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Clinical utility of bedside Contrast-Enhanced Ultrasound (CEUS) in the diagnosis of pneumonia in elderly patients: Comparison with clinical, radiological and ultrasound diagnosis

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ABSTRACT

Aims: to measure the clinical impact of contrast-enhanced ultrasound (CEUS) in the diagnosis of community-acquired pneumonia (CAP), compared to clinical, radiological and ultrasound diagnosis.

Methods: 84 patients (47/37 males/females, mean age:78,57±11,7 Y) with clinical suspicion of pneumonia and with ultrasound findings of peripheral lung lesions, were investigated with CEUS for a better characterization. Final diagnosis of 65 cap was obtained with complete disappearance of symptoms and pulmonary nodule(s); 19 neoplasms: 16 patients performed histologically with bronchoscopy; 3 refused (non-invasive diagnosis with basal CT-scan and positron emission tomography (PET) with fluorodeoxyglucose (FDG)). Sensitivity, specificity, overall diagnostic accuracy (ODA) (and corresponding AUROC) of clinical-data (CD), chest X-ray(CXR), Lung-ultrasound(LUS), CEUS were calculated with SPSS 26.0 software.

Results: Final diagnosis: 65 CAP, and 19 chest cancers. 9/65 (13%) patients died, of these 7/9 with older age and heart disease as comorbidity. CD: True-Positive (TP):23, True-negative (TN): 17; False-Positive (FP):2; False-negative (FN):42 (sens:35,4% spec:89,5% ODA10%: PPV:92%, NPV:28,8%) (AUROC±SEauc:0,46±0,076); CXR: TP: 36, TN:14; FP:5, FN:29; (sens: 55,4%; spec: 73,7%; ODA: 32%; PPV:87,5%, NPV:32,66%) (AUROC±SEauc:0,645±0,068). US: TP:59; TN: 14; FP:5, FN:6 (sens: 90,8%, spec: 73,7%, ODA: 84,9%, PPV:92,2%, NPV:70%) (AUROC±SEauc:0,9417±0,024); CEUS: TP: 63; TN: 19; FP:0; FN:2 (sens: 96,9%; spec: 100% ODA: 97,5%; PPV: 100%, NPV:90,5%) (AUROC±SEauc:0,98±0,01).

Conclusions: Clinical-data and chest X-RAYS are insufficient to obtain a correct diagnosis of CAP in elderly population; US demonstrated a good accuracy to establish CAP, but with a relatively low specificity; in these cases, CEUS is able to give a correct characterization, allowing you to save the need for a chest contrast-enhanced-CT (CECT).

Key words: Contrast-Enhanced Ultrasound, Pneumonia, Lung ultrasound, Chest X-ray, diagnostic accuracy, elderly people, bedside contrast-enhanced ultrasound

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Introduction

Community-acquired pneumonia (CAP) refers to the infectious inflammation of lung parenchyma (including alveolar wall, ie, pulmonary interstitium in general meaning) acquired outside of hospitals, including pneumonia caused by pathogens with proven latency, the onset of disease is during the latency after the patient is admitted into hospital [1]

CAP is a major cause of morbidity and mortality both in the USA and globally: CAP had an incidence of 24.8 episodes per 10,000 adults, with the highest incidence in those aged 65 to 79 years (63 cases per 10,000 adults) and 80 years and older (164.3 cases per 10,000 adults) [2]. As the burden of CAP continues to increase due to several factors, the advances in its diagnosis, prevention, and treatment have taken on even greater interest and importance [3].

The clinical symptoms and signs of CAP include cough (with or without sputum production), fever, chills, tachypnoea, tachycardia, pleuritic chest pain, dyspnoea, altered mental status, dehydration, and hemoptysis; clinical findings will include a temperature greater than 37.8°C, heart rate over 100/min, respiratory rate greater than 25/min, oxygen saturations in room air < 90%, rhonchi or focal rales on auscultation of the lungs, decreased breath sounds, and bronchophony [4].

Patient history, physical examination and laboratory tests (Clinical Diagnosis -CD-) are important when diagnosing CAP [5]. However, because clinical manifestations can be nonspecific, a definitive diagnosis of pneumonia requires the presence of new infiltrates on chest x-ray (CXR), together with respiratory symptoms consistent with a lower respiratory infection.

