Lung ultrasound in the diagnosis and follow-up of community-acquired pneumonia. A prospective multicentre diagnostic accuracy study.

(ClinicalTrials.gov Identifier: NCT00808457)

Running head: multicentre study of pneumonia

Angelika Reißig, MD
Roberto Copetti, MD
Gebhard Mathis, MD
Christine Mempel
Andreas Schuler, MD
Peter Zechner, MD
Stefano Aliberti, MD
Rotraud Neumann, MD
Claus Kroegel, MD PhD FCCP
Heike Hoyer, MSc

1 Pneumology & Allergology, Friedrich-Schiller-University Jena, Germany
2 Emergency Department, Latisana General Hospital, Latisana, Italy
3 Medical practice Rankweil, Austria
4 Department of Neurology, Helios Clinic, Erfurt, Germany
5 Department of Internal Medicine, Helfenstein Clinic, Geislingen, Germany
6 Hospital Graz West, Department of Internal Medicine, Austria
7 Clinic of Pneumology, University of Milan, IRCCS Fondazione Policlinico, Italy
8 Institut of Diagnostic and Interventional Radiology, Friedrich-Schiller-University Jena, Germany
9 Institute of Medical Statistics, Information Sciences and Documentation, Friedrich-Schiller-University Jena, Germany
Address for correspondence:
Angelika Reißig, MD, Pneumology & Allergology, Medical Clinic I
Friedrich-Schiller-University, Erlanger Allee 101, D-07740 Jena, Germany
e-mail: angelika.reissig@med.uni-jena.de

Conflict of interest statement: all authors assert no conflicts of interest, financial or otherwise, pertaining to this study.

Keywords: community-acquired pneumonia, lung ultrasound, transthoracic sonography, sensitivity, specificity, follow-up of pneumonia
**Abbreviation list**

CAP: community-acquired pneumonia

CI: confidence interval

COPD: chronic obstructive pulmonary disease

CT: computed tomography

LR: likelihood ratio

LUS: lung ultrasound
Abstract

**Background:** The aim of this prospective multicentre study was to define accuracy of lung ultrasound (LUS) in diagnosing community-acquired pneumonia (CAP).

**Methods:** 362 patients with suspected CAP were enrolled in 14 European centres. At baseline, history, clinical examination, laboratory testing and LUS were performed as well as the reference test: X-ray in two planes or low-dose CT in case of inconclusive/negative X-ray but positive LUS. In patients with CAP, follow-up between day 5-8 and 13-16 was scheduled.

**Results:** CAP was confirmed in 229 patients (63.3%). LUS revealed a sensitivity of 93.4% with 95% confidence interval of [89.2%, 96.3%], a specificity of 97.7% [93.4%, 99.6%], and likelihood ratios (LR) of 40.5 [13.2, 123.9] for positive and 0.07 [0.04, 0.11] for negative results. A combination of auscultation and LUS increased positive LR ratio to 42.9 [10.8, 170.0] and decreased negative LR to 0.04 [0.02, 0.09].

97.6% (205/210) of patients with CAP showed breath-dependant motion of infiltrates, 86.7% (183/211) an air bronchogram, 76.5% (156/204) blurred margins, 54.4% (105/193) a basal pleural effusion. During follow-up, median C-reactive protein decreased from 137 to 6.3 mg/dl at day 13-16 as well as signs of CAP: median area of lesions decreased from 15.3 to 0.2 cm², pleural effusion from 50 to 0 ml.

**Conclusions:** LUS is a non-invasive, usually available tool for diagnosing CAP with high accuracy. This is especially important if X-ray is not available or not applicable. About 8% of pneumonic lesions are not detectable by LUS. Therefore, an inconspicuous LUS does not exclude pneumonia.

**ClinicalTrials.gov Identifier:** NCT00808457


Introduction

Community-acquired pneumonia (CAP) is the most common disease recorded worldwide, and 2-3 million cases are diagnosed annually in the United States. In an appropriate clinical setting, diagnosis of pneumonia is established in case of a new infiltrate on chest X-ray. However, due to the methodological limitations of X-ray, computed tomography (CT) is regarded as “gold standard”, allowing a diagnosis of pneumonia earlier and with a higher sensitivity and specificity [1]. Limitations of CT include radiation dose, higher costs and reduced availability [2].

