.75]	107.20 [59.95 – 137.00]	58.90 [8.60 – 120.90]
Creatinine (mg/dl) (Median [IQR])	0.84 [0.66 – 1.09]	0.83 [0.65 – 1.09]	0.85 [0.70 – 1.10]
BUN (mg/dl) (Median [IQR])	17.00 [12.00 – 22.75]	17.00 [13.00 – 23.00]	16.00 [10.00 – 22.00]
In-hospital outcomes (n,%)			
Ventilation	19 (14.0)	16 (16.2)	3 (8.1)
Shock	19 (14.0)	18 (18.2)	1 (2.7)
RICU	25 (18.4)	22 (22.2)	3 (8.1)
In-hospital mortality	18 (13.2)	17 (17.2)	1 (2.7)

Length of stay (days) (Median [IQR]	8.0 [6.0 -10.0]	8.0 [6.0 – 11.0]	6.0 [4.0 – 8.0]

[+] Hypoxemia is defined as either an SpO_2 level below 90% on ambient air or a PaO_2 level below 60 mmHg, as determined by arterial blood gas analysis.

Table 2. Diagnostic performance of lung ultrasound and chest X-ray with reference to discharge diagnosis and CT scan

Reference test	Discharge diagnosis		CT scan	
	Lung ultrasound	Chest X-ray	Lung ultrasound	Chest X-ray
Sensitivity (%)	96.0 (90.0 – 99.0)	82.8 (73.9 – 89.7)	95.8 (88.3 – 99.1)	77.8 (66.4 – 86.7)
Specificity (%)	64.9 (47.5 – 80.0)	54.1 (36.9 – 70.5)	52.4 (29.8 – 74.3)	42.9 (21.8 – 66.0)
Positive predictive value (%)	88.0 (82.5 – 91.9)	82.8 (77.1 – 87.4)	87.3 (78.0 – 93.8)	82.4 (71.2 – 90.5)
Negative predictive value (%)	85.7 (69.1 – 94.2)	54.1 (41.0 – 66.5)	78.6 (49.2 – 95.3)	36.0 (18.0 – 57.5)
Likelihood ratio (+)	2.73 (1.76 – 5.24)	1.80 (1.26 – 2.59)	2.01 (1.28 – 3.16)	1.36 (0.92 – 2.01)
Likelihood ratio (-)	0.06 (0.02 – 0.17)	0.32 (0.19 – 0.54)	0.08 (0.02 – 0.26)	0.52 (0.27 – 1.00)
Accuracy (%)	87.5 (80.7 – 92.6)	75.0 (66.7 – 82.0)	86.0 (77.3 – 92.3)	69.9 (59.5 – 79.0)
AUC	0.80 (0.72 – 0.88)	0.68 (0.56 – 0.79)	0.74 (0.63 – 0.85)	0.60 (0.48 – 0.72)

Table 3. Comparison of ultrasound findings between initial (LUS 1) and follow-up (LUS 2) assessments

	LUS 1	LUS 2	p
Largest consolidation size (cm) (n=66)	3.68 [2.50 – 6.86]	3.13 [1.64 – 6.27]	0.009
Number of consolidations (n=66)	2 [1 – 3]	2 [1 – 2]	0.017
LUS score (n=75)	13 [9 – 17]	11 [6 – 18]	0.002

Table 4. Association of lung ultrasound parameters with in-hospital outcomes in patients with community-acquired pneumonia

	Mortality	Non-mortality	OR (95% CI)	p
Largest consolidation size (cm) (n=84)	6.24 [3.46 – 7.69]	3.36 [1.72 – 6.86]	1.10 (0.96 – 1.29)	0.174
Number of consolidations (n=84)	2 [1 – 4]	2 [1 – 3]	1.38 (0.99 – 1.94)	0.055
LUS 1 (n=95)	17 [10 – 23]	12 [6 – 17]	1.09 (1.01 – 1.16)	0.021
LUS 2 (n=75)	22 [12 – 24]	10 [5 – 16]	1.19 (1.06 – 1.34)	0.004
Δ LUS (LUS2-LUS1) (n=75)	4 [1 – 6]	-1 [-4 – 0]	1.70 (1.22 – 2.38)	0.002

Table 5. Cutoff points of ΔLUS in predicting in-hospital mortality

Δ LUS cutoff	Sensitivity (%)	Specificity (%)	LR (+)	LR (-)	PPV	NPV
≥ -1	100.0 (63.1 – 100)	45.5 (34.0 – 58.9)	1.83 (1.49 – 2.32)	-	18.2 (8.19 – 32.7)	100 (88.9 – 100)
≥ 0	88.9 (51.8 – 99.7)	57.6 (44.8 - 69.7)	2.10 (1.46 - 3.01)	0.19 (0.03 - 1.24)	22.2 (10.1 – 39.2)	97.4 (86.5 – 99.9)
≥ 1	77.8 (40.0 - 97.2)	86.4 (75.7 – 93.6)	5.70 (2.83 - 11.5)	0.26 (0.08 - 0.88)	43.8 (19.8 - 70.1)	96.6 (88.3 - 99.6)

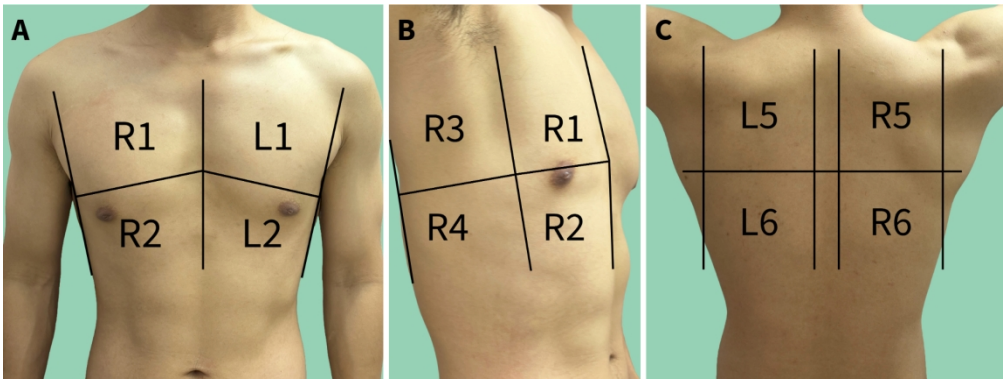
AUC = 0.89 (95% CI 0.80 - 0.95)

Figure legends

Figure 1. Division of 12 lung zones, with six zones allocated to each hemithorax. The zones are divided as follows: each hemithorax is segmented into anterior, lateral, and posterior chest areas, demarcated by the anterior and posterior axillary lines. Each area on either side is further divided into an upper and a lower half: A) Anterior Chest Area: The right hemithorax is divided into an upper zone (R1) and a lower zone (R2); the left hemithorax is divided into an upper zone (L1) and a lower zone (L2). B) Lateral Chest Area (Right Side): Features an upper lateral zone (R3) and a lower lateral zone (R4). The left lateral view is not shown. C) Posterior Chest Area: Illustrates the right upper (R5) and lower (R6) zones, and the left upper (L5) and lower (L6) zones.

Figure 2. **Lung Ultrasound Scores (LUSS) for assessing lung aeration, ranging from 0 to 3**. A) demonstrates LUSS 0, characterized by the presence of A-lines, indicative of normal lung aeration. B) LUSS 1, where there are three or more B-lines per intercostal space, accompanied by irregular or thickened pleura. C) LUSS 2, displaying confluent B-lines, with or without sub-pleural consolidations. D) LUSS 3, featuring large consolidations with a height greater than 1 cm.