Although it may seem self-evident, an essential question in the management of patients with CAP is whether the diagnosis is in fact correct. CAP can present in variable ways, some of which are similar to other conditions such as acute bronchitis, viral respiratory tract infections and cardiac failure. Older Patients with several comorbidities (Chronic Heart failure, dementia, COPD etc.) who are more likely to develop CAP, may not be able to give a reliable description of symptoms. Patients may present with two or more conditions at once, confusing the diagnostic process [6]. This may occur as a coincidence or alternatively be due to a cause–effect relationship between them. Examples of the latter include that a chest infection can precipitate either an exacerbation of cardiac failure or an acute coronary syndrome [7]. Actually CXR is universally considered "the gold standard" imaging for diagnosis of CAP [5]. Over recent years, studies have reported that there is misdiagnosis of pneumonia because of difficulty interpreting CXR in patients with multiple comorbidities, especially cardiac and pulmonary comorbidities. Misdiagnosis may lead to delayed antimicrobial treatment or overuse of antibiotics [5]. A multicenter study demonstrated that only 43.5% of patients with opacities on CECT had opacities noted on CXR. The sensitivity, specificity, and positive predictive values for chest radiograph were 43.5%, 93.0%, and 26.9%, respectively, indicating that CXR had poor sensitivity and positive predictive values for detecting pulmonary opacities [8]. The role of lung ultrasound (LUS) in the diagnosis of pneumonia is becoming more and more important; two different metanalyses demonstrated high values of sensitivity for detection of pneumonia but a relatively low specificity (from 72 to 86%) [9, 10]. Recently, In a multicenter study, LUS was demonstrated a powerful tool to improve CAP diagnosis in the ED, reducing diagnostic uncertainty from 73% to 14% [11]. In Italian study [12], LUS performed at hospital admission was proven to be useful for ruling in the diagnosis and bacterial etiology of CAP and for ruling out mortality in patients with CAP

Newly, contrast-enhanced US (CEUS) was used (and debated) for diagnosis of pulmonary nodules [13] and also for pneumonia [14, 15]. Actual WFSUMB guidelines [13] refer use of CEUS in patients with a history of pneumonia only if the course is complicated or if CEUS might help to differentiate between potential differential diagnoses.

We prospectively investigated the role of clinics, CXR, ultrasound and CEUS in the diagnosis of CAP in the elderly population(>60 Y [16]) in which clinical presentation of CAP pneumonia is variable and often not typical (in comparison younger people affected by CAP pneumonia) [17] and spiral CT is difficult to perform. Secondary aim was the clinical impact of ceus in characterizing peripheral nodules highlighted by lung ultrasound.

Table 1. Subdivision of pneumonia based on dimensions (row), sex and number (columns)

	Pneumonia							
	Males			Males	Females		Females	Total
Dimensions (Mm)	**1**	**2**	**Multiple**		**1**	**2**		
10-20	4	1		5	2		2	7
20-30	2			2	2		2	4
30-40	10	3	2	15	10	1	11	26
40-50	5	2		7	6		6	13
50-60	2			2	3		3	5
60-100	6			6	4		4	10
Total	**29**	**6**	**2**	**37**	**27**	**1**	**28**	**65**

Materials and Methods

84 patients (47/37 males/females, mean age:78,57±11,7 Y) with clinical suspicion of pneumonia and with ultrasound findings of peripheral lung lesions (but unable to perform chest CECT because of chronic renal failure), were investigated with CEUS for a better characterization. Final diagnosis in 19 patients was lung cancers: 16 patients performed bronchoscopy; 3 refused (non-invasive diagnosis with basal CT-scan, and positron emission tomography (PET) with fluorodeoxyglucose (FDG) [18]); in 65 patients CAP was obtained. 56 consolidations were single, 7 doubles and 2 multiples. Subdivision based on their size is expressed in Table 1.

CD was based on: New onset of cough or expectoration, or aggravation of existing symptoms of respiratory tract diseases, with or without purulent sputum, chest pain, dyspnea, or hemoptysis, Fever, Signs of pulmonary consolidation and/or moist rales; Peripheral white blood cell count (WBC)>10^*10^9/L or <4 3 10^9/L, with or without a left shift [19, 20]; CXR was executed in two projections in the emergency department; ultrasound was performed bed-side when patient entered the Internal Medicine Department; bedside LUS was performed by a single skilled operator (with approximately 30 years of ultrasound experience) during the clinic visit, using a handheld system (CERBERO version 4.0, ATL Milan, Italy). This system is composed by a portable ultrasound probe, comprising a miniconvex probe (abdominal and cardiological), and a linear probe. It uses two types of WiFi and USB wired connection, it works with a mobile app compatible with most iOS, Android and Windows devices; Image transmission is via internal 5G Wi-Fi and no external networks are required. We used the method described by Soldati et al [21] to perform the LUS, with division of the lung in 13 areas subjected to ultrasound exploration. At LUS Pneumonia appears as a hypoechogenic area with poorly defined borders and with the presence of B-lines at the far-field margin. The pleural line is less echogenic in the area affected by lung consolidation and lung sliding is reduced or absent (Figure 1).

Pneumonia can be represented as a consolidation: we can observe small (Figure 2a), big (Figure 2b) or "hepatized" consolidation (Figure 2c) (when the consolidation appears to have the consistency of hepatic parenchyma). In the case of consolidations, branching echogenic structures – representing air bronchograms – are seen in the infected area (Figure 2c). Air bronchograms may show intrinsic dynamic centrifugal movements due to breathing. This finding is called dynamic air bronchogram: it attests bronchial patency and rules out obstructive atelectasis. Multiple lenticular echoes, representing air trapped in the smaller airways, are also frequently observed. Fluid bronchograms (Figure 2d), described in post obstructive pneumonia, are identified as anechoic tubular structures with hyperechoic walls but without color Doppler signals. Fluid bronchograms are frequently observed in pneumonia in children.