Lung ultrasound (LUS) represents a new technique for diagnosing pleural and pulmonary diseases [3-9]. The primary objective of this study was to determine the accuracy of LUS in diagnosing CAP compared to chest X-ray in two planes and, in case of equivocal or negative X-ray but positive LUS results, to low-dose CT. Secondly, the appropriateness of LUS for CAP follow-up was explored.

Methods

This was an international, multicentre, prospective, observational study in patients with suspected CAP in 14 European centres (two University hospitals, seven hospitals of internal medicine, one of pulmonary medicine, two practices and two emergency departments).

The institutional review board approved the study protocol (number 2055-06/07) and patients provided written, informed consent before enrolment. This study is registered at ClinicalTrials.gov, NCT00808457, and is reported according to the STARD statement [10].

Patients

Patients with clinically suspected CAP were enrolled in the study. Suspicion of CAP was raised clinically (fever > 38.0°C, cough, purulent expectoration, dyspnea) and/or on the basis of typical auscultation findings (rales or bronchial breath sounds).
Patient history regarding comorbidity/risk factors was documented on day 0. Clinical symptoms of pneumonia were assessed on day 0, between day 5-8 and day 13-16. Clinical examination at the same time points was focused on auscultation. Laboratory testing included C-reactive protein and leucocytes on day 0 and between day 13-16.

Inclusion criteria were patients with suspected CAP who are able to undergo chest X-ray in two planes as well as age over 18 years. Exclusion criteria involved prior systemic antibiotic therapy, hospital-acquired pneumonia and/or severe immunosuppression, more than 24 hours between LUS and X-ray/low-dose CT, X-ray findings known to the sonographer, pregnancy and/or lactation.

**Lung ultrasound**

Lung ultrasound was performed first. Patients in whom a chest X-ray had already been performed at the time of the ultrasound investigation could be enrolled, if LUS was performed within 24 hours after X-ray and if the X-ray findings were neither available nor known to the sonographer.

Sonography was conducted using a 5 or 3.5 MHz convex scanner, respectively, while examination by a 7.5 MHz linear scanner was occasionally performed. Patients were examined posteriorly in a seated and anteriorly in a supine position. A systematic examination of all intercostal spaces was performed by experienced physicians who have done at least 100 chest ultrasounds.

Sonography was assessed for the number, location, shape, size, and breath-dependant movement of pneumonia. Furthermore, the incidence of necrotic areas, positive air bronchogram, fluid bronchogram, as well as local and/or basal pleural effusion was reviewed on day 0, between day 5-8 and between day 13-16.
Chest radiography

All patients underwent postero-anterior and lateral chest radiography on day 0 and if possible between days 13 to 16. X-rays were analysed by independent experts in chest radiology unaware of LUS results.

Computed tomography

In the case of inconclusive X-ray or in the case of positive sonography and negative X-ray, a low-dose CT was performed without contrast medium, using 120 kV, 20 to 40 mA and a reconstructed layer thickness of 4 mm (multi-slice CT; effective radiation dose in the range of 0.4 mSv) or 120 kV, 50 mA and a reconstructed layer thickness of 5 mm (one-line CT; effective radiation dose in the range of 1.2 mSv). If other diagnoses are suspected, a spiral/multi-slice CT with contrast agent could be performed. CTs were analysed by experts in chest radiology unaware of the sonographic and X-ray results.

Statistical analysis

The primary objective was to estimate the diagnostic accuracy of LUS as index test (positive/negative/equivocal) compared to X-ray on two planes followed by CT in case of inconclusive or negative X-ray but positive ultrasound as the reference test (negative/positive). A total sample size of 300 patients was considered as necessary and feasible to estimate a sensitivity of 80% with a precision (half of the 95% confidence interval (CI)) of 5.1% if the prevalence of CAP was 80%. According to the study protocol sensitivity, specificity and likelihood ratios (LR) were estimated excluding equivocal LUS results (primary analysis). All three test categories were included in an analysis of robustness. Exact 95% CI were calculated for sensitivity and specificity assuming a binomial distribution. Asymptotic CIs were computed
for LR [18]. Baseline characteristics, clinical, sonographic and laboratory data were displayed by adequate descriptive statistics. Agreement of LUS and X-ray diagnoses was assessed by the kappa coefficient. Bland-Altman plots were constructed to compare the extension of pneumonic lesions measured by LUS and X-ray. Data were analysed using SAS (version 9.2; SAS Institute, Cary, NC).