Figure 3. Flowchart of patient enrollment and outcomes in the study



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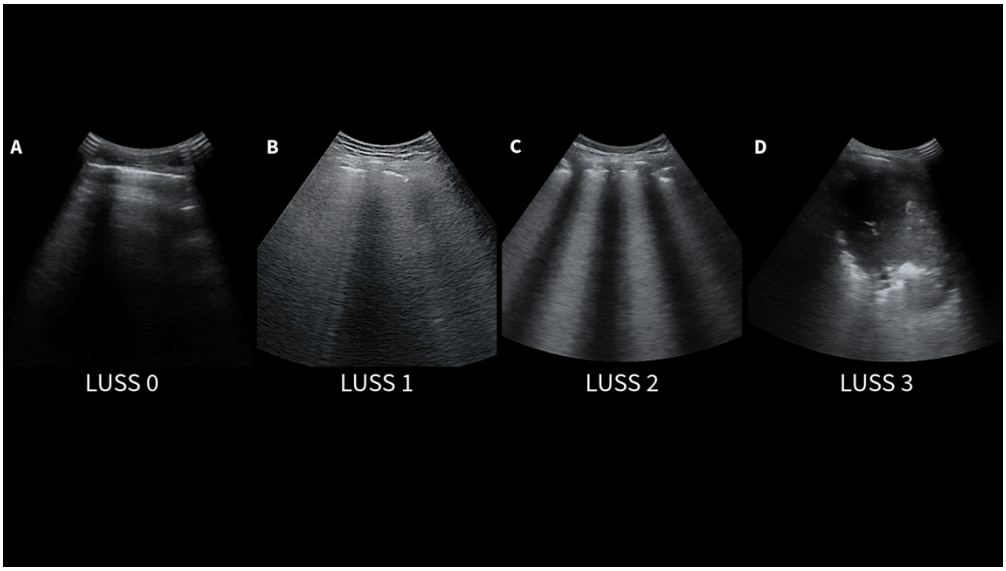
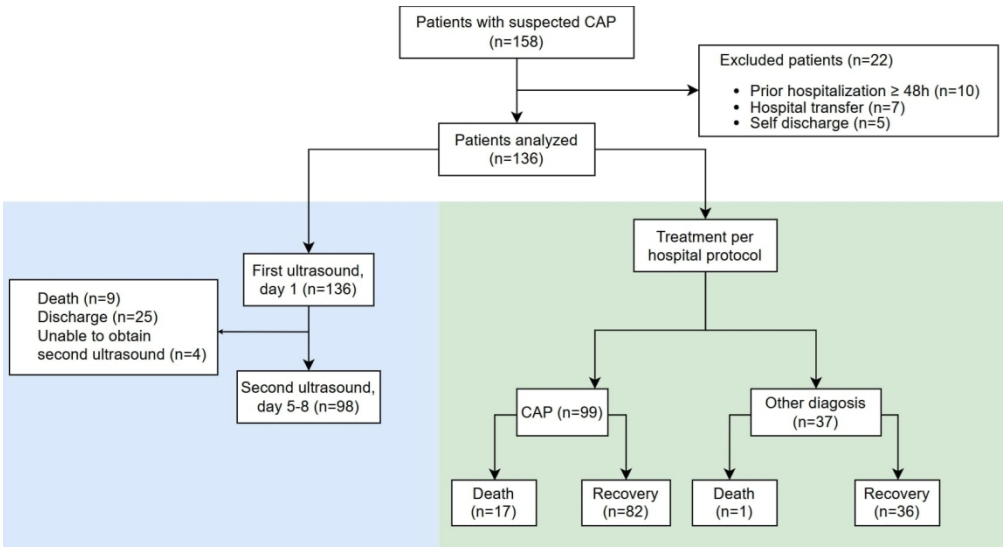


Lung Ultrasound Scores (LUSS) for assessing lung aeration, ranging from 0 to 3. A) demonstrates LUSS 0, characterized by the presence of A-lines, indicative of normal lung aeration. B) LUSS 1, where there are three or more B-lines per intercostal space, accompanied by irregular or thickened pleura. C) LUSS 2, displaying confluent B-lines, with or without sub-pleural consolidations. D) LUSS 3, featuring large consolidations with a height greater than 1 cm.

677x381mm (72 x 72 DPI)



Flowchart of patient enrollment and outcomes in the study

596x321mm (72 x 72 DPI)

Supplement Table 1. Ultrasound findings in confirmed CAP case with positive LUS (n=95)

	n (%)
Consolidation + / – interstitial syndrome	84 (88.4)
On left side only	11 (13.1)
On right side only	21 (25.0)
On both side	52 (61.9)
Number of consolidations	2 [1 – 3]
Largest consolidation size (cm)	3.67 [2.14 – 6.92]
Air bronchogram	56 (66.7)
Dynamic air bronchogram	46 (54.8)
Static air bronchogram	10 (11.9)
Interstitial syndrome	11 (11.6)
Focal	5 (45.4)
Bilateral	6 (54.6)
Pleural effusion	48 (50.5)
On left side only	9 (9.5)
On right side only	18 (18.9)
On both side	21 (22.1)
LUS score	12 [8-18]

Supplement Table 2. Ultrasound findings from the first and second examinations

	First ultrasound				Second ultrasound			
	Overall (n=136)	Pneumonia (n=99)	No pneumonia (n=37)	p	Overall (n=98)	Pneumonia (n=78)	No pneumonia (n=20)	p
Consolidation + / – interstitial syndrome	95 (69.9)	84 (84.8)	12 (32.4)	**<0.001**	69 (70.4)	61 (78.2)	8(40.0)	**0.001**
On left side only	11 (8.1)	11 (13.1)	0 (0.0)	0.349	14 (14.3)	13 (16.7)	1 (5.0)	0.288
On right side only	23 (16.9)	21 (25.0)	2 (16.7)	0.725	19 (19.4)	16 (20.5)	3 (15.0)	0.756
On both side	61 (44.9)	52 (61.9)	10 (83.3)	0.203	36 (36.7)	32 (41.0)	4 (20.0)	0.118
Number of consolidations	2 [1 – 3]	2 [1 – 3]	2 [1 – 4]	0.421	2 [1 – 2]	2 [1 – 2]	1 [1 – 3.5]	0.589
Largest consolidation size (cm)	3.73 [2.21 – 7.52]	3.67 [2.10 – 6.95]	5.87 [2.28 – 9.54]	0.283	3.46 [1.92 – 7.35]	3.76 [1.83 – 7.37]	2.98 [2.08 – 8.04]	0.918
Air bronchogram	64 (67.7)	56 (66.7)	8 (66.7)	1.000	55 (79.7)	48 (78.7)	7 (87.5)	1.000
Dynamic air bronchogram	50 (52.6)	46 (54.8)	4 (33.3)	0.221	36	35 (77.4)	1 (12.5)	**0.024**
Static air bronchogram	14 (14.7)	10 (11.9)	4 (33.3)	0.071	19	13 (21.3)	6 (75.0)	**0.004**
Interstitial syndrome	21 (15.4)	12 (12.1)	9 (24.3)	0.080	15 (15.3)	12 (15.4)	3 (15.0)	1.000
Focal	10 (7.4)	5 (5.1)	5 (13.5)	0.092	8 (8.2)	7 (9.0)	1 (5.0)	1.000
Bilateral	11 (8.8)	7 (7.1)	4 (10.8)	0.477	7 (7.1)	5 (6.4)	2 (10.0)	0.629
Pleural effusion	57 (41.9)	50 (50.5)	7 (18.9)	**0.001**	43 (43.9)	39 (50.0)	4 (20.0)	**0.022**

On left side only	11 (8.1)	10 (10.1)	1 (2.7)	0.288	9 (9.2)	8 (13.3)	1 (5.0)	0.681
On right side only	20 (14.7)	18 (18.2)	2 (5.4)	0.100	16 (16.3)	15 (25.2)	1 (5.0)	0.180
On both side	26 (19.1)	22 (22.2)	4 (10.8)	0.150	18 (18.4)	16 (26.5)	2 (10.0)	0.516
Pleural effusion volume (ml)	378.0 [171.0 – 564.0]	356.0 [167.0 – 493.0]	654.0 [474.0 – 766.0]	**0.011**	440.0 [240.0 – 678.0]	411.0 [240.0 – 650.0]	643.0 [560.0 – 714.0]	0.109
LUS score	13 [7.0 – 18.0]	12 [8 – 18]	15 [4 – 22]	0.935	9 [3 – 17]	11 [5 – 17]	4 [0 – 10]	**0.003**

Supplement table 3. Results of lung ultrasound and chest X-ray compare to confirm CAP cases at discharge

	Pneumonia (n= 99)	No pneumonia (n=37)
Lung ultrasound		
Positive	95	13
Negative	4	24
Chest X-ray		
Positive	82	17
Negative	17	20

Supplement table 4. Results of lung ultrasound and chest X-ray compare to CT scan

	CT positive (n= 72)	CT negative (n = 21)
Lung ultrasound		
Positive	69	10
Negative	3	11
Chest X-ray		
Positive	56	12
Negative	16	9

Supplement table 5. Clinical status of patients at the time of first and second ultrasounds and at discharge

	At 1st ultrasound	At 2nd ultrasound	At discharge
Ventilation, n (%)	0/95 (0%)	2/75 (2.7%)	9/75 (12.0%)
RICU admission, n (%)	0/95 (0%)	6/75 (8.0%)	14/75 (18.7%)
Shock, n (%)	2/95 (2.0%)	7/75 (9.3%)	12/75 (16.0%)

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Lung ultrasound for the diagnosis and monitoring of pneumonia in a Tuberculosis-Endemic setting: a prospective study

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LUNG ULTRASOUND FOR THE DIAGNOSIS AND MONITORING OF PNEUMONIA IN A TUBERCULOSIS-ENDEMIC SETTING: A PROSPECTIVE STUDY

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Word count: 3509 words

Abstract

Lung ultrasound (LUS) has proven high diagnostic accuracy for community-acquired pneumonia (CAP) in developed countries. However, its diagnostic performance in resource-limited settings with high pulmonary tuberculosis (TB) incidence is less established. Additionally, the role of LUS in monitoring CAP progression remains underexplored.

