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ATTN: Editorial Board of Internal and Emergency Medicine

Dear Sirs

We are pleased to submit our manuscript entitled "**LUNG ULTRASOUND IN INTERNAL MEDICINE EFFICIENTLY DRIVES THE MANAGEMENT OF PATIENTS WITH HEART FAILURE AND SPEEDS UP THE DISCHARGE TIME",** for consideration as original research article to your journal.

Heart failure (HF) is the leading cause of hospitalization in Internal Medicine.

Lung ultrasound (LUS) has been demonstrated to be a valid tool for the assessment of pulmonary congestion by the quantification of the B-lines. Our previous work has aimed to support the daily use of *point of care* ultrasound in Internal Medicine.

This study goes further.

It focuses on the potential of LUS in tailoring diuretic therapy and determining discharge time in HF patients in an Italian University Hospital Internal Medicine department.

In line with our previous studies, the results of this one confirm that LUS is an essential tool in the management of patients with HF. Furthermore, the study stresses the real need for appropriate timing and modality in the use of LUS in Internal Medicine. This may be different from what is required in emergency and critical care settings. Until the technique comes into common use in different departments, it is plausible that LUS will evolve with different facets and needs accordingly.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other peer-reviewed media. All Authors listed have contributed sufficiently to the project to be included as Authors, and all those who are qualified to be Authors are listed in the author by-line.

All Authors have approved the manuscript and agree with its submission. We hope that the Editorial board and the Reviewers will agree on the interest of our study for your journal.

I look forward to hearing from you.

Yours faithfully,

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LUNG ULTRASOUND IN INTERNAL MEDICINE EFFICIENTLY DRIVES THE MANAGEMENT OF PATIENTS WITH HEART FAILURE AND SPEEDS UP THE DISCHARGE TIME

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Abstract

Lung ultrasound (LUS) is a valid tool for the assessment of heart failure (HF) through the quantification of the B-lines. This study in HF patients aims to evaluate if LUS: 1) can accelerate the discharge time; 2) can efficiently drive diuretic therapy dosage; 3) may have better performance compared to the amino-terminal portion of B type natriuretic peptide (NT-proBNP) levels in monitoring HF recovery.

A consecutive sample of 120 HF patients was admitted from the Emergency to the Internal Medicine Department (Verona University Hospital). The Chest X Ray (CXR) group underwent standard CXR examination on admission and discharge. The LUS group underwent LUS on admission, 24, 48 and 72 hours later, and on discharge. The Inferior Cave Vein Collapsibility Index, ICVCI, and the NT-proBNP were assessed.

LUS discharge time was significantly shorter if compared to CXR group ($p<0.01$). During hospitalization the LUS group underwent an increased number of diuretic dosage modulations compared to the CXR group ($p<0.001$). There was a stronger association between partial pressure of oxygen in arterial blood (PaO2) and B-lines compared to the association between PaO2 and NT-proBNP both on admission and on discharge ($p<0.001$). The B-lines number was significantly higher on admission in patients with more severe HF and ICVCI was inversely associated with B-lines number ($p<0.001$).

The potential of LUS in tailoring diuretic therapy and accelerating the discharge time in HF patients is confirmed. Until the technique comes into common use in different departments, it is plausible that LUS will evolve with different facets accordingly.

Keywords: lung ultrasound (LUS); heart failure (HF); Internal Medicine; discharge time.

Introduction

Recently, lung ultrasound (LUS) has emerged in different clinical settings [1-5] for the evaluation of patients with acute respiratory failure. In particular, the main fields of LUS applications are: pneumothorax (PNX), interstitial syndrome, lung consolidation and pleural effusion [6-8].

Heart failure (HF) is a clinical syndrome characterized by typical symptoms and signs caused by structural and/or functional cardiac abnormalities, resulting in a reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress [9].

The prevalence of HF is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people >70 years of age and it is the leading cause of hospitalization [10].

LUS has been demonstrated to be a valid tool for the assessment of pulmonary congestion [11-13] through the quantification of the B-lines. B-lines are defined as laser-like vertical hyperechoic reverberation artifacts that emerge from the pleural line (previously defined as "comet tails"). Multiple B-lines are the sonographic sign of lung interstitial syndrome. Their number increases along with decreasing air content and increase in lung density [4,14]. Clearing of B-lines significantly correlates with improved clinical symptoms and signs of HF. B-lines due to cardiogenic pulmonary edema are usually bilateral, and usually spread or recover symmetrically [4]. Their regular distribution allows differentiation between cardiogenic pulmonary edema, acute respiratory distress syndrome (ARDS) and pulmonary fibrosis [4,14].