Results

Between November 2007 and February 2011, fourteen European centres recruited 397 patients. Thirty-five patients had to be excluded due to violations of inclusion criteria (n=3) or an equivocal reference test (n=32) (Figure 1). The remaining 362 patients underwent LUS and X-ray examinations. Sixty-three (17.4%) patients had low-dose CT, 46 of them according to the study protocol. In the remaining 17 patients, X-ray diagnoses were confirmed by a spiral CT which was performed additionally to exclude other differential diagnoses (Figure 1). Finally, CAP was confirmed by the reference test in 229 (63.3%) of 362 patients. The proportion of CAP by centre varied between 26.7% and 100%. Follow-up-examinations were carried out on patients with sonographically detected CAP between day 5 and 8 (n=164) and day 13 and 16 (n=137) (Figure 1).

Baseline characteristics of the patients

The patients had a median age of 63.8 (range 19-95) years and male gender was slightly overbalanced (63.0%). Ninety-five percent were inpatients. The baseline characteristics of the patients are shown in Table 1.

Diagnostic accuracy of lung ultrasound
At baseline, CAP was diagnosed by LUS in 214 (59.1%) patients, 142 (39.2%) patients had negative, and 6 (1.7%) had equivocal findings (Figure 1, Table 2). Excluding patients with equivocal results, pneumonia was correctly diagnosed by LUS in 211 out of 226 patients with confirmed CAP, resulting in a sensitivity of 93.4% with 95% CI of [89.2%, 96.3%]. No signs of pneumonia were found in 127 out of 130 patients without CAP, resulting in a specificity of 97.7% [89.2%, 96.3%]. The LR for negative and positive LUS findings were 0.07 [0.04, 0.11] and 40.46 [12.21, 123.87], respectively. For the exploration of robustness, patients with equivocal LUS were included in the calculation as a third category. Sensitivity and specificity were marginally reduced to 92.1% [87.8%, 95.3%] and 95.5% [90.4%, 98.4%].

Auscultation typical for CAP was 3.2 times more likely in patients with than without CAP (Table 1). A combination of auscultation and LUS increased the positive LR to 42.9, 95% CI [10.8, 170.0] and decreased the negative LR to 0.04 [0.02, 0.09].

In comparison to LUS, X-ray alone revealed 199 (55.0%) positive, 138 (38.1) negative and 25 (6.9%) equivocal findings (Table 2). In patients with unequivocal X-ray results, pneumonia was correctly diagnosed by X-ray in 199 (92.6%) of 215 CAP patients and correctly ruled out in 122 (100%) patients. Since X-ray was a part of the final diagnosis, these figures should not be interpreted as sensitivity and specificity. However, comparing LUS to X-ray, 26 cases of LUS-detected CAP were missed or equivocal by X-ray, whereas X-ray detected 14 cases of CAP which were missed by LUS.

**Sonomorphology of CAP at baseline and during follow-up**

Patients with sonographically detected and confirmed pneumonia (n=211) showed consolidations, most frequently on the right side (45.5%), and in 15.2% on both sides of the lung (Table 3). 22.6% of the patients had more than one lesion at baseline. The shape of the lesions
was mostly polygonal (51.2%) or oval (46.3%) with blurred margins (76.5%). Median surface extension of the lesions at baseline in cm (interquartile range) was 3.2 (1.7-5.0) and depth 3.7 (2.2-5.7). Nearly all consolidations revealed breath-dependant motion (97.6%) and 86.7% had an air bronchogram (Figure 2), whereas only 8.1% showed a fluid bronchogram. A basal pleural effusion was evident in 54.4% at baseline with a median volume of 50 ml. During follow-up, the median number of symptoms per patient reduced from three to one, median C-reactive protein levels declined from 137 mg/dl to 6.3 mg/dl, and leucocyte numbers decreased from 11.7 Gpt/l to 7.4 Gpt/l on day 13-16.

