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**Prognostic implication of lung ultrasound in heart failure:
pooled analysis of international cohorts**

Running title: prognostic impact of LUS in HF: pooled analysis

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Abstract

Background: Lung ultrasound (LUS) is often used to assess congestion in heart failure (HF).

In this study, we assessed the prognostic role of LUS in HF patients at admission and hospital discharge, and in an out-patient setting and explored whether clinical factors (age, sex, left ventricular ejection fraction (LVEF) and atrial fibrillation) impact the prognostic value of LUS findings. Further, we assessed the incremental prognostic value of LUS on top of AHEAD and MAGGIC clinical risk scores.

Methods and Results: We pooled data of patients hospitalized for HF or followed-up in out-patient clinics from international cohorts. We enrolled 1,947 patients, at admission (n=578), discharge (n=389) and in out-patient clinic (n=980). Total LUS B-line count was calculated for the 8-zone scanning protocol. The primary outcome was a composite of re-hospitalization for HF and all-cause death. Compared to those in the lower tertiles of B-lines, patients in the highest tertile were older, more likely to have signs of HF and higher NT-proBNP levels. A higher number of B-lines was associated with increased risk of primary outcome at discharge (Tertile3 vs Tertile1: adjustedHR= 5.74 (3.26- 10.12), $p<0.0001$) and in out-patients (Tertile3 vs Tertile1: adjustedHR= 2.66 (1.08- 6.54), $p=0.033$). Age and LVEF did not influence the prognostic capacity of LUS in different clinical settings. Adding B-line count to MAGGIC and AHEAD scores improved net reclassification significantly in all three clinical settings.

Conclusion: A higher number of B-lines in patients with HF was associated with increased risk of morbidity and mortality, regardless of the clinical setting.

Keywords: Cardiovascular diseases, Heart failure, Lung ultrasound, Cardiac oedema, B-lines, Prognosis

Introduction

Congestion is a key pathophysiological feature of heart failure (HF), and one of the main drivers of symptoms, signs, adverse remodelling and, eventually, hospitalization and premature death.(1-6) Accurate assessment of congestion can provide valuable information on the risk of adverse outcome and guide HF management.

Assessment of B-lines on lung ultrasound (LUS) emerged as a semi-quantitative, quick and reliable imaging tool to facilitate a diagnosis and quantification of pulmonary congestion in patients with acute or chronic HF (7) and improve risk stratification, as recently highlighted by an EACVI consensus document (8). Serial LUS can also be used for bedside adjustment of diuretics dose in HF. Another advantage of LUS is that it is useful in diagnosing HF correctly in primary care setting where natriuretic peptide may not be immediately available (9). Of the different LUS protocols proposed and used (4, 8, 28-zones), the 8-zone protocol combines good accuracy and reproducibility with shorter time for image acquisition and it might, therefore, be preferred to others (10). However, which clinical factors like age, sex or left ventricular ejection fraction (LVEF) may affect prognostic interpretation of LUS in patients with HF has not been well studied. Similarly, it is not known if LUS clearly improves risk stratification, mostly because of the small sample size of studies conducted so far (11, 12). Moreover, previous studies were focused either on the acute settings or the out-patients setting to assess the prognostic capacity of B-lines. However, in this paper, we take an integrative approach of assessing prognostic capacity of B-lines in different clinical setting in a pooled cohort of more than 1900 patients with HF.

Hence, in this research collaboration, we aimed to assess the prognostic relevance of B-lines in a broad-spectrum of patients with HF in different clinical settings (at admission, discharge and out-patient clinics) and according to different clinical phenotypes (age, sex, LVEF and presence/absence of atrial fibrillation (AF)). Further, we assessed the incremental

prognostic value of LUS on top of key biological markers (natriuretic peptides and eGFR) and two validated clinical risk scores in patients with HF, AHEAD and MAGGIC.

Method

Patient population

This retrospective study is the collaboration between eight cardiology centres wherein we pooled the patient-level data from eight cohort studies: (*Supplementary table 1*).

- i) **The Nancy cohort study (admission):** Included patients hospitalised for acute HF at “Département de Cardiologie Medicale”, Nancy, France from April 3, 2014 to August 4, 2015 (13). LUS was performed once, within 3 days of admission.
- ii) **The AHF-core study (admission and discharge):** An ongoing cohort study (NCT03327532) which includes patients hospitalised for acute HF in the two university hospitals of Grand-Est region of France. LUS was conducted within 72 hrs of admission and again before discharge.
- iii) **The Pisa cohort study (admission and discharge):** Included patients hospitalized for acute HF in the Cardiology Department in Pisa from October 2004 to October 2008 (3, 14). LUS was conducted within 24 hours of admission and before discharge.
- iv) **The Siena cohort study (admission and discharge):** Included patients with new-onset or worsening HF in sinus rhythm admitted to the Cardiovascular Diseases Unit in Siena (15). LUS was performed within 12 hours of admission and before discharge.
- v) **The Perugia cohort study (discharge):** Included patients hospitalised for acute HF at the Division of Cardiologia e Fisiopatologia Cardiovascolare in Perugia from April 2014 to October 2014 (16). LUS was conducted at discharge.
- vi) **Nis cohort (out-patients):** The out-patient cohort enrolled patients with HFpEF referred to Cardiology Clinic of the Niska Banja Institut, Nis University, Serbia from June 1, 2016 to February 1, 2018 (17).

