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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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(Article begins on next page)

Verona (Italy), June 29th 2017

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,

Chiara Mozzini, MD, PhD Department of Medicine, Section of Internal Medicine, University of Verona,
Piazzale L.A. Scuro, 10, 37134 Verona, Italy chiaramozzini@libero.it

TEL. +0039-0458124262 FAX: +0039-0458027496

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

4

5 Chiara Mozzini*¹, Marco Di Dio Perna¹, Giancarlo Pesce², Ulisse Garbin¹, Anna Maria Fratta
6 Pasini¹, Andrea Ticinesi³, Antonio Nouvenne³, Tiziana Meschi³, Alder Casadei⁴, Maurizio Soresi⁵
7 and Luciano Cominacini¹

8

9 ¹Department of Medicine, Section of Internal Medicine, University of Verona

10 Piazzale L.A. Scuro, 10, 37134 Verona, Italy

11 ²Department of Diagnostic and Public Health, Unit of Epidemiology and Medical Statistics,
12 University of Verona, Piazzale L.A. Scuro, 10 - 37134 Verona, Italy

13 ³Internal Medicine and Critical Subacute Care Unit, Geriatric/Rehabilitation Department, and
14 Department of Clinical and Experimental Medicine, University of Parma Via A. Gramsci, 14
15 43126 Parma, Italy

16 ⁴Ultrasound Association of South-Tyrol, Bolzano Health, District, Piazza W.A.Loew-Cadonna 12,
17 39100 Bolzano, Italy

18 ⁵ Biomedical Department of Internal Medicine and Medical Specialities, University of Palermo,
19 Via del Vespro, 141-90127 Palermo, Italy

20

21 ***Corresponding author: Chiara Mozzini, MD, PhD**

22 **Department of Medicine, Section of Internal Medicine, University of Verona, 10, Piazzale**
23 **L.A. Scuro 37134 Verona, Italy**

24 **Tel. +39-0458124262 fax: +39-0458027496 e- mail: chiaramozzini@libero.it**

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1 **Abstract**

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

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

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

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

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

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1 **Introduction**

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

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

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

10 LUS has been demonstrated to be a valid tool for the assessment of pulmonary congestion [11-13]
11 through the quantification of the B-lines. B-lines are defined as laser-like vertical hyperechoic
12 reverberation artifacts that emerge from the pleural line (previously defined as “comet tails”).

13 Multiple B-lines are the sonographic sign of lung interstitial syndrome. Their number increases
14 along with decreasing air content and increase in lung density [4,14]. Clearing of B-lines
15 significantly correlates with improved clinical symptoms and signs of HF. B-lines due to
16 cardiogenic pulmonary edema are usually bilateral, and usually spread or recover symmetrically
17 [4]. Their regular distribution allows differentiation between cardiogenic pulmonary edema, acute
18 respiratory distress syndrome (ARDS) and pulmonary fibrosis [4,14].

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

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

25 This study goes further.

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

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1 **Materials and Methods**

2 **- Ethics statement**

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

7 **- Study setting and population**

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

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

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

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

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

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- 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 Societa` 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

1 and on discharge in both groups to test the partial pressure of oxygen (PaO₂) as indicator of HF
2 severity (on admission) and recovery (on discharge).

3 **- Statistical analysis**

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

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

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

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1 **Results**

2 The baseline demographic and clinical characteristics of the patients on admission are reported in

3 Table 1. All patients were classified in NYHA IV class.

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

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	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