Disease remission could be also demonstrated sonographically. The proportion of patients with air bronchogram decreased from 86.7% to 71.2% (47/66), the area of pneumonic lesions from 15.3 to 6.0 to 0.2 cm² as well as the median volume of pleural effusion from 50 ml to 0 ml on day 13-15 compared to baseline (Table 3). Pneumonic lesions appeared sonographically smaller compared to X-ray. In patients with only one lesion, the measured cranio-caudal and ventro-dorsal extensions differed by 1.1 cm and 1.4 cm on average. Bigger lesions showed a greater difference.

**Concordance between LUS and X-ray during follow-up**

In 112 CAP patients correctly diagnosed by LUS and X-ray at baseline, both examinations were repeated between days 13-16. Concordant results were observed in 85 (75.6%) patients (35 negative, 48 positive, 2 equivocal). Eleven patients were still diagnosed with CAP by LUS but not by X-ray. Vice versa, 9 CAP were detected by X-ray but missed by LUS. Seven patients with equivocal X-ray had negative results for LUS. A kappa of 0.57, 95% CI [0.43, 0.70] was estimated.
Discussion

This is the first prospective multicentre study dealing with lung ultrasound in the diagnosis and follow-up of CAP. These results show an excellent sensitivity of 94% and specificity of 98%, comparable with chest X-ray in two planes. LR above 10 and below 0.01 are considered to rule in or rule out diagnosis in most circumstances [12]. Combining typical auscultation and positive LUS finding was about 43 times more likely in patients with CAP and provides strong evidence to rule in the disease. Double negative findings were 0.04 times less likely in patients with CAP, which may be used to rule out CAP. These figures refer to patients with clear LUS findings. Patients with equivocal results need undergo further diagnostic procedures. This applied to 1.7% of patients after LUS and 6.9% after X-ray. However, comparing X-ray and LUS in diagnosing CAP, it should be mentioned that chest X-ray missed / was inconclusive in about 7% of the cases that were detected by LUS.

In about 8% of patients, CAP may not be detected by LUS, because ultrasound may only detect lesions reaching the pleura. This is in good accordance with two current studies [3,13]. In the first study, six of 82 patients (7%) did not reveal subpleural alterations. In the second study, patients with primarily X-ray confirmed CAP underwent LUS; 28 of 342 patients (8%) had negative LUS and positive X-ray findings [14]. Parlamento et al. [14] found only one patient of 32 (3%) with negative ultrasound and positive X-ray. Nevertheless, in this study, only 66% of the patients underwent X-ray in two planes. Another study in children [15] who underwent X-ray in one plane also showed a high rate of positive LUS. In the present study, CAP was confirmed in about two thirds of patients, as in the study by Parlamento et al. [14].

CAP was characterised by echopoor lesions with breath-dependant motion, evidence of air bronchogram in about 87%, blurred margins in 75% and basal effusion in half of the patients. In
other studies, air bronchogram was detectable in about 70%-97% [3, 13, 16] and a basal effusion was reported in 34%-61% [3, 13-16].

The three false positive LUS results were retrospectively reviewed and confirmed as false positive LUS. A fluid bronchogram was identified in 17 patients only. This sign reflects airways filled with fluid or secretions following airway-obstruction. Differential diagnosis of lung carcinoma should be taken into account in these cases. In only one patient with fluid bronchogram, a lung carcinoma was diagnosed three months later.

Necrotic areas within pneumonic lesions were found in only two patients. These echopoor zones within pneumonic infiltrates reflect microabscesses. One patient with microabscess developed empyema. In the other patient, pneumonia showed a complete recovery under antibiotic therapy.

Comparing size of pneumonic lesions in X-ray and LUS, infiltrates were smaller in LUS because sonography may only detect areas directly contacting the pleura. If the lesion becomes broader in central pulmonary regions, it escapes sonographic detection. This finding is in agreement with a study in clinically and radiologically confirmed pneumonia, where the extension of sonographic lesions seemed to be smaller than seen on X-ray in 53 cases (41%) [16].