The plasma concentration of natriuretic peptides (NPs) can be used as an initial HF diagnostic test, especially in the setting of dyspnoea of unclear aetiology. Elevated NPs help to establish an initial working diagnosis. They are considered predictors of prognosis of HF and are used to dictate the intensity of the diuretic therapy [15,16].

Our previous studies [17,18] strongly supported the daily use of *point of care* ultrasound in Internal Medicine.

This study goes further.

The main objectives of this study are: 1) to test if LUS use can speed up the discharge time in HF patients; 2) to test if LUS can efficiently drive diuretic therapy dosage; 3) to compare the performance of LUS and of the amino-terminal portion of B type natriuretic peptide (NT-proBNP) levels in monitoring HF recovery.

Materials and Methods

- Ethics statement

The study was conducted in accordance with the ethical standards laid down in the Helsinki Declaration of 1975 and its late amendments. The participants provided written consent prior to starting the study (for collecting and publishing data). The procedure did not require a particular approval by the local Ethical Committee.

- Study setting and population

The study setting was the Internal Medicine department of the University Hospital of Verona, Italy, already certified as a first level ultrasound centre by the Società Italiana di Medicina Interna (SIMI).

Authors studied a consecutive sample of 120 patients (aged 70-94).They were admitted from the Emergency Department to the Internal Medicine Department of the University Hospital of Verona with the clinical diagnosis of HF.

Exclusion criteria were: concomitant acute coronary syndrome, pneumonia, chronic obstructive pulmonary disease, lung cancer or metastases, lung fibrosis, previous pneumonectomy or lobectomy, breast prothesis, obesity.

The study was conducted in winter 2016-2017 and spring 2017.

Patients were classified according to New York Heart Association (NYHA) classes [19].The NYHA functional classification was used to describe the severity of symptoms and exercise intolerance at admission. HF was classified according to the recent guidelines of the European Society of Cardiology [9]: patients with normal left ventricular ejection fraction (LVEF) (≥50%, HF with preserved EF, HFpEF), patients with reduced LVEF (<40%, HF with reduced EF, HFrEF), patients with an LVEF in the range of 40–49% (HFmrEF).

- Description of the study protocol

Patients were subdivided in two groups: the Chest X Ray group (CXR) and the LUS group.

The CXR group underwent a standard CXR examination on admission and on discharge.

The LUS group underwent LUS on admission, 24, 48 and 72 hours later, and on discharge.

Trans-thoracic echocardiography at rest was performed in all patients in order to classify the LVEF on admission.

Trans-thoracic echocardiography was performed by an Internal Medicine specialist (CM) and a colleague (MDDP) (they were certified by the Societa` Italiana di Ecografia Cardiovascolare, SIEC). LUS examinations were performed by CM, who was certified by the Società Italiana di Ultrasonologia in Medicina e Biologia (SIUMB), together with MDDP.

All ultrasound examinations were performed using an EnVisor C HD Philips equipped with linear, convex and sector transducers. The sector probe was the first choice of use for LUS examination, and the convex and the linear ones were also available. LUS examinations were performed with patients in the supine or near-supine position for the anterior scanning, and in the sitting position for the dorsal scanning. A B-lines score, defined as the total number of the detectable B-lines was determined, according to the approach proposed by Gargani and Volpicelli [4,20].

Inferior Cave Vein (ICV) maximum and minimum diameter and its collapsibility index (Inferior Cave Vein Collapsibility Index, ICVCI) were measured in subcostal view in M-mode, 2 cm from the right atrial junction in the LUS group. ICVCI was calculated according to the formula [(ICV max-ICV min)/ICV max]x 100. These measurements were obtained using a convex transducer. The ICVCI% cut-offs were:>75 (hypovolemia), ≥ 40 and ≤ 75 (euvolemia) and <40 (hypervolemia).

NT-proBNP dosage was obtained from peripheral venous blood samples (Immunochemistry Analyzer, COBAS 6000) in the LUS group on admission and on discharge. Urine output and diuretic dosage were carefully reported daily. Arterial blood samples were collected on admission and on discharge in both groups to test the partial pressure of oxygen (PaO_2) as indicator of HF severity (on admission) and recovery (on discharge).