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

6

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

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

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

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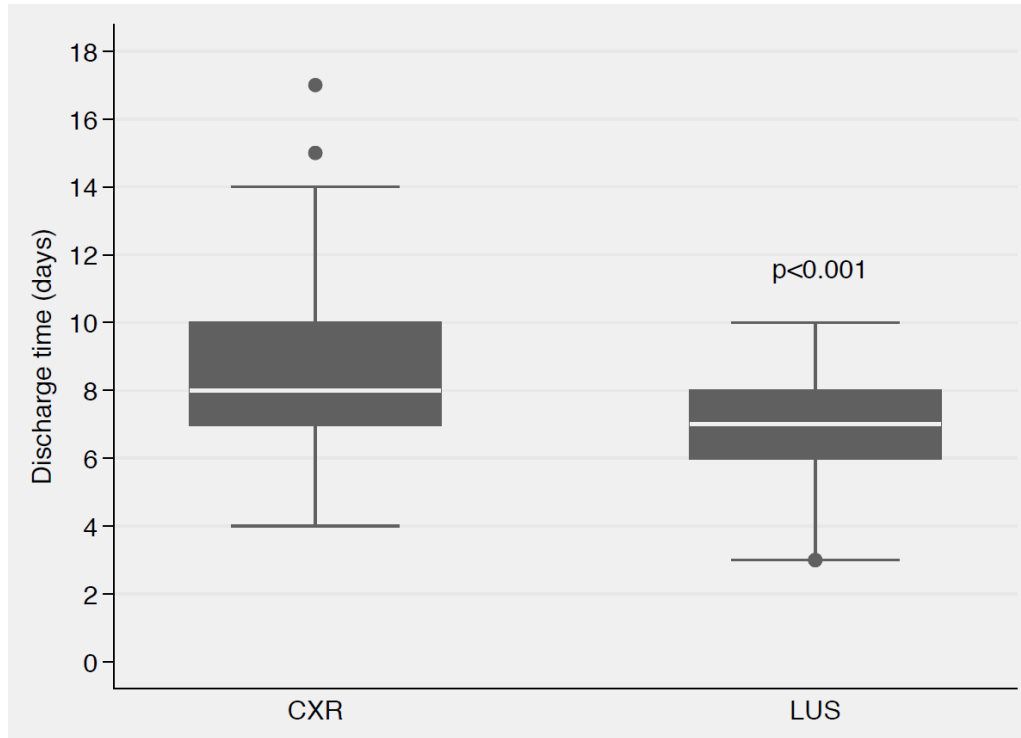
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1 **Fig.1: Discharge time (measured as hospitalization days) for the CXR and the LUS groups.**



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

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5 LUS discharge time was significantly shorter if compared to the CXR group: median (range)

6 CXR: 8 (4-17) ; LUS 7 (3-10), p-value for difference: $p<0.001$.

7 In the stepwise multivariate regression model, LUS discharge time was significantly shorter if

8 compared to CXR group (coefficient: -1.812, 95%CI: -2.719,-0.906; $p<0.001$). The PaO₂ on

9 admission was also significantly associated with discharge time, with higher PaO₂ levels

10 associated with shorter hospital stay (coefficient: -0.063; 95%CI: -0.107, -0.018; $p=0.006$). The

11 use of diuretics was also included in the final stepwise model with the above two variables, but its

12 association with time to discharge did not reach statistical significance (coefficient: 0.688; 95%CI:

13 -0.166,1.541; $p=0.113$).

1 During hospitalization the LUS group underwent to an increased number of diuretic dosage
2 modulations if compared to the CXR group ($p < 0.01$). In the CXR group, 33% (20 out of 60) of the
3 patients, had a single diuretic modulation, while 67% (40 out of 60) had two; on the other hand,
4 none of the patients in the LUS group had only one diuretic modulation, 12% had two modulations
5 (7 out of 60), and 88% (53 out of 60) had three.