Objectives To validate the diagnostic performance, monitoring, and prognostic utility of lung ultrasound for CAP in a high pulmonary tuberculosis incidence setting.

Design Prospective single-center cohort study

Setting Pulmonary department of a tertiary hospital in Vietnam.

Participants A total of 158 patients suspected of having CAP were enrolled, with 136 (mean age 62 years, 72.8% male) included in the final analysis.

Interventions Patients underwent LUS and chest X-ray (CXR) within 24 hours of admission, with a follow-up LUS on day 5-8.

Primary and Secondary Outcome Measures.

The primary outcome was the diagnostic accuracy of LUS and CXR compared to discharge diagnosis. **Secondary outcomes** included the accuracy compared to CT scan results, changes in LUS parameters—consolidation size, number, and Lung Ultrasound Score (LUSS)—and their association with in-hospital mortality.

Results LUS demonstrated higher sensitivity than CXR (96.0% (95%CI 90.0%-99.0%) vs. 82.8% (95%CI 73.9%-89.7%)). LUS specificity was 64.9% (95%CI 47.5%-80.0%), compared to 54.1% (95%CI 36.9%-70.5%) for CXR. The moderate specificity for LUS was due to sonographic-similar conditions, notably TB in 5.1% of patients. Consolidation size and numbers showed marginal resolution, while LUSS showed more pronounced decreases over time. The baseline LUSS showed limited discriminative ability for predicting mortality (AUC 0.65, 95%CI 0.55-0.75), while follow-up LUSS and changes in LUSS (ΔLUSS) demonstrated higher levels of discrimination (AUC 0.81 (95%CI 0.71-0.89) and 0.89 (95%CI 0.80-0.95), respectively). For each one-point increase in ΔLUSS, the odds of in-hospital mortality went up by 70% (p=0.002). An improved LUSS effectively ruled out mortality (negative predictive value 97.4%).

Conclusion Although LUS is highly sensitive for diagnosing CAP, its specificity in TB-endemic regions warrants further caution. Serial LUS assessments, particularly monitoring LUSS

changes, are valuable for tracking disease progression and prognostication, with increasing LUSS indicating potential clinical deterioration.

Keywords: diagnosis, Lung ultrasound, LUS score, monitoring, mortality, pneumonia, Tuberculosis

Article Summary

Strengths and limitations of this study

- Diagnostic accuracy was validated against comprehensive reference standards, including discharge diagnoses and CT scan results, enhancing the reliability of the findings.
- Blinding between the sonographer and treating physician ensured that ultrasound findings did not influence clinical decisions, improving the objectivity of diagnostic and monitoring results.
- Recorded ultrasound procedures were independently reviewed by a certified expert to assess inter-observer agreement and ensure reproducible ultrasound measurements.
- The applicability of the results to outpatients is uncertain, as the study focused on inpatients whose pneumonic lesions may differ in size and resolution time.

Introduction

Community-acquired pneumonia (CAP) is the leading global infectious disease, presenting significant challenges to public health due to its high hospitalization and mortality rates [1-3]. Effective diagnosis and monitoring are crucial to improve patient outcomes and reduce the healthcare burden. Despite being frequently encountered in both outpatient and inpatient settings, pneumonia diagnosis remains complex. CAP is rarely confirmed through the gold standard of pathology. Instead, the diagnosis relies on concordant evidence of clinical symptoms, microbiological detection, and compatible imaging findings, typically new infiltrates on chest radiographs (CXR) [4]. Despite being a staple for diagnosing CAP for years, CXR may fail to detect or correctly identify pneumonic lesions [5-7].

In recent years, alternative diagnostic tools such as lung ultrasound (LUS) have emerged [8]. Besides the advantages of being radiation-free, bedside-available, and repeatable, studies have shown that LUS offers substantial diagnostic accuracy [9]. Multiple meta-analyses revealed that the LUS sensitivity for diagnosing CAP ranges from 85%-97%, with specificity between 80%-96% [10-18]. However, most of the evidence on LUS diagnostic accuracy for pneumonia was derived from developed countries. There is less emphasis on low-resource settings, where diseases such as tuberculosis (TB) and bronchiectasis can mimic pneumonia sonographically, potentially affecting diagnostic properties [17]. Furthermore, the potential of LUS in monitoring and stratifying CAP patients at risk of clinical deterioration is not well-understood. In this study, we aim to investigate the diagnostic performance of LUS in a developing country. Additionally, we seek to identify which LUS parameters can effectively monitor and prognosticate CAP.

Methods

Study design and setting

This prospective observational study was conducted at the Pulmonary Department of Cho Ray Hospital, the largest tertiary hospital in southern Vietnam, from December 2022 to June 2023. Patients or their legally authorized representatives provided written informed consent before enrollment. Ethical approval for this study was obtained from the Ethical Committee for Biomedical Research (No. 875/HĐĐĐ-DHYD). The study was conducted in accordance with the Declaration of Helsinki.

Patient and public involvement

There were no patients or public involved in the study protocol.

Participants

Patients aged 18 years or older clinically suspected of having CAP according to the American Thoracic Society criteria [19] were eligible. This included patient presenting with fever, dyspnea, cough, sputum production, and pleuritic chest pain. Patients were excluded if hospitalized for ≥48 hours before enrollment, pregnant or lactating, or tested positive for SARS-CoV-2 via rapid antigen or RT-PCR assays.

Data collection

Eligible patients were systematically identified by a pulmonologist overseeing admissions and recruited consecutively. Enrollment occurred promptly upon admission, after which data were collected and the sonographer was notified to perform the ultrasound within 24 hours of hospitalization. Patient data collected included anthropometric measurements, clinical symptoms, medical history, and laboratory findings. Information on clinical complications, including in-hospital mortality, need for invasive mechanical ventilation, admission to the respiratory intensive care unit (RICU), and discharge status, was also recorded.

An initial LUS was performed by one of two pulmonologists, each with medical sonographer certification and experience in over 50 lung ultrasounds. They were blinded to the patients' medical records. During this period, patients also underwent CXR. A follow-up LUS was performed between day 5 and 8 by the same pulmonologist. This timeframe was chosen based on the assumption that LUS can detect pulmonary changes with sensitivity comparable

to CXR and provide similar benefits [20]. Additionally, Reissig [21] demonstrated that a 5–8 day timeframe effectively detects sonographic changes in pneumonia.

Lung ultrasound procedure

LUS examinations were conducted using a 2-5 MHz curved array transducer of the DP-10 (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). Patients were examined sitting when possible; otherwise, anterior regions were assessed supine and posterior regions recumbent. The procedure assessed 12 lung zones (**Figure 1**) for pleural irregularities, size and number of consolidations, the presence of air bronchograms, number and characteristics of B-lines, and pleural effusion. Consolidation size was measured in one dimension, from the pleural line to the furthest margin. Additionally, the LUS score (LUSS), a semi-quantitative tool for lung aeration ranging from 0 to 3, was assigned to each lung zone [22]. Detailed descriptions are presented in **Figure 2**, and the global LUSS was calculated as the sum of regional scores (range 0 to 36).

