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Use of lung ultrasound in the differential diagnosis of the causes of dyspnea

Primena ultrazvuka pluća u diferencijalnoj dijagnozi uzroka dispneje

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Abstract

Background/Aim. The field of lung ultrasonography (US) is a fast-developing one, and it provides the medical community with numerous new diagnostic opportunities. The aim of this study was to examine the etiology of dyspnea on admission and assess the stage of heart failure (HF) according to the US examination of the heart and lungs. **Methods.** The cross-sectional study included a total of 110 patients treated for the symptoms of dyspnea. The study included all patients treated for any heart or pulmonary condition, as well as patients who reported the first episode of dyspnea without any previous illness. The most important diagnostic sign in the US of the lungs in patients with HF was the appearance of B-lines or "comets" (ultrasound artifacts reminiscent of comet tails), which indicate the accumulation of fluid in the interstitium of the lungs. **Results.** The mean number of registered "comets" in the total number of patients was 14.2 ± 7.4 (minimum 2, maximum 30). The mean number of "comets" among patients with HF was 18.8 ± 5.9. The mean number of "comets" among patients without HF was 8.0 ± 3.7 ($p < 0.001$). Multivariate linear regression analyses showed the association between the number of "comets" and HF ($p < 0.001$). **Conclusion.** As the assessment of present "comets" in pulmonary US examination is safe and non-invasive, it can easily be integrated into the daily clinical practice because it has been shown that the number of pulmonary "comets" is significantly higher in patients with HF compared to those with dyspnea of other etiologies.

Key words:
diagnosis, differential; dyspnea; heart failure; pulmonary edema; ultrasonography.

Apstrakt

Uvod/Cilj. Polje primene ultrazvuka (UZ) kod pregleda pluća se brzo razvija i pruža medicinskoj zajednici mnogobrojne nove dijagnostičke mogućnosti. Cilj rada bio je da se na osnovu UZ pregleda srca i pluća ispita etiologija dispneje pri prijemu bolesnika i proceni stepen slabosti srca (SS). **Metode.** Studijom preseka obuhvaćeno je ukupno 110 bolesnika lečenih zbog dispneje. Obuhvaćeni su svi bolesnici lečeni zbog bilo koje srčane ili plućne bolesti, kao i bolesnici koji su prijavili prvu epizodu dispneje bez bilo kakvog prethodnog oboljenja. Najvažniji dijagnostički znak na nalazu UZ pluća kod bolesnika sa SS bila je pojava B linija ili „kometa" (artefakti koji podsećaju na repove kometa), koje ukazuju na nakupljanje tečnosti u intersticijumu pluća. **Rezultati.** Srednji broj registrovanih „kometa" kod ukupnog broja bolesnika bio je 14,2 ± 7,4 (minimum 2, maksimum 30). Srednji broj „kometa" kod bolesnika sa SS bio je 18,8 ± 5,9. Srednji broj „kometa" kod bolesnika bez SS bio je 8,0 ± 3,7 ($p < 0,001$). Multivarijantna linearna regresiona analiza pokazala je povezanost između broja „kometa" i postojanja SS ($p < 0,001$). **Zaključak.** S obzirom na to da je procena prisustva „kometa" tokom UZ pregleda pluća bezbedna i neinvazivna, lako se može integrisati u svakodnevnu kliničku praksu, jer je pokazano da je broj plućnih „kometa" bio značajno veći kod bolesnika sa SS u odnosu na bolesnike kod kojih je dispneja bila druge etiologije.

Ključne reči:
dijagnoza, diferencijalna; dispneja; srce, insuficijencija; pluća, edem; ultrasonografija.

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Introduction

With the constant demographic changes and the increase in the population age, there is a constant increase in the prevalence of heart failure (HF) in the general population, as noticed more than two decades ago [1]. The timely and correct diagnosis is of high importance for the clinicians [2]. The most commonly used methods for the assessment of the existence of HF are echocardiography and the measurements of the natriuretic peptide (NP) [3], which is a plasma biomarker of cardiac stress and HF [4]. Contrary to the traditional beliefs that the lungs are not suitable for the ultrasound (US) examination, the area of lung US is fast developing, and it provides the medical community with numerous new diagnostic opportunities [5]. Specifically, since the relationship between the alveolar interstitial syndrome and the US finding of lung "comets" (ULCs) (the so-called anterior B-lines) was described, lung US has become increasingly common. The "comets" are multiple and bilateral comet tail-like artifacts that indicate the presence of reduced air content in the lungs [5]. Lung US can also be used for monitoring the progress of illness or recovery among patients with acute HF, especially monitoring decongestion, as it is non-invasive and can be used bedside. It provides the lower necessity for repeated chest X-rays and exposure of patients to radiation. It can also be useful in the assessment of the prognosis of HF among patients, as their persistence is associated with a higher likelihood of readmission in the first six months after the initial hospitalization [6].