vii) The Hull cohort study (out-patient): Included patients with HF attending a specialist clinic for a routine follow-up visit from April 2016 to March 2017 (18).

viii) The Barcelona cohort study (out-patient): Included patients with HF attending a routine clinical appointment from 6 July 2016 to 31 July 2017(19).

Main exclusion criteria in the cohorts were: (i) Inability to provide informed consent; (ii) Important lung disease potentially affecting LUS findings, such as pulmonary fibrosis, previous pneumectomy or lobectomy, pulmonary cancer or metastases; (iii) Other severe diseases hampering image acquisition.

Each cohort study was conducted in accordance with the Declaration of Helsinki and was approved by the respective Ethics Committees. Validation of the methodology has been performed and published previously (13).

Lung ultrasound and B-line count methods

LUS was performed by experienced cardiologists and resident doctors at each site using 28-zone scanning protocol in all cohorts except in the Siena and Barcelona cohort studies (15, 19), where the 8-zone method was used, as described below (*Figure 1S*). Subsequently, we used the following method to calculate the sum of B-lines for 8-zones from 28-zone LUS results:

B-line count method (*Figure 1S*): we grouped the 28 zones of LUS (4) in eight zones (20) as follows:

I) parasternal and midclavicular zones in second and third intercostal space on right side (4 zones grouped in 1 zone).

II) parasternal and midclavicular zones in second and third intercostal space on left side (4 zones grouped in 1 zone).

III) anterior and mid-axillary zones in second and third intercostal space on right side (4 zones grouped in 1 zone).

IV) anterior and mid-axillary zones in second and third intercostal space on left side (4 zones grouped in 1 zone).

V) para-sternal and midclavicular zones in fourth and fifth intercostal space on right side (4 zones grouped in 1 zone).

VI) anterior and mid-axillary zones in fourth and fifth intercostal space on right side (4 zones grouped in 1 zone).

VII) para-sternal and midclavicular zones in fourth intercostal space on left side (2 zones grouped in 1 zone).

VIII) anterior and mid-axillary zones in fourth intercostal space on left side (2 zones grouped in 1 zone).

Thereafter, we summed the highest number of B-lines seen in one of the 4 or 2 zones of each group to obtain their total count.

Study outcome

The primary outcome of this study was a composite of re-hospitalization for HF and all-cause death and the secondary outcomes were components of the primary outcome. All patients were followed-up in each institution, and patients and their relatives were contacted regularly by email or phone to collect clinical events of interest.

Statistical analyses

We combined the patient-level data from above-mentioned cohorts to constitute admission cohort (AHF-core, Nancy, Siena and Pisa cohort), discharge cohort (AHF-core, Pisa, Siena and Perugia cohort) and out-patient cohort (Nis, Hull and Barcelona cohort). Categorical variables are presented as percentages and continuous variable are presented as

mean \pm standard deviation for normally distributed data and median, 25th and 75th percentiles for skewed data. For each cohort of admission, discharge and out-patients, patients were divided into 3 groups according to the tertiles of B-lines.

Time-to-event comparisons were analysed using log-rank test and Cox proportional hazards models. Survival probabilities were estimated using the Kaplan-Meier method and plotted as survival curves with cohort specific tertiles of B-line counts. Cox proportional-hazards models were then used to obtain crude and adjusted hazard ratios (HR). The Cox models were adjusted for age and sex in M1 model and for age, sex, eGFR, systolic blood pressure in M2 model and adjustment variables of M2 model and natriuretic peptides (Z score of BNP and NT-proBNP) in M3 model. Further, Cox models were adjusted for cohort as a factor because of differences between the cohorts. Further, we tested the association of outcome with B-lines while adjusting for E/e' on top of M3 model. To illustrate the association of tertiles of B-lines with outcome according to age, sex, LVEF and presence/absence of AF, forest plots were created for admission, discharge and out-patient cohorts. In addition, we assessed the association of tertiles of B-lines of upper and lower LUS zones with the primary outcome.

The incremental prognostic value of B-line counts on top of risk models (clinical/biological model, MAGGIC score and AHEAD score) was assessed by calculating continuous net reclassification improvement after adding total B-line counts to clinical/biological model, MAGGIC and AHEAD score. The clinical/biological model included age, sex, eGFR, systolic blood pressure, and natriuretic peptides (Z score of BNP and NT-pro-BNP). The MAGGIC score is based on 13 variables and predicts morbidity (21) and mortality in patients with HF (21, 22). The AHEAD score is a simple risk stratification tool for patients with HF based on 5 risk factors which are AF, haemoglobin <130 g/l for men

and 120 g/l for women, elderly (age>70years), abnormal renal function (creatinine>130 $\mu\text{mol/l}$) and diabetes mellitus (23).