- Statistical analysis

Categorical and continuous characteristics on admission are summarized as percentages and means with standard deviations respectively. Differences in the distribution of the baseline characteristics between CXR and LUS groups were tested using the Chi-squared test, the Student's T-test, or the Mann Whitney's U test, as appropriate. A quantile regression model was adopted to test the difference in the number of days of hospitalizations from admission to discharge in the CXR group vs the LUS group, using a stepwise forward approach (with $p<0.20$ for entry and $p>=0.25$ for removal) to select the variables to include in the multivariate model. The associations between the number of B-lines, the NT-proBNP levels, PaO2, and ICVCI measured in the 60 patients of the LUS group on admission and on discharge were estimated using Spearman's rank correlation coefficients (rho).

The correlations of the number of B-lines and NT-pro-BNP, were log-transformed to achieve normal distribution, with PaO2, as well as the correlation between number of B-lines and ICVCI. They were evaluated using linear regression models using the data on admission and on discharge, taking into account intra-subject variability using cluster-robust standard errors.

The velocity of clearance of log (number of B-lines) at 0, 24, 48, and 72 hours after admission according to HF severity was evaluated using a two-way ANOVA model with time-dependent repeated measures. Statistical analyses were performed using STATA 14.2.

Results

The baseline demographic and clinical characteristics of the patients on admission are reported in Table 1. All patients were classified in NYHA IV class.

Table 1: Demographic characteristics at baseline/admission of the enrolled patients.

	CXR group (n=60)	LUS group (n=60)	p-value
Age (years)	83.7 (0.9)	83.8 (0.9)	0.970
Sex (females)	38 (63%)	37 (62%)	0.850
Ejection Fraction			**0.009**
preserved	28 (47%)	22 (37%)	
mid-range	10 (17%)	25 (42%)	
reduced	22 (37%)	13 (22%)	
Ischemic Heart Disease	24 (40%)	25 (42%)	0.853
Valvular Heart Disease	19 (32%)	25 (42%)	0.256
Type 2 Diabetes Mellitus	17 (28%)	21 (35%)	0.432
SBP (mmHg)	137.8 (2.7)	131.8 (2.8)	0.126
DBP (mmHg)	74.4 (1.5)	72.3 (1.3)	0.245
Heart rate (beats/minute)	82.2 (2.2)	87.5 (2.2)	0.096
Creatinine (mg/dL)	1.30 (0.07)	1.35 (0.08)	0.640
Therapy (on admission)			
Ace-inhibitors	28 (47%)	29 (48%)	0.855
β-blockers	42 (70%)	38 (63%)	0.439
Diuretics	40 (67%)	51 (85%)	0.019
Statins	29 (48%)	29 (48%)	1.000
Anti-coagulants	21 (35%)	27 (45%)	0.264
Anti-aggregants	30 (50%)	25 (42%)	0.360
PaO2 (mmHg)	70.3 (1.3)	62.9 (1.1)	<0.001

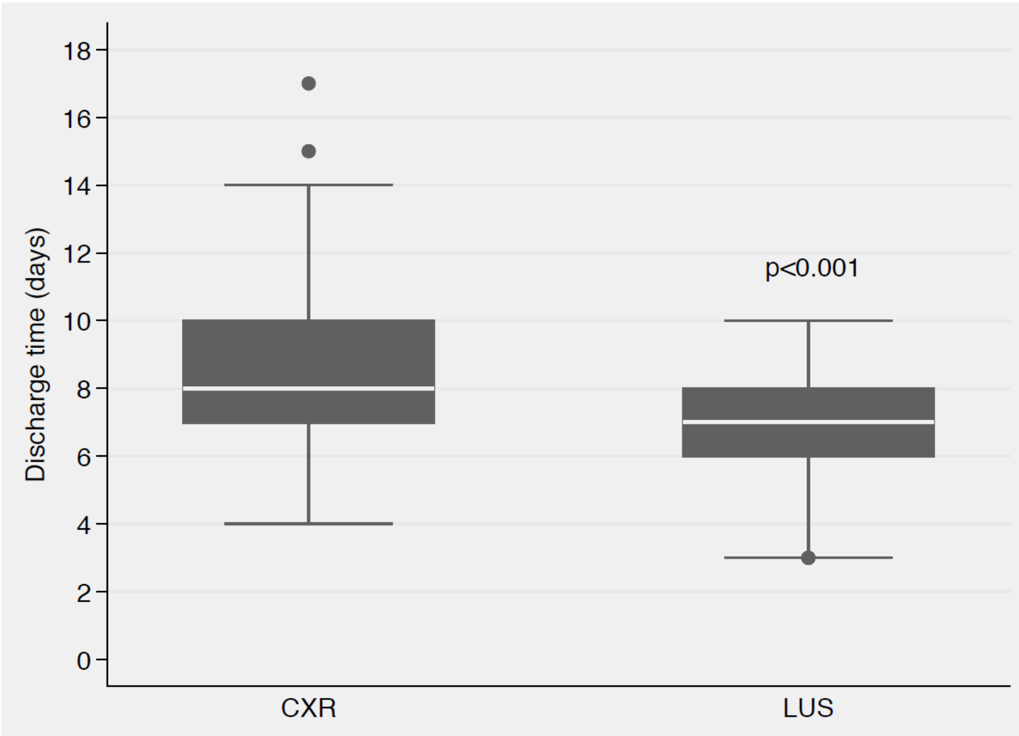
Data are expressed in n (%) or mean standard deviation (SD). CXR: chest X-ray; DBP: diastolic blood pressure; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFmfEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction; LUS: lung ultrasound; NT-pro-BNP: N-terminal fragment brain natriuretic peptides; PaO2: partial pressure of oxygen in arterial blood; SBP: systolic blood pressure.