Pleural effusion is easily detected on LUS and appears as an anechoic area in the pleural space (Figure 2d,e). A honeycomb organization of fibrin is observed in pleural empyema [23] (Figure 2f).

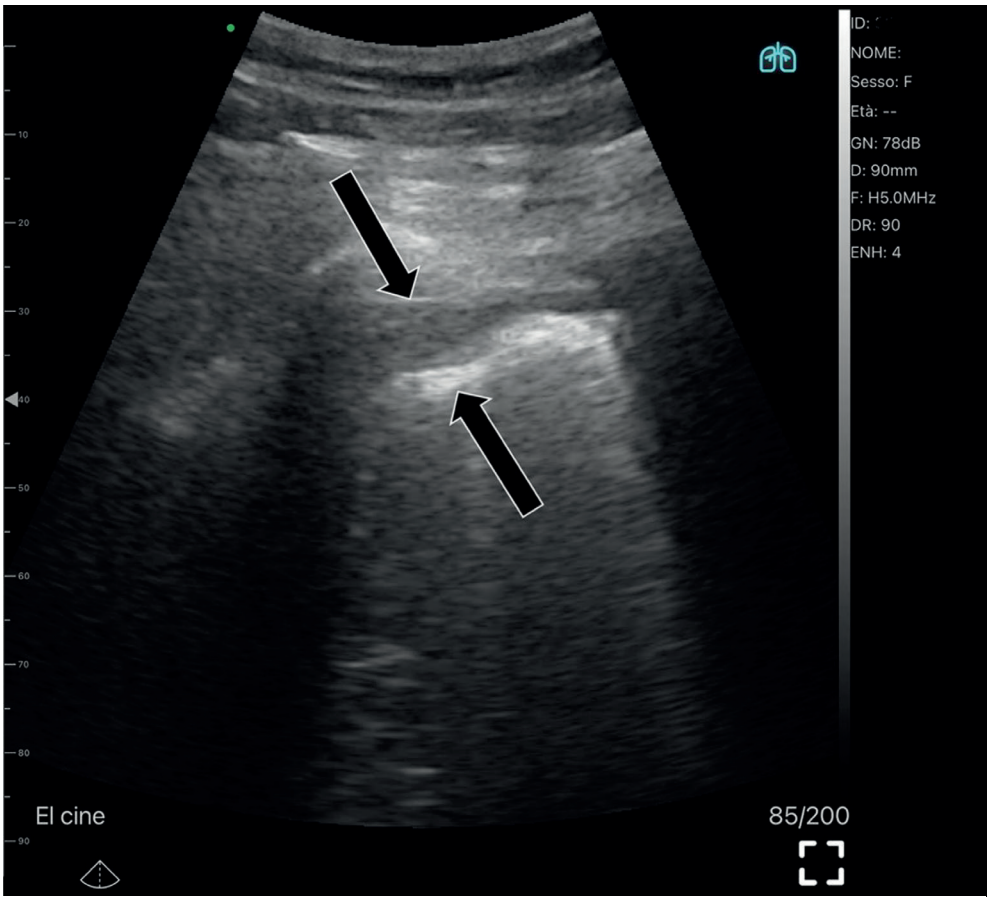

Figure 1. Interstitial Pneumonia: hypoechogenic area with poorly defined borders (arrows) and with the presence of B-lines at the far-field margin; in details, this margin, separating the tissue-like lung consolidation from the normal lung, is fragmented and fuzzy (shred sign) [22].

Pneumonia is characterized by a marked treelike vascularity on color-doppler system (CDS) (Figure 3).

Vessels seen in pneumonia correspond to branches of the pulmonary artery, where, as a result of the hypoxic situation, a different extent of vasoconstriction occurs (Figure 3a and 3b). On CDS, an enhanced Resistive Index (RI) indicates the degree of pulmonary vasoconstriction. Therefore, high RI values in CDS of the pulmonary artery are seen in complete pneumonic lung consolidation (Figure 3c). In contrast, bronchial arteries react to hypoxemia with vasodilatation, similar to the response of systemic arteries. Typically, an arterial monophasic flow profile with low RI values, indicative of bronchial arteries, could also be seen in pneumonia [24]. Sometimes, LUS is not able to distinguish pneumonia from cancer (Figure 4)

CEUS was performed bed-side with portable system, a commercially available ultrasound machine, equipped with Plane wave technology, was used for this study (MINDRAY MX7, Shenzhen Mindray Bio-Medical Electronics Co., China), that works with a new ultrasound technology called zone sonography [25, 26] and based on Plane-Wave Imaging (PWI) [27] with Pixel compounding [28]. Conventional (baseline and contrast-enhanced) ultrasonography is based technically on Delay and Sum (DAS) technique [29]; the DAS technique uses several transmissions of US signals focused in one or more regions to scan the entire area to be analyzed and to form the scan lines that will be used to reconstruct the final image. This process is time-consuming and limits the frame rate to approximately 30 to 40 frames per second. Zone sonography yields