The finding of lung consolidation or focal interstitial syndrome (one or multiple zones involved unilaterally) was consistent with a pneumonia diagnosis [23]. In cases where bilateral interstitial syndrome was identified, additional ultrasound features such as irregular and thickened pleura, diminished lung sliding, the nonhomogeneous distribution of B-lines and subpleural consolidations were required to differentiate pneumonia from cardiogenic pulmonary edema [24, 25].

To assess inter-observer reliability, we recorded ultrasound procedures, randomly selected 30 recordings, and sent them to an expert with registered ultrasound certification to review. We then compared the interpretations of the ultrasound videos between the sonographers and the expert.

Chest radiography procedure

Every patient received a posteroanterior CXR (DRX-Ascend System, Carestream, New York, USA) within 24 hours of admission. A board-certified radiologist, blinded to the patient's clinical and LUS findings, independently reviewed these radiographs.

Diagnosis of community-acquired pneumonia

Upon discharge, the final diagnosis was confirmed by a panel of two independent pulmonologists who reviewed the patient's clinical and laboratory findings, radiology, microbiological results, and overall clinical course. The assessors were blinded to the LUS

data. In case of disagreement, a third expert was consulted, with consensus from at least two experts required for the conclusion.

For patients undergoing CT scans, the result served as a secondary reference for assessing LUS diagnostic values. Scans were obtained using 128-slice Optima CT 660 (GE Healthcare, Chicago, IL, USA) and interpreted independently by a board-certified radiologist blinded to prior clinical and imaging data.

Diagnosis of pulmonary tuberculosis

All pneumonia-suspected patients underwent acid-fast bacilli (AFB) staining of at least two sputum samples per the national guideline due to high TB prevalence, supplemented by GeneXpert MTB/RIF and TB culture when indicated. Gastric aspiration or bronchoalveolar lavage for TB workup was performed on a case-by-case basis. Active pulmonary TB diagnosis required compatible symptoms, radiographic findings, and microbiological confirmation (positive AFB stain, GeneXpert MTB/RIF, or *M. tuberculosis* culture). Patients with a history of previous treatment for TB but no active disease were excluded.

Study endpoints

The primary end-point was the diagnostic accuracy of LUS and CXR as index tests compared with the discharge diagnosis. Additional end-points included diagnostic accuracy compared with CT scan results, changes in three LUS parameters (consolidation size, number of consolidations, and LUSS) and their association with in-hospital mortality.

Statistical analysis

A total sample size of 70 and 84 patients was needed to estimate a sensitivity of 85% and specificity of 93% (according to Alzahrani's meta-analysis [17]), with a precision of 10% assuming the prevalence of CAP was 70%. Normality was assessed using histograms and the Shapiro-Wilk test. Non-normal variables were described by medians and interquartile ranges, while normal variables were described by means and standard deviations. Group differences were analyzed with t-tests for normal data and Mann-Whitney U tests for non-normal data. The Wilcoxon Signed-Rank Test assessed LUS parameters over time, while the Chi-Square or Fisher's Exact Test evaluated categorical variable differences.

For diagnostic properties, sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios of LUS and CXR were calculated. McNemar's test was employed to assess statistical differences in sensitivity and specificity between LUS and CXR. The optimal

LUSS cutoff was established using the Youden index. Logistic regression identified associations between mortality and ultrasound parameters but was limited to univariable analysis due to the small number of events. A p-value <0.05 indicated statistical significance. Data were processed using STATA/MP 17.0 software (StataCorp, College Station, TX, USA).

Results

Characteristics of patients suspected of CAP

Between December 2022 and June 2023, 158 patients were enrolled (**Figure 3**). Exclusions for hospitalization ≥48 hours prior to admission, self-discharge, and hospital transfers left 136 patients for final analysis. The mean age was 62 ± 17 years and 72.8% were male. Demographic and clinical characteristics are presented in **Table 1**. Hospital mortality was 13.2%.

CAP was confirmed in 99 patients (72.8%) at discharge. CT scans were conducted in 93 patients, with the median time from admission to scan of 2 [IQR 1-4] days. CAP was confirmed through CT in 72/93 cases (77.4%).

Diagnostic value of LUS and CXR

LUS showed a sensitivity of 96.0% (95%CI 90.0%-99.0%) and specificity of 64.9% (95%CI 47.5%-80.0%), while CXR had a sensitivity of 82.8% (82.8%, 95%CI 73.9%-89.7%) and specificity of 54.1% (95%CI 36.9%-70.5%).

CXR sensitivity was significantly lower than LUS (p=0.002), but specificities did not differ significantly (p=0.103, McNemar's test; **Table 2** and **Supplement Table 1**). Using CT as a secondary reference standard, the performance of LUS showed a sensitivity of 95.8%, comparable to its sensitivity measured against discharge diagnosis as the reference standard. However, specificity was lower at 52.4% (95%CI 29.8-74.3%). Results of LUS and CXR compared to CT scan are shown in **Supplementary Table 2.**

LUS missed lesions not reaching the pleura in two cases, subsequently confirmed by CT scan. In two other false negative cases without CT scans, CAP was confirmed by experts based on clinical signs, elevated inflammatory markers, CXR-detected lesions, and positive responses to antibiotics. On the other hand, LUS incorrectly identified pneumonia in 13 patients due to tuberculosis (n=6), lung cancer (n=2), heart failure (n=2), bronchiectasis (n=1), COPD with fibrosis (n=1), and interstitial lung disease (n=1).

Among 136 patients, *Mycobacterium tuberculosis* was detected in respiratory specimens of 7 individuals (6 false positives and 1 true positive, as the patient had *Pseudomonas aeruginosa* in sputum culture, making it CAP with *M. tuberculosis* co-infection). The 6 tuberculosis cases were older adults (median age 60 [IQR 59–64] years) presenting with a short symptom duration (≤2 weeks). Laboratory tests revealed elevated inflammatory markers: white blood

cell count 13.25 [9.8-15.8] G/L, neutrophil predominance (85.5% [82.5-96.4%]), and elevated CRP (134.7 [115.0-178.1] mg/L), resembling non-TB CAP. CT scans showed consolidations in all 6 patients, with 5 exhibiting abscesses or cavitation; other findings included bronchiectasis, multiple small nodules, and pleural effusion. While LUS detected the consolidations, it could not visualize the cavitary lesions in these patients.

Sonographic characteristics of CAP at baseline and monitoring

The time to perform the LUS was under 10 minutes (median 9 minutes 38 seconds). The inter-rater variability was low, with Cohen's kappa value of 0.89 (p<0.001) for pneumonia diagnosis and 0.85 (p<0.001) for LUSS assessment.

Sonographic characteristics of cases where LUS detected and confirmed CAP upon discharge are detailed in **Supplement Table 3**. In six cases with bilateral interstitial patterns, findings such as irregular and thickened pleura, reduced lung sliding, and subpleural consolidations helped distinguish pneumonia from cardiogenic pulmonary edema. Echocardiography performed in these six cases also confirmed the findings.

Follow-up LUS was performed in 98 out of 136 patients (72.1%), including 75 with pneumonia and 23 without. The median time between admission and the follow-up ultrasound was 5 [5–6] days. At the time of the second ultrasound, 24 patients had been discharged (15 pneumonia patients and 9 non-pneumonia patients), while 10 had died, including 9 with pneumonia. Among those still hospitalized, two pneumonia patients required mechanical ventilation, and six were in RICU (**Supplement Table 4**). In pneumonia patients, follow-up scans showed only a slight reduction in the size and number of consolidations after 5–8 days, whereas the LUSS demonstrated a more significant reduction (**Table 3**).

The prognostic value of lung ultrasound

The association of LUS parameters with in-hospital mortality is detailed in **Table 4**. Consolidation size or count were not associated with mortality risk. The global LUSS was associated with mortality (unadjusted OR=1.09, 95%CI 1.01-1.16, p=0.021). The baseline LUSS had an AUC of 0.65 (95% CI 0.55-0.75), indicating modest discrimination for predicting mortality, with an optimal cut-point of 17 (52.9% sensitivity, 73.1% specificity). At the second evaluation, the LUSS demonstrated an improved discrimination, with an AUC of 0.81 (95%CI 0.71-0.89) and an optimal cut-point of 21 (66.7% sensitivity, 87.9% specificity) and the unadjusted OR was 1.19 (95%CI 1.06–1.34, p=0.004).