In addition, we conducted an intra-class correlation analysis to assess the inter-observer variability of the cardiologists involved in B-lines quantification in each centers (n=7) (24). The resulting intra-class correlation of the assessors of the B-lines in this study was 0.80 (95%CI 0.65 - 0.91) supporting a good reproducibility of the B-lines assessment across centers.

The two-tailed significance level was set at $p < 0.05$. All analyses were performed using SAS version 9.4.6 (SAS Institute Inc., Cary, NC) and R version 3.6.1 (2019-07-05).

Results

Baseline characteristics

In the admission (N= 578) and discharge cohort (N= 389), the median age was 78 years, 41% of the participants were women and approximately 45% participants had LVEF<40% (**Table 1**). The number of B-lines (maximum number possible = 80) in admission cohort was ≤ 15 in tertile 1, 16-29 in tertile 2 and >29 in tertile 3; at discharge, B-lines were ≤ 11 in tertile 1, 12-22 in tertile 2 and >22 in tertile 3. In the out-patient cohort (N= 980), median age was 72 years, 31% of the participants were women and around 31% participants had LVEF< 40%. The number of B-lines was ≤ 1 in tertile 1, 2-6 in tertile 2 and >6 in tertile 3.

Overall, patients in tertile 2 and tertile 3 were older and more likely to have clinical signs of congestion and atrial fibrillation than those in tertile 1; they also had a higher median BNP/NT-pro-BNP, but LVEF was similar. Median AHEAD and MAGGIC score were both higher in patients with a higher number of B-lines in discharge and out-patient cohorts (all p-values <0.05), whereas, AHEAD score was also higher in tertile 2 and tertile 3 compared to tertile 1 in admission cohort.

Prognostic capacity of B-lines at admission, discharge and out-patient setting

Over a median follow-up of 180 (90-589), 126 (75 - 180) and 829 (527 - 968) days, the primary outcome occurred in 39% (n=226), 48% (n=188) and 30% (n=296) of patients in admission, discharge and out-patient cohorts, respectively. Higher B-line count was significantly associated with higher frequency of primary outcome in all the cohorts (All p-values < 0.001) (**Figure 1**).

In the discharge cohort, compared to tertile 1, tertile 2 and tertile 3 were significantly associated with increased risk in fully adjusted model (HR T2 vs T1: 1.80 (1.01 - 3.22),

p=0.046 and T3 vs T1: 5.81 (3.30 - 10.25), p<0.0001)). When further adjusting on E/e', the association of higher number of B-line counts with the primary outcome remained significant in the discharge cohort (tertile 1 vs tertile 2 and tertile 3 combined, HR: 3.26 (1.24 – 8.54), p= 0.016).

In the out-patient cohort, tertile 3 was significantly associated with increased risk in adjusted clinical model (HR = 3.42 (1.22 - 9.59)), however when the model was further adjusted with natriuretic peptides no association was observed between number of B-lines and outcome.

Further, higher B-line count was not associated with increased risk of hospitalization for HF or death at admission and in out-patient cohort in fully adjusted model whereas, higher B-line count at discharge (tertile 3 vs tertile 1) was associated with significantly increased risk of both, hospitalization for HF and death (*supplementary Table 2*).

In the admission and discharge cohorts, higher number of B-lines in upper zone (tertile 3 vs tertile 1) were significantly associated with increased risk of outcomes whereas higher number of B-lines in lower zone were less predictive. In contrast, a higher number of B-lines in upper zone and in lower zone were both significantly associated with increased risk in out-patient cohort with similar HR: (2.40 (1.12 - 5.13), p=0.024 and 2.55 (1.03 - 6.30), p= 0.043. respectively. (**Supplementary table 3**)

Association of B-lines with primary outcome according to clinical variables

In the admission cohort, the association of B-lines with primary outcome was affected by the underlying heart rhythm (p-interaction =0.0016) (**Figure 2**). In the discharge cohort, the association of B-lines with primary outcome was influenced by sex (p-interaction=0.007) whilst in the out-patient cohort, the prognostic capacity of B-lines was not influenced by any clinical variables (all p-interaction > 0.05).

Incremental prognostic value of risk scores by adding number of B-lines counts

In admission and discharge cohort, addition of B-lines to clinical, MAGGIC or AHEAD risk score significantly improved net reclassification for primary outcome (all p-values ≤ 0.01) (*Figure 3*). The net reclassification improvement was higher than 30% in the discharge cohort.

In out-patient cohort, addition of B-lines improved net reclassification of clinical model by 13.8% (p=0.03) and of AHEAD score by 18.9 % (p=0.03) however, the net reclassification improvement was non-significant over MAGIC score.