Limitations

First, with X-ray in two planes, an imperfect reference test was applied to 83% of patients, probably resulting in an overestimated accuracy of LUS. It is possible that small pneumonic infiltrates may escape detection, because only 17% of patients underwent CT as the approved gold standard. CT was restricted for ethical as well as financial reasons and with respect to radiation exposure to cases with positive LUS and negative/equivocal X-ray. Nevertheless, even in patients with negative LUS and positive X-ray finding, a CT scan would have been preferable.
Second, the study was restricted to untreated patients with suspicion of CAP. Patients suffering from hospital-acquired pneumonia and immunodeficiency were excluded because it is assumed that sonomorphology in these cases may differ. Therefore, these conclusions exclusively refer to CAP.

Third, most of the patients were inpatients suffering from CAP. However, it is assumed that the results are comparable to outpatients.

Fourth, the investigations were performed in a multicentre setting. Participating investigators had done at least 100 chest ultrasounds. Therefore, the results reflect the daily routine practice in experienced hands. Nevertheless, LUS represents a technique with a steep learning curve.

Fifth, in five centres contributing 23 or more patients per centre, the prevalence of CAP varied substantially between 39% and 100%. Therefore, predictive values were not reported for the study. They could be calculated for any prevalence from LR. Furthermore, in centres with small numbers of patients, LUS performed perfectly which in principle would be expected for methods with high accuracy. However, selection bias could not be ruled out. Excluding those centres with perfect LUS diagnoses and small sample sizes, sensitivity changed to 90.8%, 95% CI [85.2, 94.8] and specificity to 97.4% [92.5, 99.5].

Conclusions

- This is the first multicentre feasibility study to demonstrate that CAP may be diagnosed and followed up by LUS.
- The results show an excellent sensitivity and specificity at least comparable with chest X-ray in two planes.
• In cases with sonographic evidence of pneumonia, the diagnosis can be established.

• An X-ray or CT of the chest is necessary in cases with negative ultrasound (in about 8% of the patients), if other differential diagnoses are taken into account, or if complications occur.

• LUS offers several different applications, especially if chest X-ray is not available (in point-of-care ultrasonography, in emergency conditions, on airplanes, in rural regions, in resource limited settings, in developing countries, in pregnant women, and even in a general practitioner practice) and in immobilised patients in whom only an X-ray in one plane may be taken.

• Sonographic diagnosis of pneumonia and LUS follow-up allows for rapid therapeutic decisions.
Study centres and acknowledgements

We confirm that each of the authors has contributed significantly to the paper, regarding:

1. the conception and design or analysis and interpretation of the data
2. the drafting of the article or critical revision for important intellectual content
3. final approval of the version to be published.

That means, all authors contributed to the manuscript regarding literature search, figures, study design, data collection, data analysis and interpretation as well as writing the manuscript.

The authors are indebted to:

Friedrich-Schiller-University Jena, Germany: Sylvia Fischer, Monika Möbius, Ulrike Schumacher, Christine Dietrich
Emergency Department Tolmezzo, Italy: Maurizio Vergendo, Grazia Portale
Helfenstein Clinic Geislingen, Germany: Gerhard Fenk, Florian Groß
Hospital Graz West, Austria: Fritz Flückiger, Herbert Wurzer, Susanne Rienmüller, Gerald Geyer
Clinic of Pneumology, University Milano-Bicocca, Monza, Italy: Andrea Gramegna
Medical practice Rankweil, Austria: Thomas Amann
Hospital Reutlingen, Germany: Alexander Heinzmann, Wolfgang Blank, Bernd Braun
Hospital Stolzalpe, Austria: Antonin Polach, Peter Schmidt, Ernst Deu
St. Hedwig Clinic Berlin, Germany: Jörg Kämmer, Bernd Kissig
Emergency Department, Ospedale Maggiore Policlinico, Milan, Italy: Roberto Cosentini, Andrea Gramegna
Medical practice Dornbirn, Austria: Hubert Bertolini, Markus Ammann
Hospital Sigmaringen, Germany: Martin Mauch
Diakonissen-Hospital Schladming, Austria: Harald Simader, Rudolg Kaiser
Pulmonary Clinic Lostau gGmbH, Germany: Cornelia Schirpke, Kathrin Ludwig
References


Legends

Figure 1: Flow chart.