All mortality cases had worsening LUSS. Changes in Lung Ultrasound Score (ΔLUSS) over time were also analyzed). Patients whose LUSS increased from the initial to the follow-up examination were more likely to die in the hospital. Specifically, each one-point rise in LUSS between the two scans was associated with a 70% increase in the odds of in-hospital death (OR 1.70, 95%CI 1.22–2.38, p=0.002). ΔLUSS had a predictive AUC of 0.89 (95% CI 0.80-0.95) for in-hospital mortality. Patients with no improvement in monitoring LUS (ΔLUSS≥0) demonstrated a sensitivity of 88.9%, specificity of 57.6%, NPV of 97.4%, and PPV of 22.2% in predicting mortality (**Table 5**).

Discussion

This study confirmed that LUS has a higher sensitivity than CXR for diagnosing community-acquired pneumonia. However, its moderate specificity may be influenced by the difficulty in differentiating pneumonia from other respiratory conditions, particularly tuberculosis. To our knowledge, this is one of the first studies to incorporate lung ultrasound score for monitoring CAP. Our findings indicate that LUSS changes over time may offer preliminary prognostic insights, potentially aiding in the identification of disease progression and mortality risk stratification.

Previous studies have shown that LUS has a high sensitivity for detecting pneumonia [14-17]. Our study aligns with these findings, demonstrating greater sensitivity than CXR. These results reaffirm LUS as a reliable tool for ruling out pneumonia. However, if ultrasound is negative but other pneumonia signs persist, further investigation and close monitoring after antibiotic treatment are necessary for a definitive diagnosis. Despite showing great sensitivity, LUS specificity was lower than in prior reports [14-17] and varied depending on the reference standard used. The lower specificity observed with CT as the standard, compared to a clinical panel combining clinical features and CXR, reflects CT's superior ability to detect detailed pulmonary changes. Studies have also shown that clinical features and CXR frequently lead to misdiagnosis of CAP compared to CT [5]. While LUS is more sensitive than CXR in detecting interstitial abnormalities and consolidations, it shares similar limitations, such as difficulty distinguishing acute from chronic changes and less detailed lung pattern analysis compared to CT. For example, B-lines on LUS may indicate acute infections or chronic fibrotic processes, and hypoechoic lesions may also signify various pathologies, including pneumonia, atelectasis, lung cancer, pulmonary embolism, or nodular scarring.

Our findings indicate that LUS has difficulty in differentiating pneumonia from other respiratory diseases, with TB being the most frequently misdiagnosed. In this study, we classified pulmonary tuberculosis as false positive rather than a type of CAP. This decision was based on the rationale that the diagnosis determines subsequent antibiotic strategies, which differ between the two conditions. While some sonographic findings (e.g., subpleural nodules, pleural effusion, consolidation with fluid collections) may suggest TB, the modality is inherently limited in detecting cavity lesions, which is a consistent radiologic feature in our TB patients, due to air within cavities preventing ultrasound penetration. This is particularly relevant in our setting, which reported the highest number of tuberculosis cases among LUS

studies on CAP. In contrast, previous research, primarily conducted in low-TB-prevalence settings, found no TB cases, while studies in endemic areas such as Liu [26] in China and Amatya [27] in Nepal, reported zero and one case, respectively. Our study's TB prevalence of 6.7% (7/105) notably surpasses the global average of 0.86% reported by a multicenter CAP study, which included non-endemic regions such as Europe (0.97%) and North America (1.02%) [28], while aligning more closely with figures from other high-burden settings, including Hong Kong [29] (8.1%) and the Philippines [30] (9.8%). These findings highlight the diagnostic challenges of LUS for pneumonia in TB-endemic regions, where sonographic presentations of TB and pneumonia often overlap. Clinically, when consolidations (with or without complementary features such as pleural effusion or subpleural nodules) appear alongside a clinical suspicion of TB, further evaluation with CT scans and TB-specific workup is indispensable. Larger, targeted studies are needed to better characterize ultrasound findings in TB.

Besides evaluating the diagnostic properties, our study aimed to observe sonographic changes in CAP over time and assess whether these changes could aid in monitoring and predicting clinical outcomes. We focused on three ultrasound parameters: consolidation size, number of consolidations, and LUSS. Previous studies in both pediatric [28-30] and adult populations [21] suggest disease remission can be observed through the resolution of lesion sizes and numbers. However, our findings indicate that changes in the size and overall number of consolidations during follow-up assessments were relatively small. These marginal changes may not be readily apparent to clinicians, making it less ideal to utilize these parameters for monitoring purposes. The difference in pneumonic lesion resolution between our study and that reported in the adult population by Reissig [21] may stem from variations in measurement methods and sample selection. We used a one-dimensional measure for the largest consolidation, whereas Reissig et al. employed a two-dimensional measure in cm^2. Additionally, for comparisons of lesion size at two time points, our initial assessment only included subjects available for a follow-up ultrasound, in contrast to Reissig's approach, which involved measuring pneumonic size in all patients, regardless of follow-up availability [21].

The LUSS has recently emerged as a useful tool for assessing severity and the baseline score is closely related to adverse outcomes in COVID-19 patients [31]. Our analysis showed that the baseline score has limited predictive value for in-hospital mortality. Instead, the dynamic changes in the LUSS during follow-up may offer a more reliable indication of mortality. Hypothetically, since the Lung Ultrasound score incorporates both consolidation and

interstitial components, and considering that changes in consolidation measurements were small, it is possible that changes in the interstitial pattern occur earlier and are more predictive of the clinical course of CAP than consolidative changes. From the clinical practice perspective, LUSS progression should alert physicians about a deteriorating clinical course. A ΔLUSS cut-off of 0 is clinically applicable as it allows for the simple categorization of patients into groups with improved or unimproved LUSS over time. Patients with no improvement in monitoring LUS (ΔLUSS ≥0) demonstrated a sensitivity of 88.9%, specificity of 57.6%, NPV of 97.4%, and PPV of 22.2% in predicting mortality. The high sensitivity and NPV suggest that a ΔLUSS≥0 is effective in identifying patients at risk of mortality, the moderate specificity and PPV indicate that ΔLUSS should be used in conjunction with other clinical indicators. Utilizing LUSS for stratification may lead to a more efficient allocation of medical resources, ensuring that attention and care are prioritized for patients with a higher risk of mortality. Timely interventions, such as escalating antibiotics, advanced imaging, microbiology workup, may prevent progression to critical illness and ultimately reduce mortality. However, as our observations are based on a limited sample size, further studies on sonographic pneumonic lesion evolution and their impact on clinical outcomes are needed to validate these findings.

This study has several limitations. First, due to ethical reasons, CT scan was not performed on all patients, leaving the possibility of missing or misidentifying pneumonic lesions. However, in those who did receive a CT scan, the performance of LUS was found to be to be comparable to both discharge diagnosis and CT imaging, indicating the former's reliability. Second, the consolidation size was recorded in a single dimension, which does not fully capture the lesion's three-dimensional volume. However, measurements in one dimension have been shown to effectively represent overall lesion volume [29]. Third, as the study focused on inpatients, its findings may not extend to outpatients, who often have smaller, more rapidly resolving lesions. Additionally, some patients were discharged before the second ultrasound, potentially skewing follow-up data away from those with milder disease. However, similar to CXR, follow-up ultrasounds may be unnecessary for patients showing early recovery, as their clinical symptoms suggest resolution without additional imaging. For patients who died early before the second ultrasound, it is plausible they had more progressive lesions, potentially amplifying our findings. Fourth, while some clinical data (e.g., mechanical ventilation and RICU admission) were recorded at the time of the second LUS, other dynamic parameters such as trends in vital signs, oxygen therapy escalation, lactate levels, or renal function were not captured. Incorporating these variables could provide a more comprehensive prognostic

assessment, as the absence of such data renders the prognostic value of LUSS less certain. For example, in patients with clear signs of deterioration, conducting an intensive LUS protocol may offer limited benefit, whereas follow-up LUS could be more valuable for those with uncertain trajectories. Future research should explore integrating LUSS with dynamic clinical data to improve risk stratification. Finally, ultrasound is an operator-dependent tool, and its interpretation is subjective to sonographer's experience. Nevertheless, our study demonstrated high reliability between performers.