Discussion

In this pooled cohort study, we found that higher B-line counts were independently associated with the risk of hospitalization for HF and death in both in-patient and in an out-patient setting. Further, LUS predicted outcome irrespective of the clinical characteristics. Moreover, addition of B-lines to clinical, MAGGIC and AHEAD scores improved risk stratification. AF influenced the prognostic capacity of B-lines in the admission cohort but not in discharge and out-patient cohorts.

Prognostic capacity of LUS in hospitalised patients and in out-patients

In a very heterogeneous group of patients with HF, higher count of B-lines predicts mid-term risk of hospitalisation or death in different settings. The association was, however, not significant when adjusting on NP in outpatients, possibly because of limited statistical power in this relatively low risk subgroup. Similar results were reported by Platz et al., where pre-discharge higher tertiles of B-lines were associated with higher risk at short- and mid-term outcomes in patients with HF (24). Moreover, post-hoc analysis of ESCAPE trial demonstrated that persistent pulmonary congestion was associated worse prognostic outcome within 6 months of hospitalization for HF and management of congestion may be more prognostically important than improving cardiac index in these patients (25). However, no

significant association between the number of B-lines at admission and outcome was identified despite a sizeable sample size (N=578) and high risk of events in this subgroup. Our results are in line with other previous reports that assessed pulmonary congestion using chest radiography on admission and found only weak and inconsistent associations with future risk (26, 27). In contrast, discharge congestion, referred to as “residual congestion” (16), is probably the key prognostic variable, capturing the ability to decongest patients during the hospitalization which probably parallels the ability to maintain decongestion thereafter. Moreover, a recent study shows that poor in-hospital improvement in congestion is associated with poor prognosis (28). These findings indicate that a patient may still have good prognosis despite higher level of congestion if the patients responds well to the given treatment. In addition, previous studies have reported conflicting results on the prediction capacity of B-lines measured at admission (3, 29). In a study by Gargani et al., more than 50 B-lines at admission were not associated with increased risk in patients with acute HF (aHR: 4.87 (0.88 – 27.06), p= 0.07) (3) whereas, in another study higher number of B-lines (>30) was associated in adverse outcome in overall population.(29) Taken together, this suggests that residual pulmonary congestion at the time of discharge, rather than congestion at admission, is one of the major factors associated with a poor prognosis in HF. Our findings highlight the limited prognostic value of admission congestion rather than the limited value of LUS itself.

Taking advantage of the individual patient data, we found that the prognostic capacity of LUS to identify patients at a higher risk remains mostly unchanged in the sub-group analysis according to age, sex, LVEF, natriuretic peptide levels and presence/absence of AF. These results suggest that the prognostic value of B-lines is unaffected by clinical characteristics, something that is not necessarily true for other echocardiographic indices of congestion (5, 15, 30). For instance, in patients with AF, E/A ratio and E/e’ cannot be reliably measured or used to predict future risk (15).

B-lines on top of clinical risk scores for predicting risk of outcome

Another important finding of this study is that adding B-line count to clinical risk scores, like MAGGIC and AHEAD, improved the net reclassification of patients at high risk regardless of the clinical setting. Our findings concur with the previously published study, which assessed incremental capacity of B-lines on top of 4 different HF risk scores in a cohort of 123 AHF patients at discharge. The study reported that addition of B-line count significantly improved the predictive value of HF risk scores (31). This improvement is likely related to the detection of subclinical congestion not identified on physical examination. In stable HF patients, up to 50% of patients have sub-clinical congestion that can go undetected on physical examination at the time of discharge or in an out-patient setting, unless ultrasound is used (18, 32), and that worsening subclinical congestion by ultrasound is associated with higher natriuretic peptides and an increased risk of cardiovascular events. Hence, LUS can improve the ability of AHEAD or MAGGIC score to identify the patients at higher risk. In addition, LUS significantly improved net reclassification in a clinical/biological model that included powerful prognosticators such as natriuretic peptides. This may be related to LUS specifically evaluating pulmonary congestion, which is intrinsically related to dyspnoea, whereas natriuretic peptides are possibly related to less specific congestion patterns and influenced by renal function and the presence of AF (13).

Clinical implications

Congestion assessment using LUS can provide important prognostic information in patients with HF irrespective of the phenotype and clinical setting (33). LUS can be implemented systematically along with clinical examination at the time of discharge and during follow-up visits to identify the patients at higher risk, especially those who do not have

clinical signs of congestion (18). Nowadays, it is becoming easy and practical to conduct LUS in any setting with the availability of hand-held devices and transducers that can be easily connected to mobile devices, including smartphones. Moreover, natriuretic peptides assessment is not always available across all hospitals or to many primary care providers; and when it is, it will take time to obtain results (9). Findings from LUS can be interpreted in real time and serial examinations can quantify and monitor response to treatment, particularly diuretics (34). Although results were disappointing for LUS-guided management in hospitalised patients (35), LUS-guided management after discharge was associated with clinical benefits in several clinical trials in patients with HF (36, 37). Recent studies demonstrate that novice residents with limited or no previous experience in LUS can acquire proficiency in reliably quantifying B-lines with minimal training (38, 39). Moreover, LUS can be easily performed by nurses and other healthcare providers, which reinforces the incentive to use LUS for assisting with management in this context (40).