6

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

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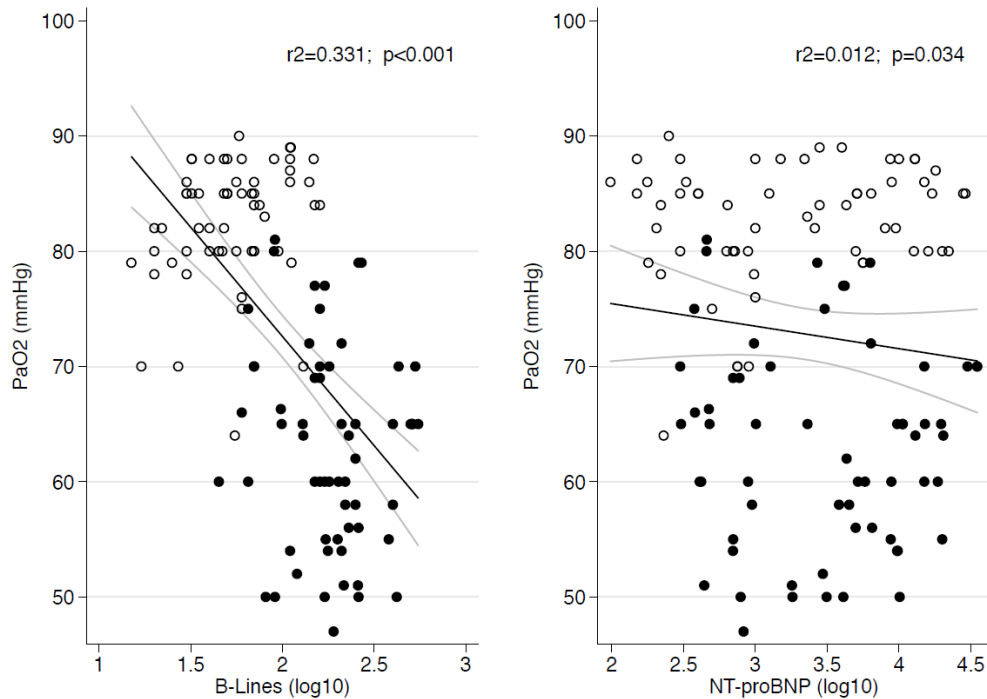
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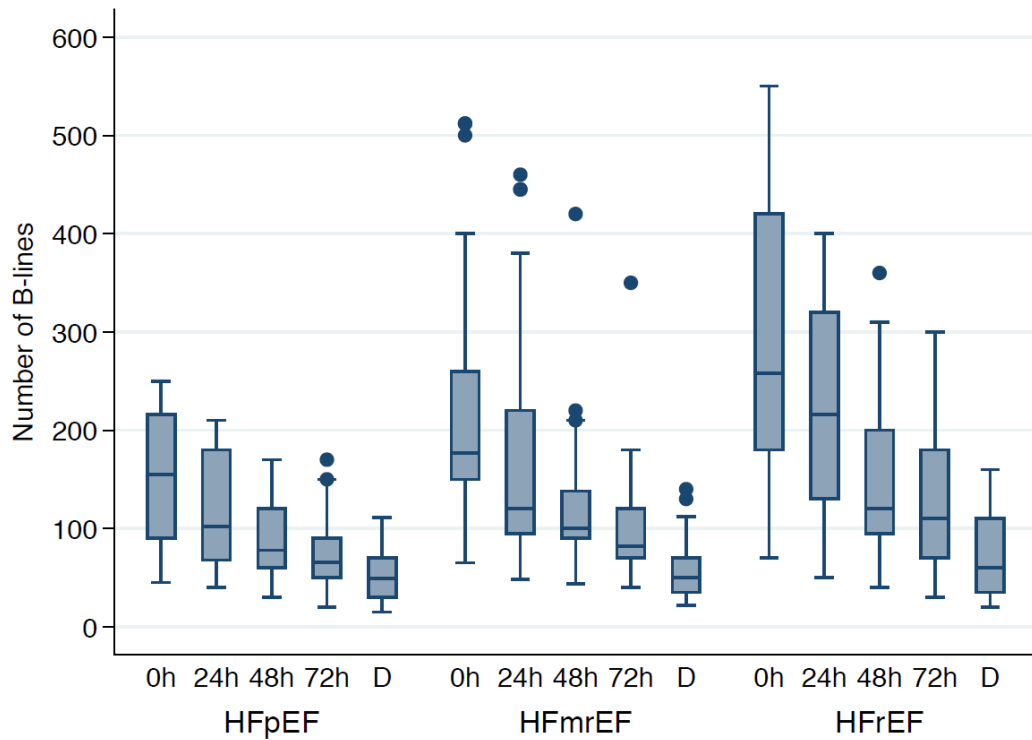
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1 **Fig. 2: The associations between PaO₂ and B-lines on admission and discharge (on the left),**
 2 **and PaO₂ and NT-pro-BNP on admission and discharge (on the right) in the LUS group.**



3
 4 PaO₂: partial pressure of oxygen in arterial blood (mmHg); NT-pro-BNP: N-terminal fragment
 5 brain natriuretic peptides; LUS: lung ultrasound, black dots: admission; white dots: discharge;
 6 $p<0.001$
 7
 8 The number of the B-lines was significantly higher on admission in patients with more severe
 9 HF ($p<0.01$) (Figure 3). Overall the B-lines diminished of -23%, -39%, and -50% after 24, 48, and
 10 72hours respectively, compared to the number of the B-lines on admission. There was not
 11 interaction between time and severity of HF ($p=0.866$). This indicates that, despite the velocity of
 12 clearance in absolute numbers was quicker in the groups with higher B-lines on admission, the
 13 relative velocity in B-lines clearance was similar across the three groups of HF severity.