Conclusion

LUS serves as a non-invasive, rapid, and bedside-accessible modality with high sensitivity for detecting CAP. However, the sonographic similarities between pneumonia and other respiratory conditions, such as TB, particularly endemic region, require careful interpretation and consideration of the clinical scenario, as well as further workup, to ensure accurate diagnosis. Monitoring with LUS revealed that consolidation size and total lesion resolved slowly. In contrast, changes in the LUSS were more notable. An increasing LUSS was strongly predictive of in-hospital mortality, making it a valuable tool for monitoring disease progression and stratifying patients at risk.

Abbreviation

AFB: acid-fast bacilli

AUC: Area Under the Curve

CAP: Community-Acquired Pneumonia

COPD: Chronic Obstructive Pulmonary Disease

CT: Computed Tomography

CXR: Chest X-Ray

ΔLUSS: Change in Lung Ultrasound Score

LUS: Lung Ultrasound

LUSS: Lung Ultrasound Score

NPV: Negative Predictive Value

OR: Odds Ratio

PPV: Positive Predictive Value

RICU: Respiratory Intensive Care Unit

RT-PCR: Reverse Transcription Polymerase Chain Reaction

TB: Tuberculosis

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Author contributions

QKTL, NVH, and VLT conceptualized the study and designed the data collection instruments with input from TTT, KND, NTN, PTHN, and LP. Lung ultrasound training and support were provided by LP. QKTL and TTT coordinated and supervised data collection at the study sites, with KND and NTN supervising their respective sites. Data acquisition and management were carried out by QKTL, NDM, LNH, and NTN. QKTL, TTT, and PTHN analyzed and interpreted the data. QKTL and TTT wrote the manuscript with critical input from LP and VLT. All authors

collaboratively reviewed and approved the final manuscript. Quoc-Khanh Tran-Le is the guarantor of the study.

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Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable

Ethics approval

Ethical approval for this study was obtained from the Ethical Committee for Biomedical Research (No. 875/HĐĐĐ-DHYD). The study was conducted in accordance with the Declaration of Helsinki.

Data statement

Please send any requests for access to the datasets to khanhtlq@ump.edu.vn

References

1. World Health Organization. Disease burden and mortality estimates, 2000 - 2016. https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html. Date last updated: December 9 2020. Date last accessed: January 25 2023.
2. Ferreira-Coimbra J, Sarda C, Rello J. Burden of Community-Acquired Pneumonia and Unmet Clinical Needs. Advances in therapy. 2020;37(4):1302-18.
3. Almirall J, Serra-Prat M, Bolíbar I, *et al.* Risk Factors for Community-Acquired Pneumonia in Adults: A Systematic Review of Observational Studies. Respiration; international review of thoracic diseases. 2017;94(3):299-311.
4. Waterer G. What is pneumonia? Breathe (Sheffield, England). 2021;17(3):210087.
5. Claessens YE, Debray MP, Tubach F, *et al.* Early Chest Computed Tomography Scan to Assist Diagnosis and Guide Treatment Decision for Suspected Community-acquired Pneumonia. American journal of respiratory and critical care medicine. 2015;192(8):974-82.
6. Self WH, Courtney DM, McNaughton CD, *et al.* High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. The American journal of emergency medicine. 2013;31(2):401-5.
7. Upchurch CP, Grijalva CG, Wunderink RG, *et al.* Community-Acquired Pneumonia Visualized on CT Scans but Not Chest Radiographs: Pathogens, Severity, and Clinical Outcomes. Chest. 2018;153(3):601-10.
8. Jones BP, Tay ET, Elikashvili I, *et al.* Feasibility and Safety of Substituting Lung Ultrasonography for Chest Radiography When Diagnosing Pneumonia in Children: A Randomized Controlled Trial. Chest. 2016;150(1):131-8.
9. Mathis G. Pneumonia. In: Laursen CB RN, Volpicelli G, eds. Thoracic Ultrasound (ERS Monograph). Sheffield: European Respiratory Society; 2018. pp. 87–101.
10. Chavez MA, Shams N, Ellington LE, *et al.* Lung ultrasound for the diagnosis of pneumonia in adults: a systematic review and meta-analysis. Respiratory research. 2014;15(1):50.
11. Hu QJ, Shen YC, Jia LQ, *et al.* Diagnostic performance of lung ultrasound in the diagnosis of pneumonia: a bivariate meta-analysis. International journal of clinical and experimental medicine. 2014;7(1):115-21.
12. Ye X, Xiao H, Chen B, *et al.* Accuracy of Lung Ultrasonography versus Chest Radiography for the Diagnosis of Adult Community-Acquired Pneumonia: Review of the Literature and Meta-Analysis. PloS one. 2015;10(6):e0130066.
13. Berlet T. Thoracic ultrasound for the diagnosis of pneumonia in adults: a meta-analysis. Respiratory research. 2015;16(1):89.
14. Xia Y, Ying Y, Wang S, *et al.* Effectiveness of lung ultrasonography for diagnosis of pneumonia in adults: a systematic review and meta-analysis. Journal of thoracic disease. 2016;8(10):2822-31.
15. Llamas-Álvarez AM, Tenza-Lozano EM, Latour-Pérez J. Accuracy of Lung Ultrasonography in the Diagnosis of Pneumonia in Adults: Systematic Review and Meta-Analysis. Chest. 2017;151(2):374-82.
16. Long L, Zhao HT, Zhang ZY, *et al.* Lung ultrasound for the diagnosis of pneumonia in adults: A meta-analysis. Medicine. 2017;96(3):e5713.
17. Alzahrani SA, Al-Salamah MA, Al-Madani WH, *et al.* Systematic review and meta-analysis for the use of ultrasound versus radiology in diagnosing of pneumonia. Critical ultrasound journal. 2017;9(1):6.
18. Orso D, Guglielmo N, Copetti R. Lung ultrasound in diagnosing pneumonia in the emergency department: a systematic review and meta-analysis. European journal of emergency medicine : official journal of the European Society for Emergency Medicine. 2018;25(5):312-21.
19. Niederman MS, Mandell LA, Anzueto A, *et al.* Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. American journal of respiratory and critical care medicine. 2001;163(7):1730-54.

20. Metlay JP, Waterer GW, Long AC*, et al.* Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. American journal of respiratory and critical care medicine. 2019;200(7):e45-e67.
21. Reissig A, Copetti R, Mathis G*, et al.* Lung ultrasound in the diagnosis and follow-up of community-acquired pneumonia: a prospective, multicenter, diagnostic accuracy study. Chest. 2012;142(4):965-72.
22. Via G, Storti E, Gulati G*, et al.* Lung ultrasound in the ICU: from diagnostic instrument to respiratory monitoring tool. Minerva anestesiologica. 2012;78(11):1282-96.
23. Volpicelli G, Elbarbary M, Blaivas M*, et al.* International evidence-based recommendations for point-of-care lung ultrasound. Intensive care medicine. 2012;38(4):577-91.
24. Copetti R, Soldati G, Copetti P. Chest sonography: a useful tool to differentiate acute cardiogenic pulmonary edema from acute respiratory distress syndrome. Cardiovascular ultrasound. 2008;6:16.
25. Soldati G, Demi M. The use of lung ultrasound images for the differential diagnosis of pulmonary and cardiac interstitial pathology. Journal of ultrasound. 2017;20(2):91-6.
26. Liu XL, Lian R, Tao YK*, et al.* Lung ultrasonography: an effective way to diagnose community-acquired pneumonia. Emergency medicine journal : EMJ. 2015;32(6):433-8.
27. Amatya Y, Rupp J, Russell FM*, et al.* Diagnostic use of lung ultrasound compared to chest radiograph for suspected pneumonia in a resource-limited setting. International journal of emergency medicine. 2018;11(1):8.
28. Omran A, Eesai S, Ibrahim M*, et al.* Lung ultrasound in diagnosis and follow up of community acquired pneumonia in infants younger than 1-year old. The clinical respiratory journal. 2018;12(7):2204-11.
29. Urbankowska E, Krenke K, Drobczyński Ł*, et al.* Lung ultrasound in the diagnosis and monitoring of community acquired pneumonia in children. Respiratory medicine. 2015;109(9):1207-12.
30. Berce V, Tomazin M, Gorenjak M*, et al.* The Usefulness of Lung Ultrasound for the Aetiological Diagnosis of Community-Acquired Pneumonia in Children. Scientific reports. 2019;9(1):17957.
31. Song G, Qiao W, Wang X*, et al.* Association of Lung Ultrasound Score with Mortality and Severity of COVID-19: A Meta-Analysis and Trial Sequential Analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2021;108:603-9.