Limitations

Our study has some limitations. First, although this is a patient-level pooled analysis of eight cohorts, the admission, discharge and out-patient cohorts were moderate in size limiting the generalisability of the results. Second, individual cohorts had some differences in available baseline data, method of variable measurements and patient selection. Third, experienced practitioners in each institution assessed LUS; however, there could have been inter-observer variability. Further, B-line counts could be different depending on cohort studies, possibly because of the different LUS protocol (patient position, transducer settings) of the cohort studies. Despite these differences, we found strong association of B-lines with outcomes in discharge and out-patient cohorts, adding to generalisability of our results. LUS findings are pragmatically relevant in a broad array of clinical settings and centres. Fourth, in the Nancy cohort and AHF-core, patients underwent LUS assessment within 3 days from their

admission, whereas in Siena and Pisa patient underwent LUS within 12 hours and 24 hours from admission, respectively: it is possible that prior administration of diuretic therapy may have influenced B-line counts in these patients.

Conclusion

In this study, a higher number of B-lines in patients with HF was associated with increased risk of morbidity and mortality and improved risk stratification, regardless of the clinical setting or patients' profile.

Table 1: Baseline characteristics according to the tertiles of B-lines in highest number of B-lines per zone method in each clinical setting

Max counts = 80	In patients - Admission				In patients - Discharge				Out-patients												
	Tertile 1 (Counts <=15) (n=204)		Tertile 2 (Counts 16-29) (n=190)		Tertile 3 (Counts >29) (n=184)		P-value	Tertile 1 (Counts <=11) (n=140)		Tertile 2 (Counts 12-22) (n=123)		Tertile 3 (Counts >22) (n=126)		P-value	Tertile 1 (Counts <=1) (n=319)		Tertile 2 (Counts 2-6) (n=341)		Tertile 3 (Counts >6) (n=320)		P-value
	n	median (IQR)/n (%)	n	median (IQR)/n (%)	n	median (IQR)/n (%)		n	median (IQR)/n (%)	n	median (IQR)/n (%)	n	median (IQR)/n (%)		n	median (IQR)/n (%)	n	median (IQR)/n (%)	n	median (IQR)/n (%)	
Age, yrs	204	74.0 (66.5 - 80.0)	190	77.5 (70.0 - 82.0)	184	79.0 (75.0 - 85.0)	< 0.0001	140	75.0 (67.0 - 80.0)	123	80.0 (75.0 - 85.0)	126	80.5 (76.0 - 86.0)	< 0.0001	319	67.5 (58.2 - 75.0)	341	71.0 (62.1 - 78.9)	320	76.4 (69.0 - 82.3)	< 0.0001
Women, N (%)	204	77 (37.7 %)	190	80 (42.1 %)	184	82 (44.6 %)	0.38	140	44 (31.4 %)	123	65 (52.8 %)	126	53 (42.1 %)	0.002	319	99 (31.0 %)	341	114 (33.4 %)	320	96 (30.0 %)	0.62
Body mass index, kg/m ²	183	27.3 (24.1 - 30.5)	162	29.0 (26.0 - 30.9)	180	26.0 (24.0 - 28.7)	< 0.0001	98	29.0 (26.0 - 31.8)	110	28.3 (25.0 - 30.5)	119	26.0 (24.4 - 28.4)	< 0.0001	318	28.4 (25.2 - 32.5)	340	28.4 (25.3 - 31.2)	315	27.1 (24.1 - 30.2)	0.0006
Medical history, N (%)																					
Ischemic heart disease	204	83 (40.7 %)	190	88 (46.3 %)	183	95 (51.9 %)	0.088	140	59 (42.1 %)	122	54 (44.3 %)	126	61 (48.4 %)	0.59	319	128 (40.1 %)	340	153 (45.0 %)	320	154 (48.1 %)	0.12
Atrial fibrillation	188	63 (33.5 %)	181	64 (35.4 %)	174	44 (25.3 %)	0.093	127	43 (33.9 %)	118	24 (20.3 %)	118	40 (33.9 %)	0.029	314	58 (18.5 %)	339	90 (26.5 %)	316	140 (44.3 %)	< 0.0001
Prior HF	198	172 (86.9 %)	99	87 (87.9 %)	59	54 (91.5 %)	0.68	108	88 (81.5 %)	34	27 (79.4 %)	31	27 (87.1 %)	0.75	24	20 (83.3 %)	37	30 (81.1 %)	0	0 (0 %)	1
COPD	201	28 (13.9 %)	98	14 (14.3 %)	57	6 (10.5 %)	0.83	107	34 (31.8 %)	34	8 (23.5 %)	30	5 (16.7 %)	0.23	319	33 (10.3 %)	341	43 (12.6 %)	320	57 (17.8 %)	0.02