The aim of this study was to examine the etiology of dyspnea on admission and assess the stage of HF based on the findings of the US examination of the heart and lungs.

Methods

The cross-sectional study included a total of 110 patients treated for the symptoms of dyspnea. The study protocol was approved by the Ethics Committee of the Military Medical Academy in Belgrade (February 1, 2017). The study included all patients treated for any heart or pulmonary condition, as well as patients who reported the first episode of dyspnea without any previous illness. On admission, all patients went through a US examination of the lungs using the standard cardiological probe with a frequency of 2.5–3.5 MHz. Patients were either lying on the bed or sitting during the examination. The frontal and lateral thoracic walls between the second and fourth intercostal areas on the left from the parasternal line and between the second and the fifth intercostal areas on the right, all the way to the middle axillary line, with a total of 28 spots of examination, were examined. In all of them, we looked for the pulmonary "comets" that appear as a consequence of the increased interstitial fluid in the lungs. During the US examination of the heart, the following parameters were also examined: left ventricular end-diastolic volume, left ventricular end-systolic volume, left atrium volume, ejection fraction (EF), left ventricle (LV) diastolic function, the systolic pressure in the right ventricle, the ratio of transmitral flow velocity (E) to early diastolic mitral annulus velocity (E') (E/E'). E/E's relationship was determined using the tissue Doppler US. EF was determined using the modified Simpson method in two planes. LV diastolic function was examined using the blood flow over the mitral valve and through the pulmonary veins. The positive or pathological finding is defined as the bilateral existence of "comets" in all the anterolateral areas or lateral areas. The total score is calculated as the number of observed "comets" and reflects the grade of the pulmonary stasis [5]. At the initiation of the treatment and on discharge, patients' weight was measured, and chest X-ray imaging was done. On admission, patients' brain natriuretic peptide (BNP) level was examined as well. The additional data were taken from patient history, including age, gender, and presence of any risk factor for HF (high blood pressure, atrial fibrillation, diabetes mellitus, prior myocardial infarction, hyperlipidemia, chronic cardiomyopathy).

Statistical analyses were done using the methods of analytical and descriptive statistics. The correlation was examined using the Spearman correlation. The univariate linear regression model was used to examine the association between the examined variables and the number of "comets". According to the New York Heart Association (NYHA) classification, if the specific symptoms of HF, such as the existence of heart murmurs, edema on the extremities, and distension of neck veins, were present, chest X-ray characteristics and BNP were excluded from analysis due to co-linearity with HF. All variables that were shown to be significant were entered into the multivariate linear regression model with a number of "comets" as an outcome variable. For the determination of diagnostic accuracy of the number of "comets" for the HF as an outcome, we examined the sensitivity, specificity, and total area under the receiver operating characteristic (ROC) curve (AUC-ROC). Statistical processing and analysis were done in the SPSS version 22.0.

Results

The average age of the participants was 68.3 ± 15.5 years, and just over half (n = 58; 52.7%) of them were females.

The number of ULCs in patients with and without HF is presented in Figure 1. The mean number of registered ULCs among the total number of patients was 14.2 ± 7.4 (minimum 2, maximum 30). The mean number of ULCs among patients with HF was 18.8 ± 5.9. The mean number of ULCs among patients without HF was 8.0 ± 3.7 ($p < 0.001$).

Patients with confirmed HF had a significantly higher number of registered ULCs than patients who had symptoms of dyspnea but without confirmed HF.

The mean value of the number of ULCs in patients with normal X-ray findings was 7.5 ± 3.4, while the average number of ULCs in patients with pulmonary stasis found on X-ray imaging was significantly higher (18.0 ± 6.3). The average number of ULCs in patients with and without pulmonary stasis is presented in Figure 2.