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

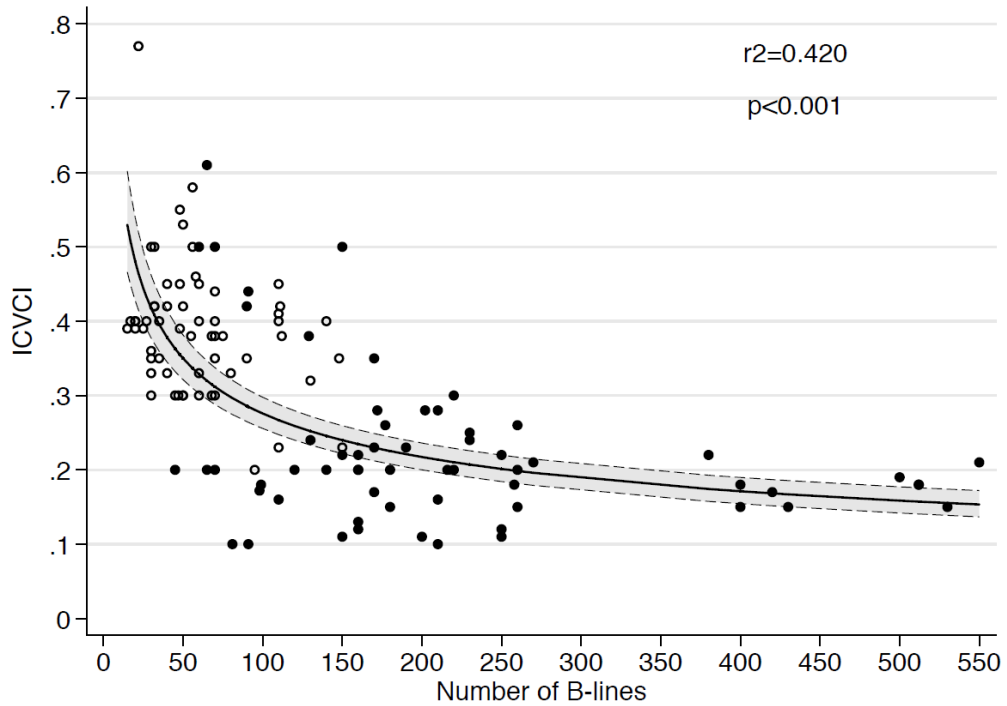


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 4 D: discharge time; HFpEF: heart failure with preserved ejection fraction; HFmrEF: heart failure
 5 with mid-range ejection fraction; HFrfEF: heart failure with reduced ejection fraction.

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



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

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7 PaO₂ (mmHg) on discharge was 98±1 for both groups without oxygen supply.

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1 **Discussion**

2 LUS is becoming a standard tool in critical care for the early diagnosis of acute respiratory failure
3 [21]. The “decision tree” used to guide this diagnosis is the well-known Bedside Lung Ultrasound
4 Evaluation (BLUE) protocol [21]. The advantage of this protocol is its rapidity.

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

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

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

18 In this context, the main finding of this study is that LUS speeds up the discharge time in HF
19 patients, that is one of the most common admission diagnosis in the Internal Medicine department.

20 To the Authors’ knowledge, this is the first study about LUS that examines this point. This result
21 may be due to different reasons. The LUS operator is not blinded to the patients’ clinical
22 conditions (while the Radiologist usually has only an information summary about them).

23 Furthermore, the possibility of performing LUS bedside at any moment allows for an easier
24 management of the therapy. In fact, in this study the LUS group underwent an increased number of
25 diuretic dosage modulations compared to the CXR group. Remarkably, the LUS group discharge
26 time was shorter although with a lower PaO₂ on admission.

1 The second important result of this study concerns the B-lines and their role in monitoring HF
2 recovery. The results of this study show a stronger association between PaO₂ and B-lines
3 compared to the association between PaO₂ and NT-proBNP both on admission and on discharge.
4 The B-lines are not mentioned in HF ESC guidelines [9]. In this study the reduction of the B-lines
5 does not occur in accordance with the NT-proBNP levels, suggesting that serum NT-proBNP may
6 not reliably indicate pulmonary congestion having been resolved. These results lead us to consider
7 this molecule a useful marker for the discrimination of the possible origin of respiratory failure,
8 but it is not so precise in monitoring HF recovery. NT-pro-BNP has proved to be effective only in
9 excluding/confirming congestive HF. These data support the use of this molecule in the Critical
10 care setting rather than in the Internal Medicine department. Moreover, it has been established that
11 NPs levels are affected by age, as known, [27] or by other conditions as such as body mass index
12 [28], myocardial ischemia and hypoxia even in the absence of left ventricular dysfunction [29],
13 hormonal dysfunctions [30], renal failure and diabetes [31].

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

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

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

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

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

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

8

9 **Conclusions**

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

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1 **List of abbreviations:**

2 **CXR:** Chest X ray

3 **HF:** Heart Failure

4 **HFpEF:** Heart Failure with preserved ejection fraction

5 **HFmrEF:** Heart Failure with mid-range ejection fraction

6 **HFrEF:** Heart Failure with reduced ejection fraction

7 **ICVCI:** inferior cave vein collapsability index

8 **LUS:** Lung Ultrasound.

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

10 **NYHA:** New York Heart Association

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13 **Conflict of interest:** none.

14

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

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