Drug therapy was similar in the CXR and LUS groups (angiotensin-converting enzyme inhibitors, β-blockers, statins, anticoagulant/anti-platelets drugs) except for diuretics (more frequent in the LUS group). The subjects included in the LUS group had lower PaO2 at admission compared to those included in the CXR group (mean: 62.9 vs. 70.3 $p<0.001$).

The average time required to acquire and interpret LUS was 7±1 minutes.

Figure 1 shows the discharge time (measured as hospitalization days) for the CXR and the LUS groups.

Fig.1: Discharge time (measured as hospitalization days) for the CXR and the LUS groups.



CXR: chest X-ray; LUS: lung ultrasound.

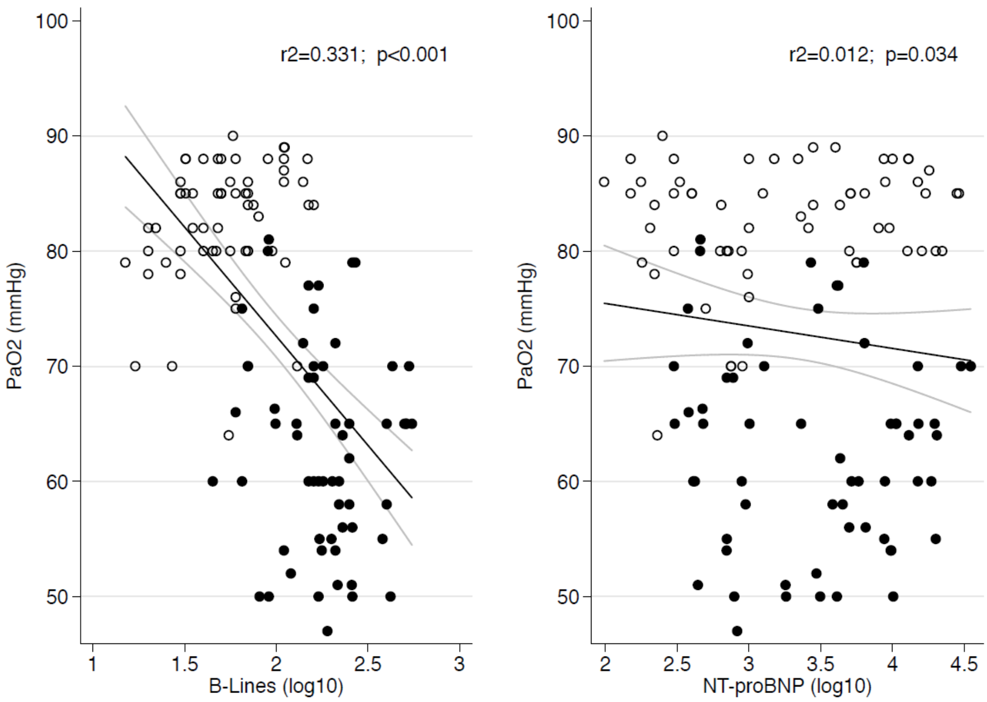
LUS discharge time was significantly shorter if compared to the CXR group: median (range) CXR: 8 (4-17) ; LUS 7 (3-10), p-value for difference: $p<0.001$.