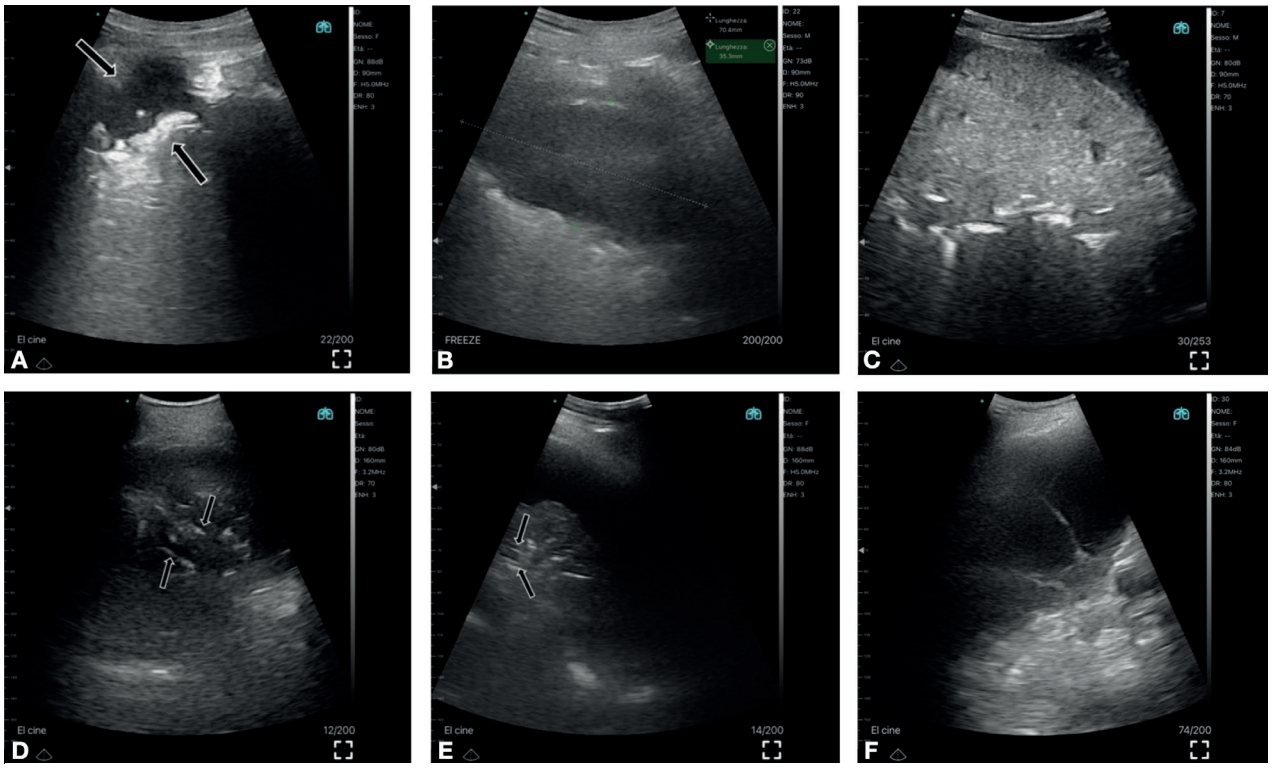

Figure 2. B-MODE typical aspects of Pneumonia at LUS: small (arrows) (a) and big size Consolidation (b); "hepatized" pneumonia (c); Air bronchogram (arrows) (d); liquid bronchogram (e); small, intermediate and big amount of pleural effusion (d, e, f); honeycomb organization, typical of pleural empyema (f)

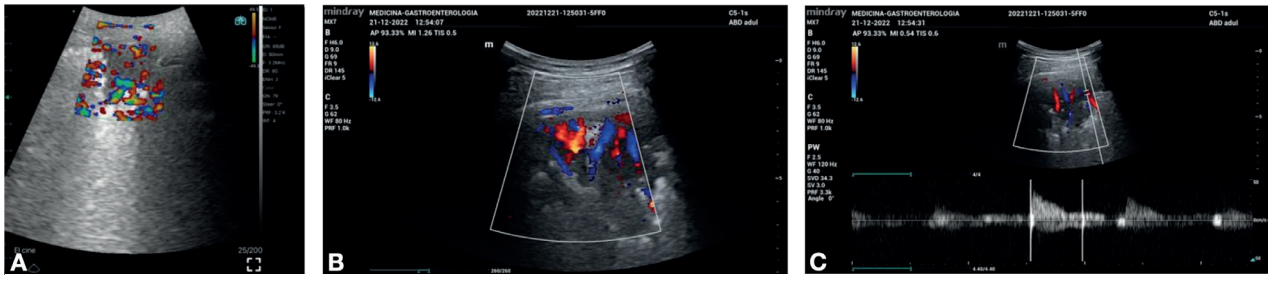

Figure 3. Color- and pulsed-doppler typical aspects of Pneumonia at LUS: small (a) and big size vascularized consolidation (b); High resistive Index (RI) at pulsed doppler examination of arteries inside pneumonia consolidation (c)

framerates as high as several thousands of images per second with a low frame rate (around 10 FPS). The system works with the simultaneous excitation of all available elements in a certain transducer to transmit and collect ultrasonic signals; At first this increase in framerate was obtained at the expense of reduced contrast and resolution. However, this drawback was skillfully addressed by Coherent Plane-Wave Compounding (CPWC) for very high frame rate ultrasonography, which introduced a trade-off between framerate and image quality; coherent plane-wave compounding has many advantages because it provides an image of a full region of interest for each ultrasonic transmission using all array elements [30]. 0.8-1.2 ml of contrast media (SonoVue, Bracco, Italy) was used. CEUS diagnosis of acute pneumonia is determined by early pulmonary arterial (PA) enhancement; marked homogeneous enhancement in all phases without parenchymal washout [13] (Figure 5).