CRT	190	48 (25.3 %)	90	21 (23.3 %)	49	19 (38.8 %)	0.12	95	20 (21.1 %)	29	2 (6.9 %)	23	11 (47.8 %)	0.003	295	52 (17.6 %)	304	28 (9.2 %)	320	45 (14.1 %)	0.009
Clinical examination																					
NYHA III/IV, N (%)	195	95 (48.7 %)	93	61 (65.6 %)	51	37 (72.5 %)	0.001	54	3 (5.6 %)	13	6 (46.2 %)	7	3 (42.9 %)	0.0003	319	34 (10.7 %)	341	46 (13.5 %)	320	100 (31.3 %)	< 0.0001
Systolic BP, mmHg	193	130 (115 - 143)	177	125 (110 - 140)	182	130 (110 - 140)	0.19	55	115 (105 - 127)	17	105 (103 - 111)	14	115 (95 - 120)	0.23	101	131 (121 - 147)	147	130 (119 - 146)	155	136 (122 - 159)	0.011
Heart rate, bpm	192	72 (64 - 87)	176	87 (78 - 95)	182	89 (85 - 96)	< 0.0001	55	74 (65 - 80)	17	80 (70 - 90)	14	75 (70 - 82)	0.26	101	69 (60- 80)	147	70 (64 - 80)	155	73 (65 - 81)	0.14
Leg edema, N (%)	200	61 (30.5 %)	190	109 (57.4 %)	184	114 (62.0 %)	< 0.0001	87	11 (12.6 %)	106	22 (20.8 %)	109	49 (45.0 %)	< 0.0001	101	20 (19.8 %)	147	39 (26.5 %)	155	79 (51.0 %)	< 0.0001
Rales, N (%)	201	72 (35.8 %)	190	146 (76.8 %)	184	155 (84.2 %)	< 0.0001	87	15 (17.2 %)	106	22 (20.8 %)	109	70 (64.2 %)	< 0.0001	101	0 (0.0 %)	147	7 (4.8 %)	155	35 (22.6 %)	< 0.0001
Medications, N(%)																					
ACEi or ARB	182	127 (69.8 %)	178	132 (74.2 %)	175	149 (85.1%)	0.002	110	79 (71.8 %)	117	92 (78.6 %)	122	97 (79.5 %)	0.34	319	281 (88.1 %)	341	290 (85.0%)	320	245 (76.6%)	0.0004
Beta-blocker	182	60 (33.0 %)	178	80 (44.9 %)	175	100 (57.1%)	< 0.0001	110	57 (51.8 %)	117	66 (56.4 %)	122	71 (58.2 %)	0.6	319	296 (92.8 %)	341	304 (89.1%)	320	275 (85.9%)	0.018
MRA	181	81 (44.8 %)	88	39 (44.3 %)	50	27 (54.0 %)	0.49	78	43 (55.1 %)	28	13 (46.4 %)	27	15 (55.6 %)	0.74	319	175 (54.9 %)	341	171 (50.1%)	320	153 (47.8%)	0.19
Loop diuretics	182	147 (80.8 %)	178	164 (92.1 %)	175	158 (90.3%)	0.003	110	104 (94.5 %)	117	105 (89.7%)	122	115 (94.3 %)	0.32	319	215 (67.4 %)	341	231 (67.7%)	320	255 (79.7%)	0.0003
Laboratory findings																					
Hemoglobin, g/dl	131	12.8 (11.6 - 14.0)	159	12.2 (10.8 - 13.6)	168	12.0 (10.9 - 13.3)	0.001	99	12.6 (11.1 - 13.9)	114	11.8 (10.5 - 13.6)	114	11.5 (10.2 - 12.7)	0.002	318	13.8 (12.6 - 14.9)	341	13.5 (12.3 - 14.5)	318	13.1 (12.0 - 14.1)	< 0.0001
eGFR, ml/min/1.73m ²	197	60.9 (47.0 - 75.9)	189	50.8 (35.4 - 72.0)	181	48.6 (37.2 - 63.1)	< 0.0001	111	53.0 (38.8 - 66.5)	116	41.4 (30.1 - 59.1)	120	45.6 (32.9 - 57.8)	0.005	319	69.7 (50.2 - 87.7)	339	64.4 (48.2 - 81.1)	319	57.7 (41.2 - 77.0)	< 0.0001
BNP, pg/ml	105	498 (252 - 795)	153	822 (576 - 1196)	154	1230 (790 - 1870)	< 0.0001	90	342 (177 - 616)	111	471 (312 - 746)	111	988 (714 - 1780)	< 0.0001	24	41 (32 - 55)	37	71 (45 - 127)	0	-	0.0003
NT pro-BNP, pg/ml	147	1664 (907 - 2981)	57	3441 (1740 - 5588)	47	4632 (2851 - 9134)	< 0.0001	41	1655 (572 - 3019)	15	7474 (1934 - 10475)	20	2344 (1820 - 7440)	0.0002	288	460 (187 - 1251)	295	783 (293 - 1740)	316	1599 (735 - 3419)	< 0.0001
Echocardiography																					
LVEF, %	204	40.0 (30.0 - 53.5)	189	40.0 (30.0 - 50.0)	183	38.0 (25.0 - 50.0)	0.38	140	40.0 (30.0 - 50.0)	123	40.0 (32.0 - 52.0)	125	40.0 (25.0 - 50.0)	0.077	319	47.0 (36.0 - 55.0)	341	47.0 (36.0 - 57.0)	320	45.0 (36.0 - 55.0)	0.56
LVEF<40%	204	97 (47.5 %)	189	84 (44.4 %)	183	93 (50.8 %)	0.48	140	64 (45.7 %)	123	52 (42.3 %)	125	60 (48.0 %)	0.67	319	101 (31.7 %)	341	108 (31.7%)	320	102 (31.9%)	1.00
Blines	204	6.0 (0.0 - 11.0)	190	24.5 (20.0 - 27.0)	184	36.0 (32.0 - 42.0)	< 0.0001	140	6.0 (3.0 - 9.0)	123	16.0 (14.0 - 20.0)	126	29.0 (26.0 - 34.0)	< 0.0001	319	0.0 (0.0 - 1.0)	341	3.0 (2.0 - 5.0)	320	12.0 (8.0 - 18.0)	< 0.0001
Scores																					
AHEAD score	204	1.5 (1.0 - 2.0)	190	2.0 (1.0 - 3.0)	184	2.0 (2.0 - 3.0)	< 0.0001	140	2.0 (1.0 - 3.0)	123	2.0 (2.0 - 3.0)	126	3.0 (2.0 - 3.0)	< 0.0001	319	1.0 (0.0 - 2.0)	341	2.0 (1.0 - 2.0)	320	2.0 (1.0 - 3.0)	< 0.0001