In the stepwise multivariate regression model, LUS discharge time was significantly shorter if compared to CXR group (coefficient: -1.812, 95%CI: -2.719,-0.906; $p<0.001$). The PaO_2 on admission was also significantly associated with discharge time, with higher PaO_2 levels associated with shorter hospital stay (coefficient: -0.063; 95%CI: -0.107, -0.018; p=0.006). The use of diuretics was also included in the final stepwise model with the above two variables, but its association with time to discharge did not reach statistical significance (coefficient: 0.688; 95%CI: -0.166,1.541; p=0.113).

During hospitalization the LUS group underwent to an increased number of diuretic dosage modulations if compared to the CXR group ($p<0.01$). In the CXR group, 33% (20 out of 60) of the patients, had a single diuretic modulation, while 67% (40 out of 60) had two; on the other hand, none of the patients in the LUS group had only one diuretic modulation, 12% had two modulations (7 out of 60), and 88% (53 out of 60) had three.

Figure 2 shows the associations of PaO_2 and the B-lines on admission and discharge and PaO_2 and NT-proBNP on admission and discharge (both expressed in log 10). The B-lines were strongly associated with the levels of PaO2, as log10 (B-lines) predicted 33% of the variability of PaO2 (r2= 0.331; $p<0.001$). On the other hand, the association between NT-proBNP and PaO2 was weaker, with log10 (B-lines) predicting only 1% of the PaO2 variability (r2= 0.012; p=0.034).

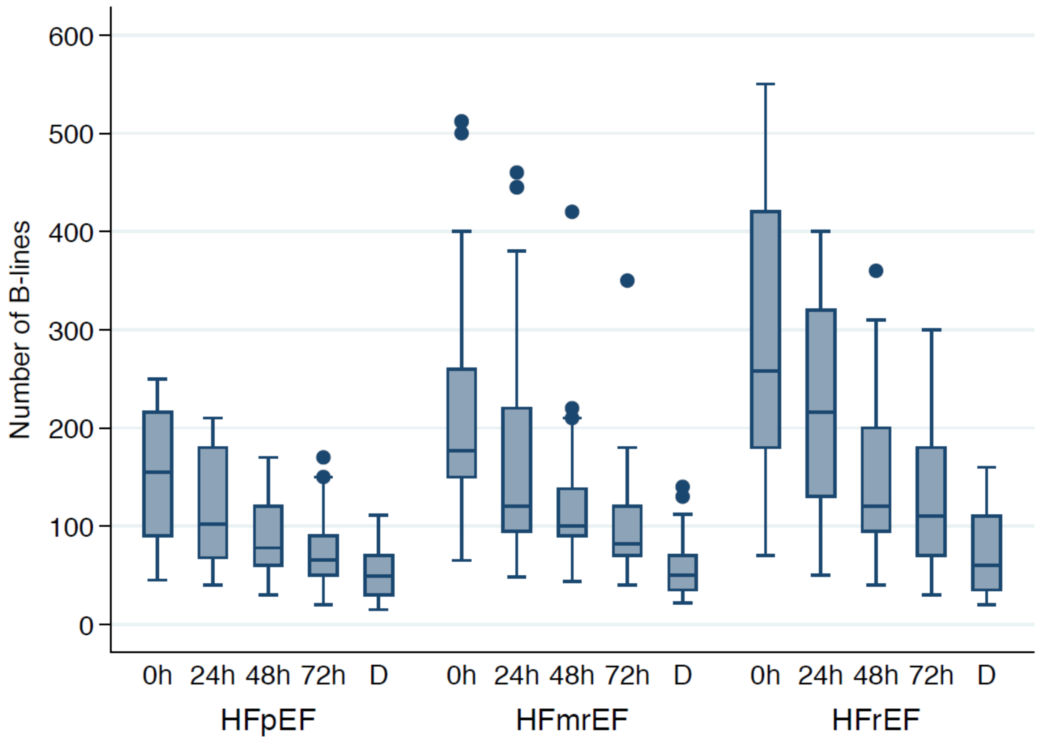
Fig. 2: The associations between PaO2 and B-lines on admission and discharge (on the left), and PaO2 and NT-pro-BNP on admission and discharge (on the right) in the LUS group.