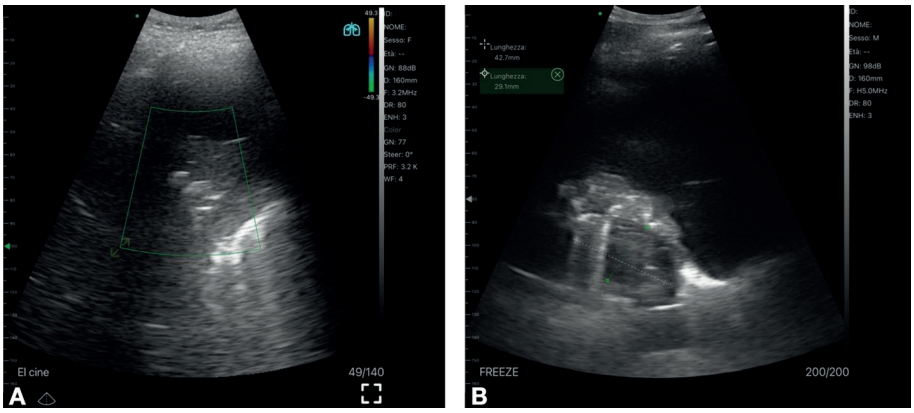

Figure 4. Hypoechoic consolidation in elderly with cough, but no fever; no vascularization at colordoppler examination: final diagnosis was pneumonia (a): hypoechoic consolidation in elderly with cough, but no fever; no vascularization at colordoppler examination: final diagnosis was lung cancer (b).

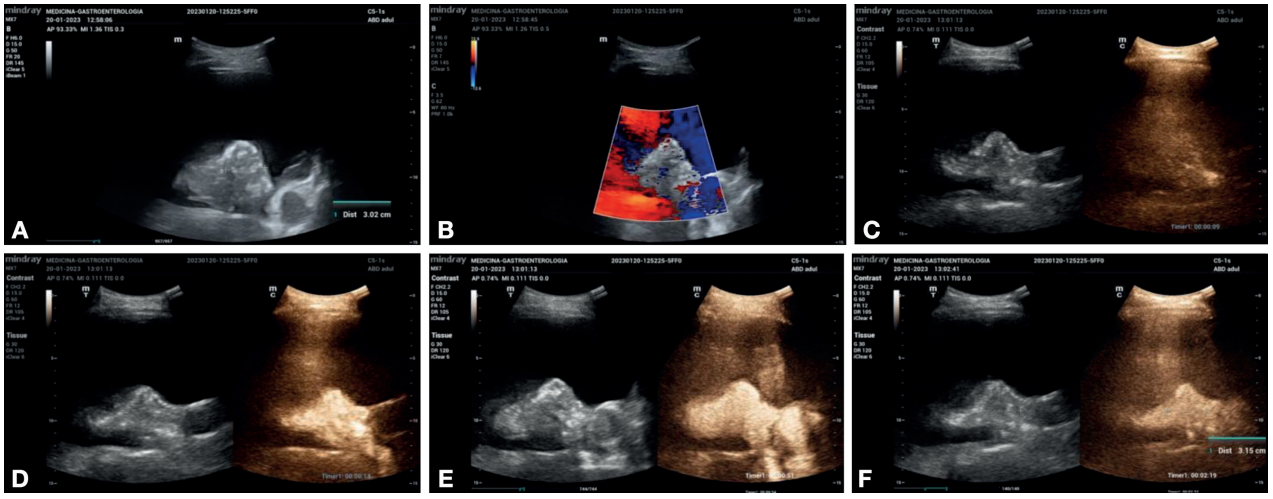

Figure 5. 86 y old male with dyspnea and cough (with history of ischemic heart disease and smoking) CXR negative for pneumonia, but with pleural effusion. LUS demonstrated a small inhomogeneous nodule (a), negative at color-doppler examination (b); CEUS examination demonstrated an early arterial vascularization (c) and subsequent hyper-enhancement (d), with persistent vascularization in portal (e) and late phase (f).

Statistics

we evaluated true positive diagnoses (positive corresponding US- and final- diagnosis), true negative ones (negative corresponding US- and final- diagnosis), False positive ones (positive false US-diagnosis and final negative ones) and false negative ones (negative false US-diagnosis and final positive ones), evaluating sensitivity, specificity, overall diagnostic accuracy (ODA), Positive Predictive Value (PPV), Negative Predictive Value (NPV) [31]. The confidence interval is calculated using the continuity-corrected score method described by Newcombe [32]. Finally, corresponding area under the curve of Receiver Operating Characteristic (AU-ROC) was calculated [33]. Correlations were calculated with X_2, with a significant value when $p<0.005$.