Figure 2: Patient suffering from pneumonia caused by Mycoplasma pneumoniae. Positive air bronchograms reflecting pneumonia are depicted on day 0 and day 6 (3A, B). X-ray shows infiltration in the right lower lobe on day 0 (3D), and post-pneumonic residua on day 15 (3E), whereas lung ultrasound shows no lesion on day 15 (3C).

Table 1: Baseline characteristics of patients (day 0).

Table 2: Baseline findings for lung ultrasound (LUS) and X-ray by final diagnosis of pneumonia: positive (+), negative (-), equivocal (?) test results. Pneumonia was confirmed by X-ray (+) or in the case of X-ray (?) and X-ray (-)/LUS(+) by computed tomography (+).

Table 3: Clinical, sonographic and laboratory findings/features at baseline and during follow-up in patients with sonographically detected and confirmed pneumonia.
Figure 1: Flow chart.

Patients with suspected CAP
n=397

Excluded patients n=35
- Violation of inclusion criteria (n=3)#
- Equivocal reference test (n=32)*

LUS (day 0)
n=362 (100%)

LUS +
n=214 (59.1%)
- CAP confirmed (true positive) n=211
  - by X-ray+ (n=173)
  - X-ray+/CT- (n=12)
  - X-ray-/CT+ (n=15)
  - X-ray?/CT+ (n=11)
- CAP excluded (false positive) n=3
  - by X-ray-/CT- (n=1)
  - X-ray?-/CT- (n=2)

LUS -
n=142 (39.2%)
- CAP confirmed (false negative) n=15
  - by X-ray+ (n=10)
  - X-ray+/CT+ (n=2)
  - X-ray?/CT+ (n=3)
- CAP excluded (true negative) n=127
  - by X-ray- (n=114)
  - X-ray-/CT- (n=5)
  - X-ray?-/CT- (n=8)

LUS ?
n=6 (1.7%)
- CAP confirmed n=3
  - by X-ray+ (n=1)
  - X-ray+/CT+ (n=1)
  - X-ray-/CT+ (n=1)
- CAP excluded n=3
  - by X-ray- (n=1)
  - X-ray-/CT- (n=1)
  - X-ray?-/CT- (n=1)

LUS follow-up data at day 5-8: n=163

LUS and/or X-ray follow-up data at day 13-16: n=137

CAP: community-acquired pneumonia; LUS: lung ultrasound; CT: computed tomography
#: prior systemic antibiotic therapy (n=2); severe immunosuppression (n=1)
*: indicated CT was not performed (n=11); inconclusive CT (n=10); CT was not performed
within 24 ours (n=4); more than 24 ours between LUS and X-ray (n=2); inconclusive X-ray as
well as inconclusive LUS (n=3); X-ray was performed, but not available (n=1); patient refused
CT (n=1)
Figure 2: Patient suffering from pneumonia caused by Mycoplasma pneumoniae. Positive air bronchograms reflecting pneumonia are depicted on day 0 and day 6 (3A, B). X-ray shows infiltration in the right lower lobe on day 0 (3D), and post-pneumonic residua on day 15 (3E), whereas lung ultrasound shows no lesion on day 15 (3C).