Table 1. Demographic and clinical characteristics of patients with and without pneumonia

	Overall (n=136)	Patients with pneumonia (n=99)	Patients without pneumonia (n=37)
Age, years (M ± SD)	62.35 ± 17.03	61.30 ± 17.83	65.14 ± 14.52
Male sex (n, %)	99 (72.8%)	73 (73.7%)	26 (70.3%)
Symptoms (n, %)			
Fever	68 (50.0)	59 (59.6)	9 (24.3)
Dyspnea	108 (79.4)	79 (79.8)	29 (78.4)
Cough	107 (78.7)	78 (78.8)	29 (78.4)
Purulent expectoration	57 (41.9)	44 (44.4)	13 (35.1)
Chest pain	45 (33.1)	30 (30.3)	15 (40.5)
Risk factors (n, %)			
Nicotine abuse	49 (36.0)	35 (35.4)	14 (37.8)
Alcohol abuse	8 (5.9)	7 (7.1)	1 (2.7)
Comorbidities (n, %)			
Diabetes mellitus	33 (24.3)	26 (26.3)	7 (18.9)
Hypertension	59 (43.4)	42 (42.4)	17 (45.9)
Coronary artery disease	15 (11.0)	9 (9.1)	6 (16.2)
COPD	22 (16.2)	10 (10.1)	12 (32.4)
Asthma	9 (6.6)	3 (3.0)	6 (16.2)
History of tuberculosis	12 (8.8)	10 (10.1)	2 (5.4)
Clinical signs upon admission (n, %)			
Temperature > 37.5°C	22 (16.2)	17 (17.2)	5 (13.5)
Hypoxemia*	94 (69.1)	73 (73.7)	21 (56.8)
MAP < 65 mmHg	7 (5.2)	6 (6.1)	1 (2.7)
Pulse > 100 l/min	57 (41.9)	46 (46.5)	11 (29.7)
Laboratory findings			
White blood cell (G/L) (Median [IQR])	11.37 [8.37 – 16.14]	11.60 [9.10 – 17. 27]	9.60 [7.49 – 14.19]
Neutrophil (G/L) (Median [IQR])	9.50 [6.05 – 14.17]	10.03 [6.90 – 15.78]	6.91 [5.25 – 11.87]
Lymphocyte (G/L) (Median – [IQR])	0.93 [0.62 – 1.51]	0.91 [0.58 – 1.45]	1.26 [0.73 – 2.05]
Neutrophil/Lymphocyte Ratio (Median [IQR])	8.90 [4.38 –19.08]	9.05 [5.14– 20.64]	7.53 [2.14 –13.49]
Hemoglobin (g/L) (M ± SD)	120.76 ± 22.59	118.03 ± 22.62	127.87 ± 20.86
Platelet (G/L) (Median [IQR])	247.0 [188.0– 313.0]	251.5 [179.3 – 316.0]	241.0 [209.0–293.0]
CRP (mg/L) (n=104) (Median [IQR])	95.60 [40.38 – 131.75]	107.20 [59.95 – 137.00]	58.90 [8.60 – 120.90]
Creatinine (mg/dl) (Median [IQR])	0.84 [0.66 – 1.09]	0.83 [0.65 – 1.09]	0.85 [0.70 – 1.10]
BUN (mg/dl) (Median [IQR])	17.00 [12.00 – 22.75]	17.00 [13.00 – 23.00]	16.00 [10.00 – 22.00]
In-hospital outcomes (n,%)			
Ventilation	19 (14.0)	16 (16.2)	3 (8.1)
Shock+	19 (14.0)	18 (18.2)	1 (2.7)
RICU	25 (18.4)	22 (22.2)	3 (8.1)
In-hospital mortality	18 (13.2)	17 (17.2)	1 (2.7)

Length of stay (days) (Median [IQR]	8.0 [6.0 -10.0]	8.0 [6.0 – 11.0]	6.0 [4.0 – 8.0]

* Hypoxemia is defined as either an SpO_2 level below 90% on ambient air or a PaO_2 level below 60 mmHg, as determined by arterial blood gas analysis.
+ Shock is defined as persisting hypotension requiring vasopressors to maintain a mean arterial pressure of ≥65 mmHg.

Table 2. Diagnostic performance of lung ultrasound and chest X-ray with reference to discharge diagnosis and CT scan

Reference test	Discharge diagnosis		CT scan	
	Lung ultrasound	Chest X-ray	Lung ultrasound	Chest X-ray
Sensitivity (%)	96.0 (90.0 – 99.0)	82.8 (73.9 – 89.7)	95.8 (88.3 – 99.1)	77.8 (66.4 – 86.7)
Specificity (%)	64.9 (47.5 – 80.0)	54.1 (36.9 – 70.5)	52.4 (29.8 – 74.3)	42.9 (21.8 – 66.0)
Positive predictive value (%)	88.0 (82.5 – 91.9)	82.8 (77.1 – 87.4)	87.3 (78.0 – 93.8)	82.4 (71.2 – 90.5)
Negative predictive value (%)	85.7 (69.1 – 94.2)	54.1 (41.0 – 66.5)	78.6 (49.2 – 95.3)	36.0 (18.0 – 57.5)
Likelihood ratio (+)	2.73 (1.76 – 5.24)	1.80 (1.26 – 2.59)	2.01 (1.28 – 3.16)	1.36 (0.92 – 2.01)
Likelihood ratio (-)	0.06 (0.02 – 0.17)	0.32 (0.19 – 0.54)	0.08 (0.02 – 0.26)	0.52 (0.27 – 1.00)
Accuracy (%)	87.5 (80.7 – 92.6)	75.0 (66.7 – 82.0)	86.0 (77.3 – 92.3)	69.9 (59.5 – 79.0)
AUC	0.80 (0.72 – 0.88)	0.68 (0.56 – 0.79)	0.74 (0.63 – 0.85)	0.60 (0.48 – 0.72)

Table 3. Comparison of ultrasound findings between initial (LUS 1) and follow-up (LUS 2) assessments

	LUS 1	LUS 2	p
Largest consolidation size (cm) (n=66)	3.68 [2.50 – 6.86]	3.13 [1.64 – 6.27]	0.009
Number of consolidations (n=66)	2 [1 – 3]	2 [1 – 2]	0.017
LUS score (n=75)	13 [9 – 17]	11 [6 – 18]	0.002

Table 4. Association of lung ultrasound parameters with in-hospital outcomes in patients with community-acquired pneumonia

	Mortality	Non-mortality	OR (95% CI)	p
Largest consolidation size (cm) (n=84)	6.24 [3.46 – 7.69]	3.36 [1.72 – 6.86]	1.10 (0.96 – 1.29)	0.174
Number of consolidations (n=84)	2 [1 – 4]	2 [1 – 3]	1.38 (0.99 – 1.94)	0.055
LUS 1 (n=95)	17 [10 – 23]	12 [6 – 17]	1.09 (1.01 – 1.16)	0.021
LUS 2 (n=75)	22 [12 – 24]	10 [5 – 16]	1.19 (1.06 – 1.34)	0.004
Δ LUS (LUS2-LUS1) (n=75)	4 [1 – 6]	-1 [-4 – 0]	1.70 (1.22 – 2.38)	0.002

Table 5. Cutoff points of ΔLUS in predicting in-hospital mortality

Δ LUS cutoff	Sensitivity (%)	Specificity (%)	LR (+)	LR (-)	PPV	NPV
≥ -1	100.0 (63.1 – 100)	45.5 (34.0 – 58.9)	1.83 (1.49 – 2.32)	-	18.2 (8.19 – 32.7)	100 (88.9 – 100)
≥ 0	88.9 (51.8 – 99.7)	57.6 (44.8 - 69.7)	2.10 (1.46 - 3.01)	0.19 (0.03 - 1.24)	22.2 (10.1 – 39.2)	97.4 (86.5 – 99.9)
≥ 1	77.8 (40.0 - 97.2)	86.4 (75.7 – 93.6)	5.70 (2.83 - 11.5)	0.26 (0.08 - 0.88)	43.8 (19.8 - 70.1)	96.6 (88.3 - 99.6)