Results

The CD of CAP started as dyspnea and cough in 22/65 (33,8%) patients, fever in 20/65 (30,7%), fever, cough and dyspnea in 14/65 (21,5%), fever and syncope in 7/65 (10,7%), fever, cough and stinging thoracic pain only in 2/65 (3%). Clinical examination had signs of pulmonary consolidation in only 23 patients, while no significant signs were in 42. Laboratory tests had inflammation signs only in 35 pts. 9/65 (13%) patients died, of these 7/9 with older age (86,42±1,61 Y vs 78,46; p<0,001) and heart disease as comorbidity.

CXR had 29/65 (44,6%) false negative diagnoses: percentage of radiological diagnoses depended on the size of the pneumonia and varied from 28.6% to 70% (Table 2). The average radiological diagnosis of CAP in elderly patients in our series was 53.4%

In particular, the average diameter of radiolucent pneumonias was smaller than that of radiopaque pneumonias: 36 mm versus 44 mm (p<0.001). Pneumonia site distribution was greater at the base (49 pts) and at the apex (1 pt) in older people (average: 81.83 years) compared to younger people (average: 69 years), where the main site was the middle field (15 pts) (p<0.001).

US: consolidation in LUS diagnosis of pneumonia was in 56/65 (86.1%). The air/fluid bronchogram was overall present in 30/65 (46.15%) of cases; it increased progressively with increasing size (p<0.05). Arterial vascularization was present only in 29/65 (44.6%) of cases and increased with increasing size (from 25% to 90%) (p<0.001). 28/65 (43%) pneumonia hadn't bronchogram neither vascularization (Table 3).

In 20/29 (70%) radiolucent pneumonias, a bronchogram was absent on LUS. This data was significantly correlated (p<0.005). Pleural effusion was present in 46/65 (70.7%) cases (mean age: 80.93+/- 10.33 years) and was absent in 19 cases (mean age: 74.32+/- 12.71 years). The presence of effusion was directly correlated with older age (p<0.05).

CEUS: The diagnosis of pneumonia included early arterial vascularization (< 6 sec), present in 44/65 patients (67.9%), while in 21 the arterial vascularization was >10 sec because either they had heart disease (14/65, i.e. 21 .5%), or bed rest or cancer (3/65, i.e. 4.6% for each), or COPD (1/65, i.e. 1.5%) In 63 cases the late CEUS vascularization presented contrast's persistence, in 2 cases (final diagnosis: organized pneumonia [34]) there was a wash out, mistakenly diagnosed as a malignant lesion [13] (Figure 6).

Finally, we evaluated the ability of CD, CXR, LUS and CEUS in the characterization of lung consolidations. We therefore evaluated 19 neoplastic lung consolidations as negative: CD diagnosed only 23/65 (35,4%), CXR diagnosed 36/65 patients (55.4%), LUS 59/65 (90,8%) patients; Overall, CEUS allowed diagnosis in 63/65 patients (96.9%) (Table 4).

CEUS arterial vasculature was predominantly homogeneous up to pneumonias of 5-6 cm, then becomes predominantly inhomogeneous (p<0.001). A vascularization on color Doppler was not correlated with death, while a non-homogeneous arterial vascularization on CEUS was predictive of death (p<0.05); Indeed, only 8% of the vasculatures were homogeneous vs 31% of the non-homogeneous ones in died

Table 2. Number of negative and positive pneumonia at chest X-Ray in comparison with consolidation dimensions: bigger was the consolidation and bigger the percentage of X-ray positivity.

	Chest X-ray diagnosis of pneumonia			
Dimensions (mm)	**Negative**	**Positive**	**Total**	**% radiological diagnosis of pneumonia**
10-20	5	2	7	28,57%
20-30	2	2	4	50,00%
30-40	12	14	26	53,85%
40-50	5	8	13	61,54%
50-60	2	3	5	60,00%
60-100	3	7	10	70,00%
Total	**29**	**36**	**65**	55,38%

Table 3. Diameter of pneumonia consolidations in comparison with bronchogram and vascularization at LUS.

Bronchogram, vascularization and us diagnosis of pneumonia										
Dimensions (mm)	**Both Not**	**(%)**	**Bronchogram (Yes)**	**(%)**	**Vascularization (Yes)**	**(%)**	**Both Yes**	**(%)**	**Total**	**Total (%)**
10-20	**4**	6,15%	**1**	1,54%	**2**	3,08%	**0**	0,00%	**7**	**10,77%**
20-30	**2**	3,08%	**0**	0,00%	**1**	1,54%	**1**	1,54%	**4**	**6,15%**
30-40	**16**	24,62%	**2**	3,08%	**3**	4,62%	**5**	7,69%	**26**	**40,00%**
40-50	**5**	7,69%	**2**	3,08%	**0**	0,00%	**6**	9,23%	**13**	**20,00%**
50-60	**1**	1,54%	**0**	0,00%	**0**	0,00%	**4**	6,15%	**5**	**7,69%**
60-100	**0**	0,00%	**3**	4,62%	**1**	1,54%	**6**	9,23%	**10**	**15,38%**
Total	**28**	43,08%	**8**	12,31%	**7**	10,77%	**22**	33,85%	**65**	**100,00%**