PaO2: partial pressure of oxygen in arterial blood (mmHg); NT-pro-BNP: N-terminal fragment brain natriuretic peptides; LUS: lung ultrasound, black dots: admission; white dots: discharge; p< 0.001

The number of the B-lines was significantly higher on admission in patients with more severe HF.(p<0.01) (Figure 3). Overall the B-lines diminished of -23%, -39%, and -50% after 24, 48, and 72hours respectively, compared to the number of the B-lines on admission. There was not interaction between time and severity of HF (p=0.866). This indicates that, despite the velocity of clearance in absolute numbers was quicker in the groups with higher B-lines on admission, the relative velocity in B-lines clearance was similar across the three groups of HF severity.

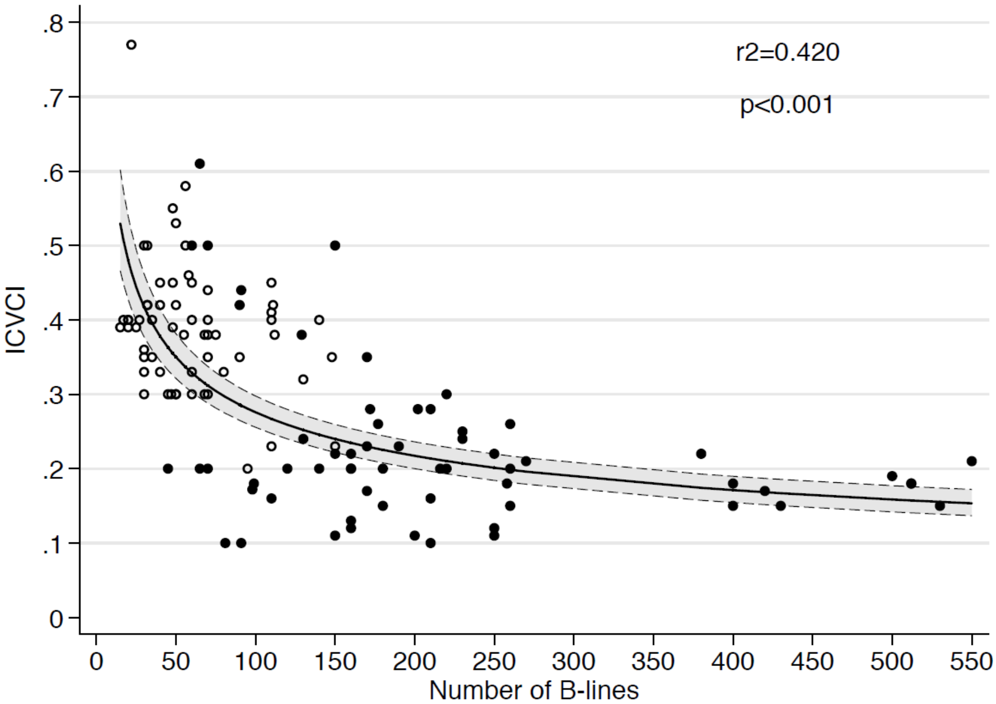
Fig. 3: Severity of Heart Failure measured by echocardiography and the B-lines clearance time (hours).



D: discharge time; HFpEF: heart failure with preserved ejection fraction; HFmfEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction.

The ICVCI was measured on admission and discharge in the LUS group. There was an inverse significant association between this index and the number of B-lines ($p<0.01$), as shown in Figure 4.

Fig. 4:The association between the ICVCI and the B-lines on admission and discharge in the LUS group.



ICVCI: Inferior Cave Vein Collapsibility Index; black square: admission; white squares: discharge; p value <0.001

PaO_2 (mmHg) on discharge was 98±1 for both groups without oxygen supply.

Discussion

LUS is becoming a standard tool in critical care for the early diagnosis of acute respiratory failure [21]. The "decision tree" used to guide this diagnosis is the well-known Bedside Lung Ultrasound Evaluation (BLUE) protocol [21]. The advantage of this protocol is its rapidity.

But LUS is not only a simple approach to discriminating among its main fields of application [6,7], LUS can be also used as a monitoring tool in HF patients.

Different studies [13,22-24] have been designed in different settings other than Emergency settings. They have been designed to define the performance of LUS compared to clinical assessment, to NPs levels and to traditional CXR in HF patients, both outpatients and inpatients. These studies have confirmed that the B-lines are prognostic markers for hospital re-admission or death in HF patients. Moreover, the prognostic value of LUS was confirmed independently of the method used to evaluate the B-lines burden (semi-quantitative, 8 zones, 28 zones, 72 zones), allowing a prognostic risk stratification on discharge. They provide an important step forward for the implementation of LUS in the clinical evaluation of HF patients.