In our study, we observed a significant difference in the total number of ULCs according to NYHA classification ($p <$

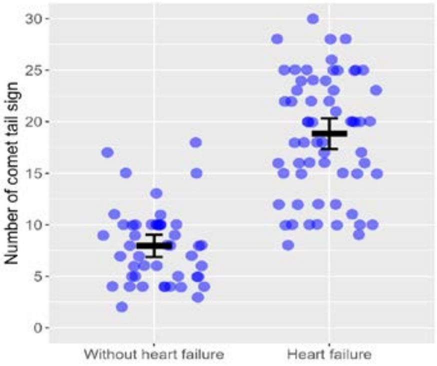

Fig. 1 – Number of ultrasound lung "comets" in relation to the presence/absence of heart failure.

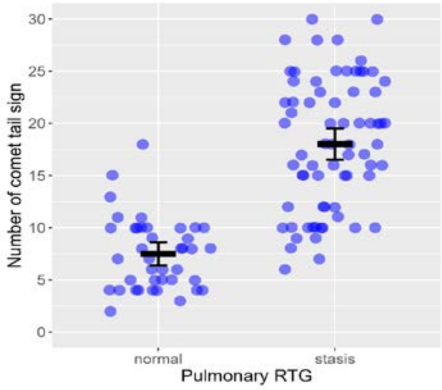

Fig. 2 – Radiography finding shows a bigger average number of ultrasound lung "comets" in relation to pulmonary stasis. RTG–X-ray.

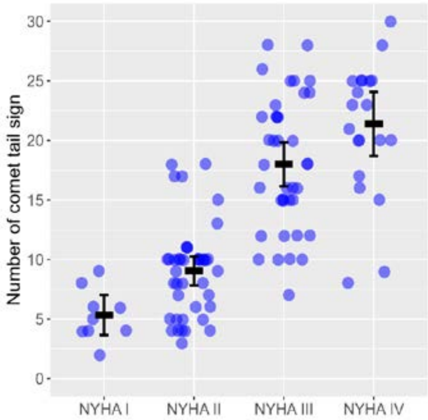

Fig. 3 – Number of ultrasound lung "comets" in patients from different classes of the New York Heart Association (NYHA) classification system.

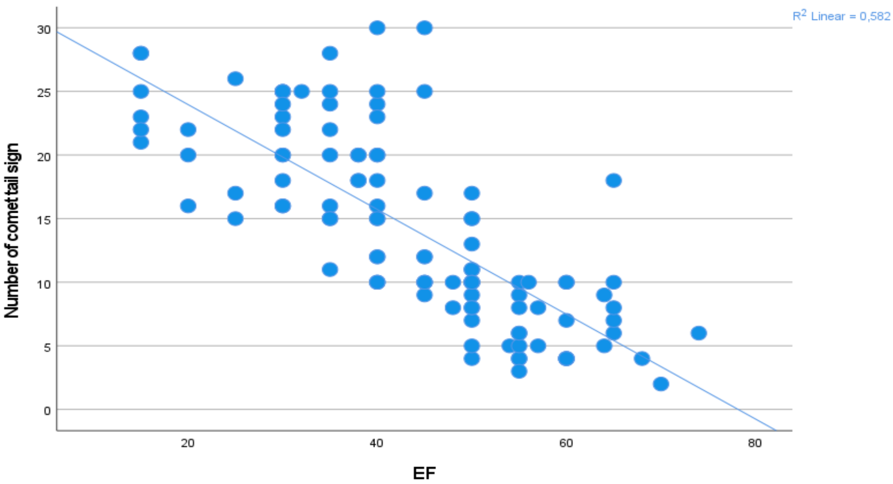

Fig. 4 – Correlation between number of ultrasound lung "comets" and ejection fraction (EF).

0.001). Patients who belonged to a higher NYHA class had a significantly higher number of registered ULCs on US examination of the lungs. Differences in the number of ULCs between patients belonging to different NYHA classes are shown in Figure 3.

There was a significant negative correlation between EF and the number of ULCs (r = -0.80, $p < 0.001$). Patients who had a lower EF had a significantly higher number of registered ULCs. The correlation between EF and the number of ULCs is presented in Figure 4.

We found a significant positive correlation between the number of ULCs and the BNP level (r = 0.79, $p < 0.001$); results are shown in Figure 5.

Patients who had high BNP values [median 3,912.5 pg/mL (minimum 28 pg/mL, maximum > 35,000 pg/mL); reference range < 100 pg/mL] had a significantly higher number of registered ULCs during the US examination of the lungs.

The total AUC-ROC for BNP was 96.9% (95% confidence interval: 91.8–99.3; $p < 0.001$) with BNP cut-off value at 3,805 pg/mL with high specificity (100%) and sensitivity (87.3%).