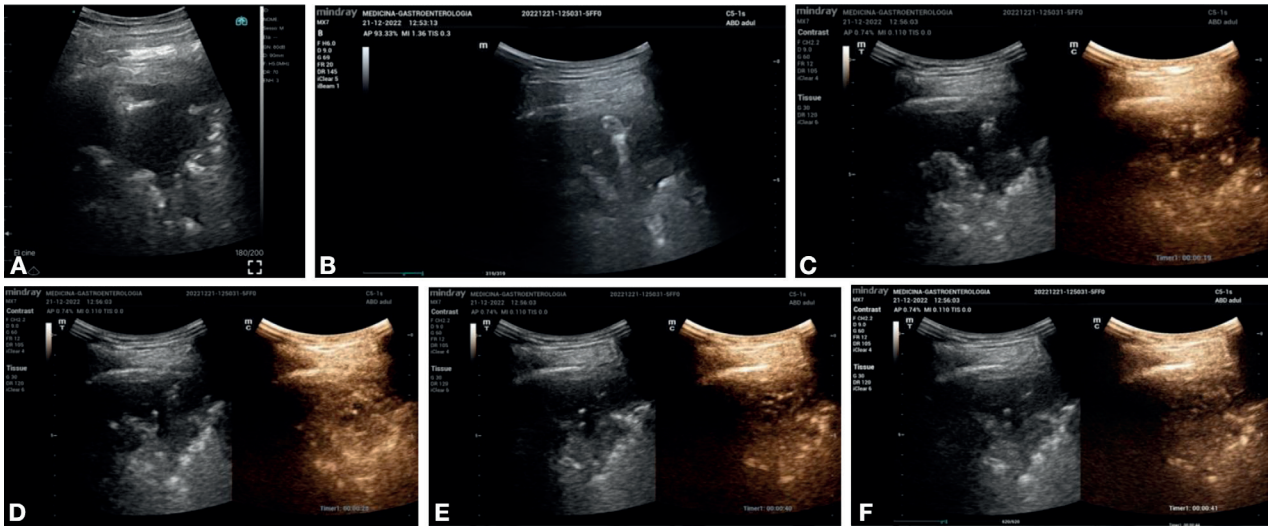

Figure 6. 82 y old male with dyspnea and fever (with history of ischemic heart disease and smoking) CXR negative for pneumonia. Hand-held LUS demonstrated a small inhomogeneous nodule (a), negative at color-doppler examination, for which CEUS was performed at the patient's bedside; conventional ultrasound confirms the lesion (b). CEUS: arterial phase demonstrates initial enhancement after 19 seconds (c), with inhomogeneous vascularization after 28 seconds (d) and weak wash-out in portal (e) and late phase (f). CEUS diagnosis of malignant lesion; after 7 days of intravenous antibiotic therapy the lesion disappeared.

patients. This data can be indirectly explained by the fact that the vascularization is imbalanced especially in larger lesions.

Discussion

The gold standard for diagnosing community-acquired pneumonia should be the identification of a microbiological pathogen isolated directly from the lung tissue. However, such a test (for example, lung puncture or biopsy) is rarely undertaken for the routine diagnosis of community-acquired pneumonia [35]. An alternative gold standard could be based on a combination of clinical symptoms; radiographic, laboratory, and microbiological findings [1]; clinical symptoms were considered inappropriate, and If the clinical setting includes sicker patients and the baseline prevalence of pneumonia is about to 10%, the revised probability of pneumonia ranges from 32% to 60% for

Table 4. True positive (True+), true Negative (True-), False Positive (False+) and False negative (False-) of clinical diagnosis, Chest X-RAY, Ultrasound and CEUS are summarized in this table. The corresponding values of Sensitivity, Specificity, Overall Diagnostic accuracy, Positive Predictive Value and Negative Predictive values are expressed. Finally, AUC ROC curves were calculated.

	True+	True-	False +	False-	Tot	
Clinical D.	23	17	2	42	84	
Chest X-Ray	36	14	5	29	84	
Us	59	14	5	6	84	
Ceus	63	19	0	2	84	
	Sens	**Spec**	**Diagnostic ACC**	**PPV**	**NPV**	**AUC**
Clinical D.	35,4%	89,5%	10%	92%	28,8%	0,46±0,076
Chest X-Ray	55,4%	73,7%	32%	87,5%	32,66%	0,645±0,068
Us	90,8%	73,7%	84,9%	92,2%	70%	0,9417±0,024
Ceus	96,9%	100%	97,5%	100%	90,5%	0,98±0,01