It is well known that the costs associated with HF hospitalization are consistent in Internal Medicine, with increased hospital stay days [25,26]. Moreover, these costs are compounded by a high rate of re-admission.

In this context, the main finding of this study is that LUS speeds up the discharge time in HF patients, that is one of the most common admission diagnosis in the Internal Medicine department. To the Authors' knowledge, this is the first study about LUS that examines this point. This result may be due to different reasons. The LUS operator is not blinded to the patients' clinical conditions (while the Radiologist usually has only an information summary about them). Furthermore, the possibility of performing LUS bedside at any moment allows for an easier management of the therapy. In fact, in this study the LUS group underwent an increased number of diuretic dosage modulations compared to the CXR group. Remarkably, the LUS group discharge time was shorter although with a lower PaO_2 on admission.

The second important result of this study concerns the B-lines and their role in monitoring HF recovery. The results of this study show a stronger association between PaO_2 and B-lines compared to the association between PaO_2 and NT-proBNP both on admission and on discharge.

The B-lines are not mentioned in HF ESC guidelines [9]. In this study the reduction of the B-lines does not occur in accordance with the NT-proBNP levels, suggesting that serum NT-proBNP may not reliably indicate pulmonary congestion having been resolved. These results lead us to consider this molecule a useful marker for the discrimination of the possible origin of respiratory failure, but it is not so precise in monitoring HF recovery. NT-pro-BNP has proved to be effective only in excluding/confirming congestive HF. These data support the use of this molecule in the Critical care setting rather than in the Internal Medicine department. Moreover, it has been established that NPs levels are affected by age, as known, [27] or by other conditions as such as body mass index [28], myocardial ischemia and hypoxia even in the absence of left ventricular dysfunction [29], hormonal dysfunctions [30], renal failure and diabetes [31].

The B-lines clearance time was longer in patients with HFrEF compared to those with HFpEF and HfmrEF. This result underlines the importance of a combined approach (ecocardiography and LUS). This fact is confirmed also by the importance of the ICVCI evaluation. In fact, the ICVCI was computed on admission and on discharge in the LUS group and a significant association between this index and the number of the B-lines was found.

Nevertheless, this study has several limitations: the sample is composed of elderly people so it is arguable that the acoustic window could be affected by the patient positioning (effort of maintaining the correct position both the supine and the sitting one).

Also the method of quantification of the B-lines could be a source of disagreement. Scan techniques can be broadly divided in two groups: the scanning modality by zones or the scanning modality by fixed points, as described in Methods section. The Authors counted the total number of the detectable B-lines in anterolateral and posterior scanning sites. This protocol is well established [4,20], nevertheless this evaluation could be even very accurate, taking too much time.

The context makes the difference. The Internal Medicine department can spend more time on the patients' clinical examination compared to the Emergency one.

It has to be recognized that the LUS technique in the B-lines identification is not fully standardized. The integration of LUS with a comprehensive multi-organ ultrasound evaluation is mandatory in order to avoid common pitfalls and misdiagnosis, as recently reviewed by Blanco and Volpicelli [32].

Further larger independent multi-centre studies are warranted to confirm the results of this work.

Conclusions

The results of this study confirm the potential of LUS in tailoring diuretic therapy and speeding up the discharge time in HF hospitalization. The study stresses the real need for appropriate timing and modality of LUS in Internal Medicine. Until the technique comes into common use in different departments, it is plausible that LUS will evolve with different facets and needs accordingly.

List of abbreviations:

CXR: Chest X ray

HF: Heart Failure

HFpEF: Heart Failure with preserved ejection fraction

HFmrEF: Heart Failure with mid-range ejection fraction

HFrEF: Heart Failure with reduced ejection fraction

ICVCI: inferior cave vein collassability index

LUS: Lung Ultrasound.

NT-pro BNP: circulating N-terminal pro- hormone of brain natriuretic peptide

NYHA: New York Heart Association

Conflict of interest: none.

Authors'contribution: CM and MDDP conceived the study and performed the ultrasound examinations; GP statistically analyzed the data, AT,AN, TM, AF, UG revised the data; LC, AC and MS revised the paper, CM wrote the manuscript.

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