131x133mm (300 x 300 DPI)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with pneumonia</th>
<th>Patients without pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=229)</td>
<td>(N=133)</td>
</tr>
<tr>
<td>Age – yr, median (range)</td>
<td>61.2 (19-91)</td>
<td>65.7 (20-95)</td>
</tr>
<tr>
<td>Male gender</td>
<td>133 (58.1)</td>
<td>95 (71.4)</td>
</tr>
<tr>
<td>Inpatients – no. (%)</td>
<td>222 (96.9)</td>
<td>122 (91.7)</td>
</tr>
<tr>
<td>Symptoms – no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>178/227 (78.4)</td>
<td>61/132 (46.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>207/228 (90.8)</td>
<td>121/133 (91.0)</td>
</tr>
<tr>
<td>Purulent expectoration</td>
<td>119/227 (52.4)</td>
<td>60/133 (45.1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>159/226 (70.4)</td>
<td>101/132 (76.5)</td>
</tr>
<tr>
<td>Thoracic pain</td>
<td>115/212 (54.2)</td>
<td>61/130 (46.9)</td>
</tr>
<tr>
<td>Auscultation typical for CAP</td>
<td>158/222 (71.2)</td>
<td>29/129 (22.5)</td>
</tr>
<tr>
<td>Duration of symptoms – d, median (range)</td>
<td>3 (1-30)</td>
<td>4 (1-28)</td>
</tr>
<tr>
<td>Comorbidity / risk factors - n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>45 (19.7)</td>
<td>61 (45.9)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>5 (2.2)</td>
<td>11 (8.3)</td>
</tr>
<tr>
<td>Bronchial carcinoma</td>
<td>4 (1.7)</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (12.7)</td>
<td>27 (20.3)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>42 (18.3)</td>
<td>39 (29.3)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>17 (7.4)</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Nicotine abuse</td>
<td>84 (36.7)</td>
<td>44 (31.1)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>3 (1.3)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Patients with pneumonia (N=229)</td>
<td>Patients without pneumonia (N=133)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Other risk factors</td>
<td>24 (10.5)</td>
<td>37 (27.8)</td>
</tr>
<tr>
<td>Laboratory findings, median (interquartile range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein – mg/dl,</td>
<td>144 (76.0-229.0)</td>
<td>42.7 (13.7-113.8)</td>
</tr>
<tr>
<td>Leucocytes – Gpt/l</td>
<td>11.7 (8.8-15.2)</td>
<td>9.3 (7.5-12.9)</td>
</tr>
</tbody>
</table>

yr: years; CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease
Table 2: Baseline findings for lung ultrasound (LUS) and X-ray by final diagnosis of pneumonia: Positive (+), negative (-), equivocal (?) test results. Pneumonia was confirmed by X-ray (+) or in case of X-ray (?) and X-ray (-)/LUS(+) by computed tomography (+).

<table>
<thead>
<tr>
<th>No.</th>
<th>Patients with pneumonia</th>
<th>Patients without pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X-ray+</td>
<td>X-ray-</td>
</tr>
<tr>
<td>LUS+</td>
<td>185</td>
<td>15</td>
</tr>
<tr>
<td>LUS-</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>LUS?</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>199</td>
<td>16</td>
</tr>
</tbody>
</table>

LUS: lung ultrasound
Table 3: Clinical, sonographical and laboratory findings / features at baseline and during follow up in patients with sonographically detected and confirmed pneumonia.