a patient with cough, fever, tachycardia, and crackles [35]. Although chest X-ray is widely recognized as a crucial step in the diagnosis of pneumonia, this technique has several limitations and two recent metanalysis demonstrated a low sensibility (from 54% to 60%) and a low specificity (from 57 to 60%) in the detection of pneumonia [9, 10]. Nowadays, Chest CT scan is considered to be more sensitive than radiography in detecting the presence of lung infiltrates and may also be useful in evaluating other conditions such as empyema, lung cancer, cavitations and multifocal infiltrates [36]. Although CT could be considered the "gold standard" technique in the diagnosis of pneumonia, it cannot be used as a first-line radiological examination in all patients with suspected pneumonia [36]. This is mainly due to the fact that it is often not available, it involves a high radiation dose, requires normal kidney function and it is costly [37]. The increased sensitivity of ultra-low-dose chest CT compared to CXR is of added value in vulnerable and immunocompromised patients [38]. Against, it was demonstrated recently that pulmonary imaging, in patients with suspected infection but no respiratory symptoms or signs, can result in the detection of clinically significant pneumonia [38]. CAP may be diagnosed and followed up by LUS, a technique that shows excellent sensitivity. LUS may be performed with any abdomen-sonography device. Therefore, LUS is a readily available diagnostic tool that does not involve radiation exposure and has wide applications especially in situations where X-ray is not available and/ or not applicable [23, 36]. LUS was useful in predicting a diagnosis of CAP, the bacterial etiology of CAP, and favorable outcome in patients with CAP [12]. Anyway, Two different metanalyses demonstrated high values of sensitivity for detection of pneumonia but a relatively low specificity (from 72 to 86%) for their characterization [9, 10]; also our series demonstrated an high sensitivity but a relatively low specificity (73,7%); in these cases CT of the chest should be performed. This technique, anyway, cannot be technically performed due to the high incidence of renal failure in an elderly population, up to 34% acute kidney failure during pneumonia in a recent study [39]. CEUS was demonstrated useful for diagnosis of pulmonary nodules [8] and also for pneumonia [9, 10]. Typically, CEUS diagnosis is based on arterial and parenchymal hyperenhancement with nearly no decrease of enhancement, but the value of CEUS is based on the reliable visualization of non-perfused areas within the pneumonia in terms of necrosis, abscess and infarction, as well as differentiation between lung consolidation and organized pleural effusion as part of complicated parapneumonic effusion/ pleural empyema [13]. Our experience demonstrated a high diagnostic accuracy, with high values of sensitivity and specificity in doubtful nodules detected by conventional LUS, that in our series (in older people) was high (about 43%). Two patients demonstrated an

atypical vascularization, mimicking a cancer; the nodules were organized Pneumonia. The main result, furthermore, was to perform a microvascularization study at bedside (with a portable us-machine), in a fragile and weak population, such as that of those over eighty, employing a safe and cheap contrast media [40]. Our experience demonstrate that CEUS may be useful in the correct characterization of pneumonia in elderly population, where LUS has no ultrasonographic signs of CAP, without having the need to use a chest CT scan with contrast medium.

The clinical relevance of the use of pulmonary CEUS in people over eighty is evident: it allows the characterization of peripheral nodules that are doubtful on conventional LUS (relatively high percentage in our series), allowing for an early diagnosis and consequent adequate therapy; this method is performed safely, even in cases of renal failure (where spiral CT is not possible) and can also be performed at the patient's bedside, with consequent saving of time and optimization of resources. Pulmonary CEUS does not replace LUS, but can simply complete it in those cases of difficult diagnosis. It is therefore possible to consider adding CEUS to the diagnostic flow chart of CAP pneumonia when the clinical, radiological and ultrasound diagnosis alone are not conclusive. In our experience this happened in 43% of cases, in a very elderly population, with many comorbidities and with the impossibility of performing a contrast-enhanced CT scan. According to the WFSUMB guidelines, recommended uses and applications of CEUS are limited only to peripheral lesions visible on thoracic US[13], so we cannot say that CEUS can replace chest CECT. For the same reason, CEUS cannot also be used as a exhaustive lung staging method, reserved to contrast-enhenced spiral CT.

The main limitations of this publication are the relatively small sample and the single center study: recent experiences (with high sample size) obtained different results about utility of CEUS in the characterization of peripheral lung nodules: Shen [41] obtained that CEUS enhancement mode is different between benign and malignant pulmonary lesions. Using dynamic CEUS (including time intensity curves -TIC-), Quarato et al [42] obtained that dynamic CEUS parameters cannot effectively differentiate between benign and malignant nodules; instead, Li et al [43] demonstrated that CEUS (and TIC) is useful and that CEUS and CECT had similar diagnostic accuracies of 80.16% and 81.75%, respectively. Quarato's experience [42] differs from ours due to the younger age of population (52 vs 78 years) and the use of older ultrasound technology, while Li's one [43] is more similar to ours, due to the older age (60 years) and to a more recent ultrasound system. These two authors also analyzed the various TIC-parameters, in order to "objectify" the various qualitative ultrasound parameters, used in our experience and described by the latest WFUMB guidelines [13].

Conclusion

In conclusions, our paper demonstrated, for the first time, clinical usefulness of CEUS in the characterization of peripheral lung nodules, especially when clinical suspicion is pneumonia in elderly population, where gold standard imaging (CECT) often can't be performed.

Abbreviations:

CAP: Community-acquired pneumonia
US: Ultrasound
CXR: Chest X Ray
CEUS: Contrast Enhanced Ultrasound

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