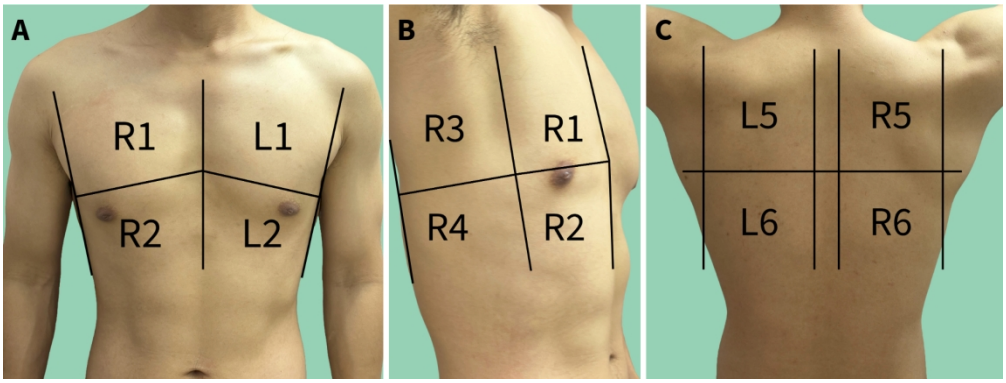
AUC = 0.89 (95% CI 0.80 - 0.95)

Figure legends

Figure 1. Division of 12 lung zones, with six zones allocated to each hemithorax. The zones are divided as follows: each hemithorax is segmented into anterior, lateral, and posterior chest areas, demarcated by the anterior and posterior axillary lines. Each area on either side is further divided into an upper and a lower half: A) Anterior Chest Area: The right hemithorax is divided into an upper zone (R1) and a lower zone (R2); the left hemithorax is divided into an upper zone (L1) and a lower zone (L2). B) Lateral Chest Area (Right Side): Features an upper lateral zone (R3) and a lower lateral zone (R4). The left lateral view is not shown. C) Posterior Chest Area: Illustrates the right upper (R5) and lower (R6) zones, and the left upper (L5) and lower (L6) zones.

Figure 2. **Lung Ultrasound Scores (LUSS) for assessing lung aeration, ranging from 0 to 3**. A) demonstrates LUSS 0, characterized by the presence of A-lines, indicative of normal lung aeration. B) LUSS 1, where there are three or more B-lines per intercostal space, accompanied by irregular or thickened pleura. C) LUSS 2, displaying confluent B-lines, with or without sub-pleural consolidations. D) LUSS 3, featuring large consolidations with a height greater than 1 cm.

Figure 3. Flowchart of patient enrollment and outcomes in the study



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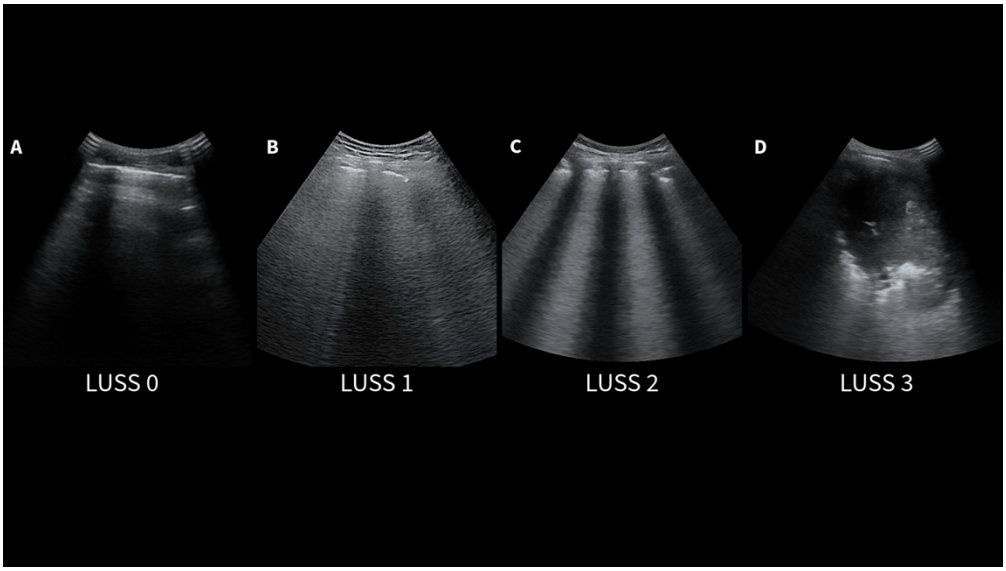
1283x479mm (38 x 38 DPI)



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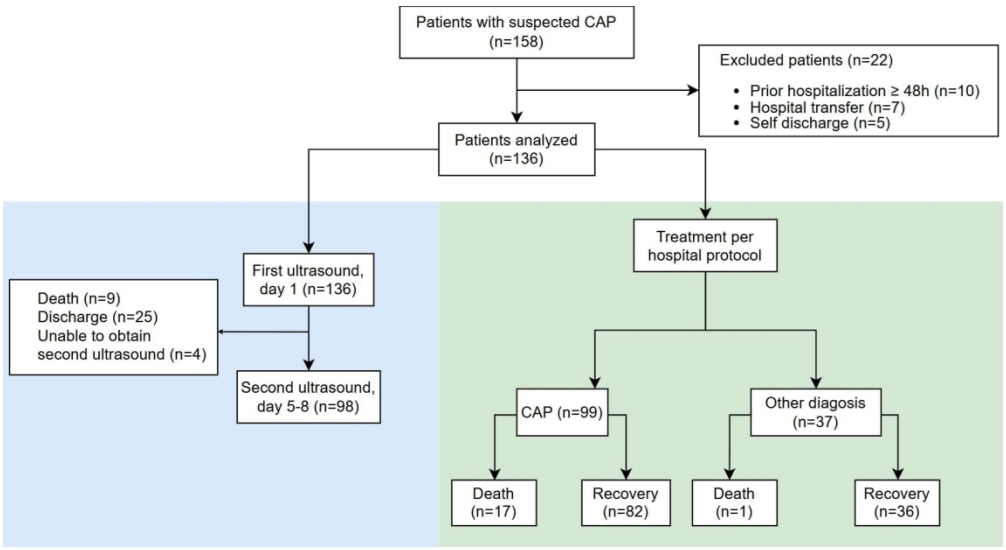
677x381mm (72 x 72 DPI)



Flowchart of patient enrollment and outcomes in the study

596x321mm (72 x 72 DPI)

Supplement table 1. Results of lung ultrasound and chest X-ray compare to confirm CAP cases at discharge

	Pneumonia (n= 99)	No pneumonia (n=37)
Lung ultrasound		
Positive	95	13
Negative	4	24
Chest X-ray		
Positive	82	17
Negative	17	20

Supplement table 2. Results of lung ultrasound and chest X-ray compare to CT scan

	CT positive (n= 72)	CT negative (n = 21)
Lung ultrasound		
Positive	69	10
Negative	3	11
Chest X-ray		
Positive	56	12
Negative	16	9

Supplement Table 3. Ultrasound findings in confirmed CAP case with positive LUS (n=95)

	n (%)
Consolidation + / – interstitial syndrome	84 (88.4)
On left side only	11 (13.1)
On right side only	21 (25.0)
On both side	52 (61.9)
Number of consolidations	2 [1 – 3]
Largest consolidation size (cm)	3.67 [2.14 – 6.92]
Air bronchogram	56 (66.7)
Dynamic air bronchogram	46 (54.8)
Static air bronchogram	10 (11.9)
Interstitial syndrome	11 (11.6)
Focal	5 (45.4)
Bilateral	6 (54.6)
Pleural effusion	48 (50.5)
On left side only	9 (9.5)
On right side only	18 (18.9)
On both side	21 (22.1)
LUS score	12 [8-18]

Supplement table 4. Clinical status of patients at the time of first and second ultrasounds and at discharge

	At 1st ultrasound	At 2nd ultrasound	At discharge
Ventilation, n (%)	0/95 (0%)	2/75 (2.7%)	9/75 (12.0%)
RICU admission, n (%)	0/95 (0%)	6/75 (8.0%)	14/75 (18
Shock, n (%)	2/95 (2.0%)	7/75 (9.3%)	12/75 (16