The number of ULCs had both high specificity (89.4%) and sensitivity (84.1%) for determining the HF; the optimal cut-off value for the number of ULCs for the determination of HF was 11. The AUC-ROC was 93.9% (95% confidence interval: 87.6–97.6, $p < 0.001$). The ROC curve for ULCs is presented in Figure 6.

Discussion

Lung US enables relatively quick and easy differentiation of various lung diseases, much more reliable than radiography. In addition, the examination is inexpensive and can be done next to the sick bed with a portable apparatus and repeated countless times. During the examination, the patient was spared from the application of contrast that potentially leads to kidney damage, from ionizing radiation, and from transport to distant parts of the hospital for multi-sliced computed tomography. Despite all the above advantages, US diagnostics of lung disease is still insufficiently applied, except in the diagnosis of pleural effusion. One of the possible reasons is the necessary training of doctors that lasts for months because the diagnosis depends on the quality of the image, which strongly depends on the experience of the person performing the imaging [7]. In patients with HF, fluid accumulates in the lungs, and the most characteristic sign on a US

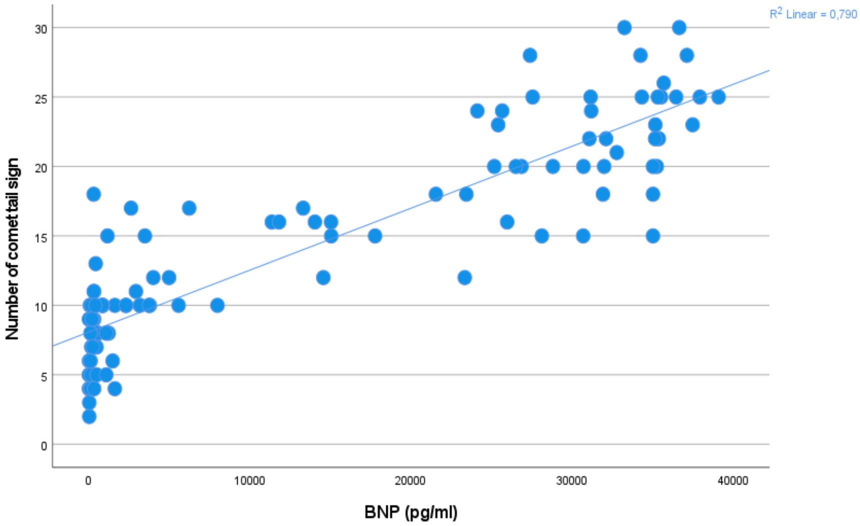

Fig. 5 – The correlation between the brain natriuretic peptide (BNP) value and the number of ultrasound lung "comets".

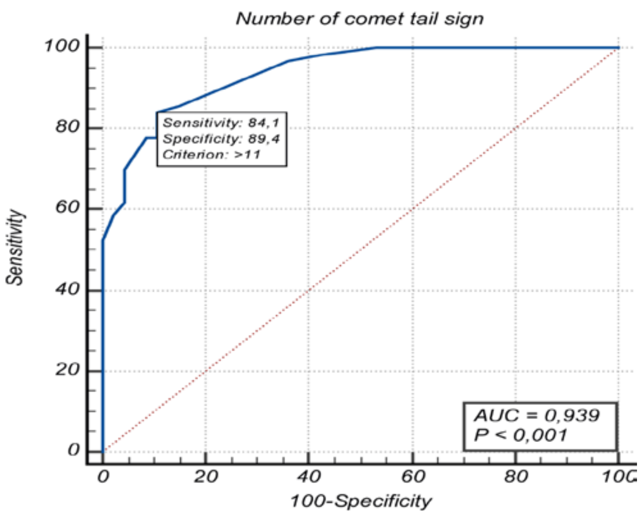

Fig. 6 – The receiver operating characteristic (ROC) curve shows the sensitivity and specificity of a number of "comets" for the prediction of heart failure (HF). AUC–area under the ROC curve.

examination of the lungs is the appearance of B-lines. These are long, vertical, hyperechoic lines that have the shape of a comet with a tail. They extend from the pleura to the inside of the lungs and move synchronously with respiration, canceling the physiological A-lines, intense and bright lines parallel to the pleura, which indicate the normal structure of the lungs [8, 9]. B-lines are the result of fluid accumulation in the interstitium, i.e., interlobular septa. They correspond to Kerley's B-lines on lung radiography in HF, i.e., horizontal lines on the periphery of the lungs, which also represent fluid accumulation in the interstitium. Ever since it was shown that recognition of multiple "comets" has high sensitivity and high specificity as a technique for evaluation of the degree of pulmonary congestion in patients with HF, the use of US as a non-invasive diagnostic tool has been established [10, 11].