<table>
<thead>
<tr>
<th>Clinical, sonographical and laboratory findings</th>
<th>Day 0 (N=211)</th>
<th>Day 5-8 (N=163)</th>
<th>Day 13-16 (N=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of symptoms* per patient, median (range)</td>
<td>3 (1-5)</td>
<td>1 (0-5)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>Auscultation typical for CAP – no./total no. (%)</td>
<td>149/204 (73.0)</td>
<td>71/159 (44.7)</td>
<td>18/133 (13.5)</td>
</tr>
<tr>
<td>Patients with LUS-detected lesions – no./total no. (%)</td>
<td>211/211 (100.0)</td>
<td>131/162 (80.9)</td>
<td>67/133 (50.4)</td>
</tr>
<tr>
<td>Location of pneumonic lesions – no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On right side</td>
<td>96/211 (45.5)</td>
<td>59/131 (45.0)</td>
<td>33/67 (49.2)</td>
</tr>
<tr>
<td>On left side</td>
<td>83/211 (39.3)</td>
<td>54/131 (41.2)</td>
<td>27/67 (40.3)</td>
</tr>
<tr>
<td>On both sides</td>
<td>32/211 (15.2)</td>
<td>18/131 (13.7)</td>
<td>7/67 (10.4)</td>
</tr>
<tr>
<td>Number of pneumonic lesions, median (range)</td>
<td>1 (1-7)</td>
<td>1 (0-3)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>Patients with more than one lesion– no./total no. (%)</td>
<td>50/211 (22.6)</td>
<td>26/131 (19.8)</td>
<td>11/67 (16.4)</td>
</tr>
<tr>
<td>Shape of the largest lesion – no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Round</td>
<td>5/203 (2.5)</td>
<td>4/121 (3.3)</td>
<td>1/61 (1.6)</td>
</tr>
<tr>
<td>Oval</td>
<td>94/203 (46.3)</td>
<td>61/121 (50.4)</td>
<td>34/61 (54.1)</td>
</tr>
<tr>
<td>Polygonal</td>
<td>104/203 (51.2)</td>
<td>56/121 (46.3)</td>
<td>27/61 (44.3)</td>
</tr>
<tr>
<td>Margin of the largest lesion – no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharp</td>
<td>48/204 (23.5)</td>
<td>25/121 (20.7)</td>
<td>11/60 (18.3)</td>
</tr>
<tr>
<td>Blurred</td>
<td>156/204 (76.5)</td>
<td>96/121 (79.3)</td>
<td>49/60 (81.7)</td>
</tr>
<tr>
<td>Total area of pneumonic lesions – cm², median (interquartile range)</td>
<td>15.3</td>
<td>6.0**</td>
<td>0.2**</td>
</tr>
<tr>
<td>Further sonographical features – no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive breath-depending motion</td>
<td>205/210 (97.6)</td>
<td>129/131 (98.5)</td>
<td>65/66 (98.5)</td>
</tr>
<tr>
<td>Clinical, sonographical and laboratory findings</td>
<td>Day 0 (N=211)</td>
<td>Day 5-8 (N=163)</td>
<td>Day 13-16 (N=137)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Echopoor necrotic zones within the lesion</td>
<td>2/209 (1.0)</td>
<td>2/131 (1.5)</td>
<td>0/66 (0.0)</td>
</tr>
<tr>
<td>Positive air bronchogram</td>
<td>183/211 (86.7)</td>
<td>98/130 (75.4)</td>
<td>47/66 (71.2)</td>
</tr>
<tr>
<td>Positive fluid bronchogram</td>
<td>17/211 (8.1)</td>
<td>10/131 (7.6)</td>
<td>4/66 (6.1)</td>
</tr>
<tr>
<td>Evidence of local pleural effusion</td>
<td>89/210 (42.4)</td>
<td>57/153 (37.3)</td>
<td>21/99 (21.2)</td>
</tr>
<tr>
<td>Evidence of basal pleural effusion</td>
<td>105/193 (54.4)</td>
<td>66/149 (44.3)</td>
<td>28/119 (23.5)</td>
</tr>
<tr>
<td>On left side</td>
<td>67/193 (34.7)</td>
<td>44/149 (29.5)</td>
<td>16/119 (13.4)</td>
</tr>
<tr>
<td>On right side</td>
<td>69/191 (36.1)</td>
<td>43/149 (28.9)</td>
<td>17/119 (14.3)</td>
</tr>
<tr>
<td>Amount of basal pleural effusion – ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On left side, median (interquartile range)</td>
<td>50 (30-200)</td>
<td>10 (0-100)**</td>
<td>0 (0-0)**</td>
</tr>
<tr>
<td>On right side, median (interquartile range)</td>
<td>50 (20-150)</td>
<td>10 (0-80)**</td>
<td>0 (0-0)**</td>
</tr>
<tr>
<td>Laboratory findings, median (interquartile range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein – mg/dl,</td>
<td>137 (76-234)</td>
<td>Not done</td>
<td>6.3 (1.9-20.0)</td>
</tr>
<tr>
<td>Leucocytes – Gpt/l</td>
<td>11.7 (9.0-15.1)</td>
<td>Not done</td>
<td>7.4 (6.0-9.0)</td>
</tr>
</tbody>
</table>

* Fever > 38.0 °C, cough, purulent expectoration, dyspnea, thoracic pain

** defined as zero if present at baseline and disappeared during follow-up

# refer to patients with lesions

CAP: community-acquired pneumonia; LUS: lung ultrasound