There were significant differences in the number of ULCs on the US examination of heart and lung between patients with and without HF, with and without signs of pulmonary stasis on X-ray, in patients in different NYHA classes. We also found a significant negative correlation between EF and the number of ULCs. ULCs were previously shown to be markers of pulmonary congestion in patients with HF, and our results confirm the possibility of their use for diagnostic information in patients coming to the emergency department with the symptoms of dyspnea [12]. As there were significant differences in the number of ULCs according to NYHA classes, our results indicate that the ULCs may be used not only to check for the presence of HF but also as a tool to assess the grade of HF, which is also shown in previous studies [12].

We also examined the correlation between the commonly used parameter for the prediction of HF, BNP levels, and the number of ULCs, as well as its diagnostic accuracy, in order to compare the possibilities for the use of pulmonary US instead of the use of the BNP.

The measurement of the levels of BNP is used as a screening method for numerous heart diseases and commonly for assessing the progression of HF [13, 14]. The BNP levels were excluded from our final multivariate linear regression model, as there was high co-linearity with the HF, indicating a significant association between the two variables. That is in line with the results from the previous studies [15]. In our study, the total diagnostic accuracy of the number of ULCs and BNP in the prediction of HF was comparable, as the total AUC-ROC was 0.939 for the number of ULCs and 0.969 for the BNP, with BNP cut-off value at 3,805 pg/mL having the specificity of 100%. The high sensitivity of BNP (87.3 %) is in line with previous results [15], but we have also found the high specificity (100.0%), which was not reported in the Indian study [15], and the use of BNP is still a matter of disagreement [16].

Since the diagnostic accuracy of the BNP and of the ULCs appears to be comparable, there is a pronounced importance of the use of the pulmonary US assessments, especially in resource-limited settings, like low, or middle-income countries or even rural areas in developing countries in which there may not be all biochemical and molecular markers readily available. Furthermore, in some instances, the BNP seems unreliable or requires careful interpretation. These cases include racial differences, gender differences, the differences between people with different body mass index, the association of BNP levels with renal diseases, or heart diseases such as arrhythmias [17].

The study showed that when the cut-off was set at 11 ULCs, the sensitivity and specificity for the prediction of the existence of HF were 84.1% and 89.4%, respectively. That is significantly higher from, for instance, the sensitivity and specificity of Papanicolao smear for the detection of cervical cancer [18]. As the assessment of ULCs is safe and non-invasive, it can easily be integrated into daily clinical practice. Some clinicians argued that the approach we examined, using the 28 different spots for the examination of ULCs, is time-consuming and difficult for the examiner and examinee. Therefore, the new method, which is simplified and based on the seven zones compared to the previous 28 zones, was developed and was shown to correlate with diastolic functional parameters of the LV, the level of mitral regurgitation, NYHA functional classification, radiologic score, and N-terminal prohormone brain NP, all showing that this method is reliable, along with being rapid and non-invasive [10]. One study conducted in India also examined the sensitivity and specificity of the ULC assessment in the diagnosis of HF and found even higher results for both sensitivity (91%) and specificity (100%) [15]. However, the cut-off presented in the aforementioned study was 13–15 ULCs, while in our study, we used the stricter cut-off of 11 and also presented significant results regarding specificity and sensitivity.

Still, there are no developed protocols for the assessment of the quantity of pulmonary edema using the US [10]. One of the developed approaches is the so-called "28-sector" approach, which shows a linear correlation with the radiologic lung water score [10, 19, 20]. That practically means that the number of identified ULCs is correlated with the extravascular lung water examined by the X-ray or even invasive thermodilution methods.

All these findings lead to the examination of the possibility of using ULCs as a tool for diagnosis and monitoring the degree of HF for the differential diagnosis of cardiac from non-cardiac dyspnea [5].

Conclusion

The number of ULCs is significantly higher in patients with HF than in those with dyspnea of other etiologies. The number of ULCs shows a significant correlation with the clinical picture, lung radiography, NYHA class, BNP, and parameters of systolic and diastolic function of the heart. As the assessment of ULCs is safe and non-invasive, it can easily be integrated into daily clinical practice.

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