MAGGIC score	204	22.0	190	22.0	184	22.0	0.26	140	18.0	123	21.0	126	22.0	< 0.0001	319	14.0	341	17.0	320	21.0	< 0.0001
		(18.0 - 27.0)		(19.0 - 25.0)		(20.0 - 27.0)			(14.0 - 22.0)		(18.0 - 24.0)		(19.0 - 24.0)		(9.0 - 20.0)		(12.0 - 22.0)		(16.0 - 26.0)		

ACEi: ACE inhibitor; ARB: angiotensin receptor blocker; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronization therapy; HF: heart failure; MRA: mineralocorticoid receptor antagonist; LVEF: left ventricular ejection fraction

Figure 1: Crude and adjusted hazard ratios for association between B-lines and primary outcome for B-line count

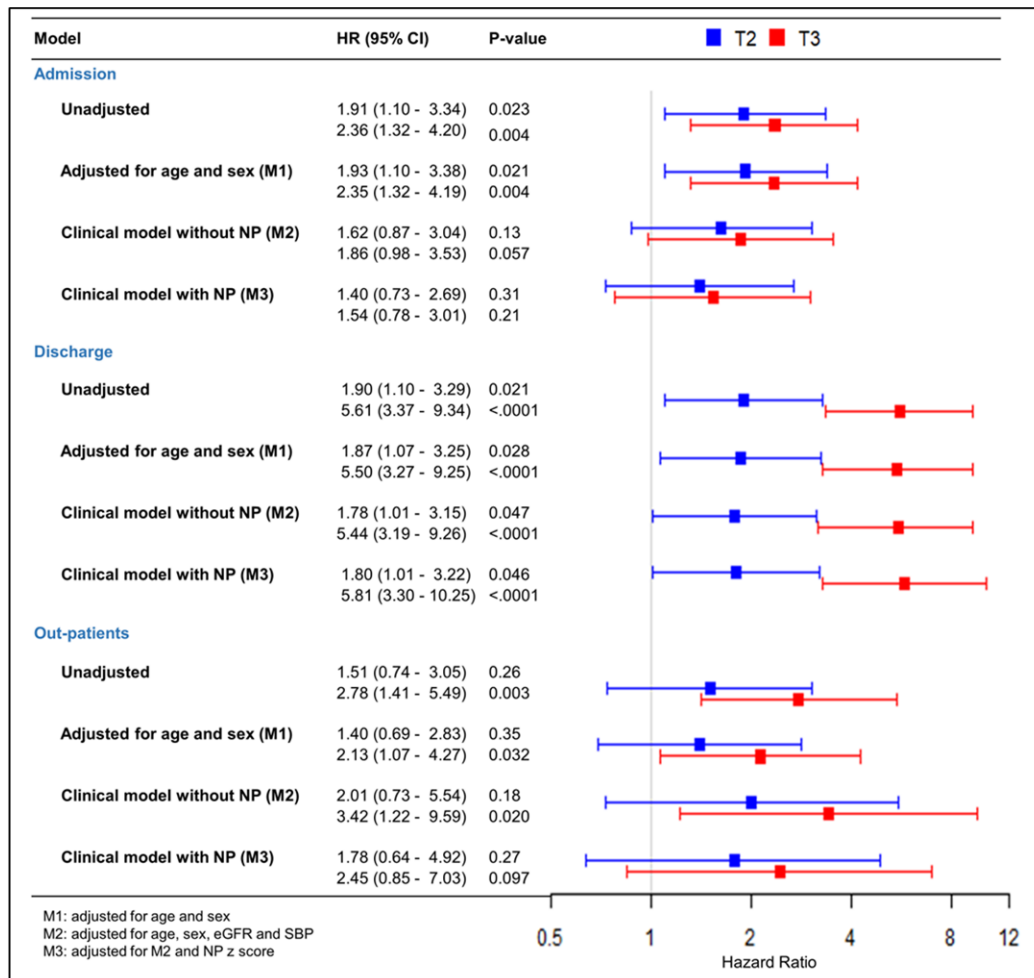
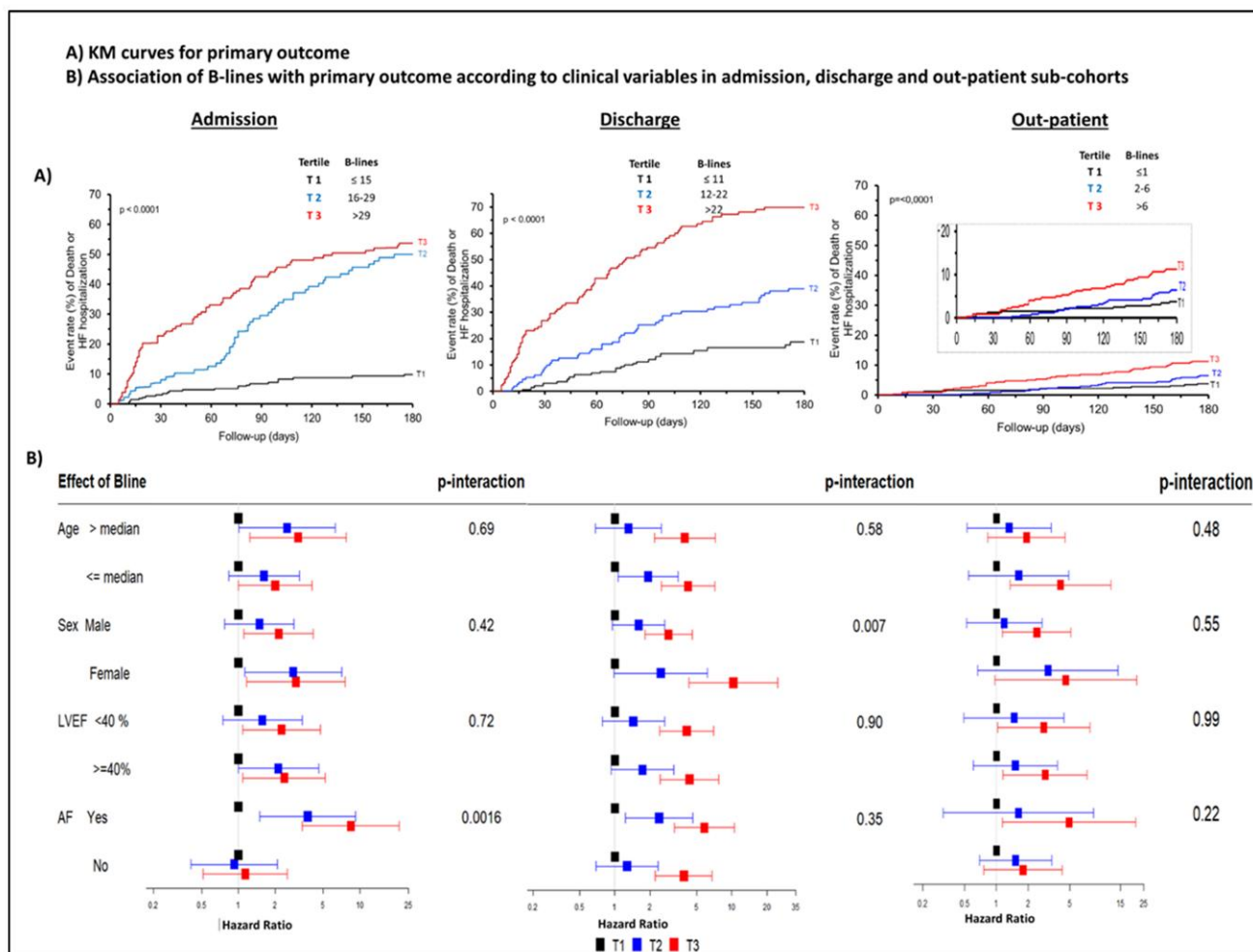
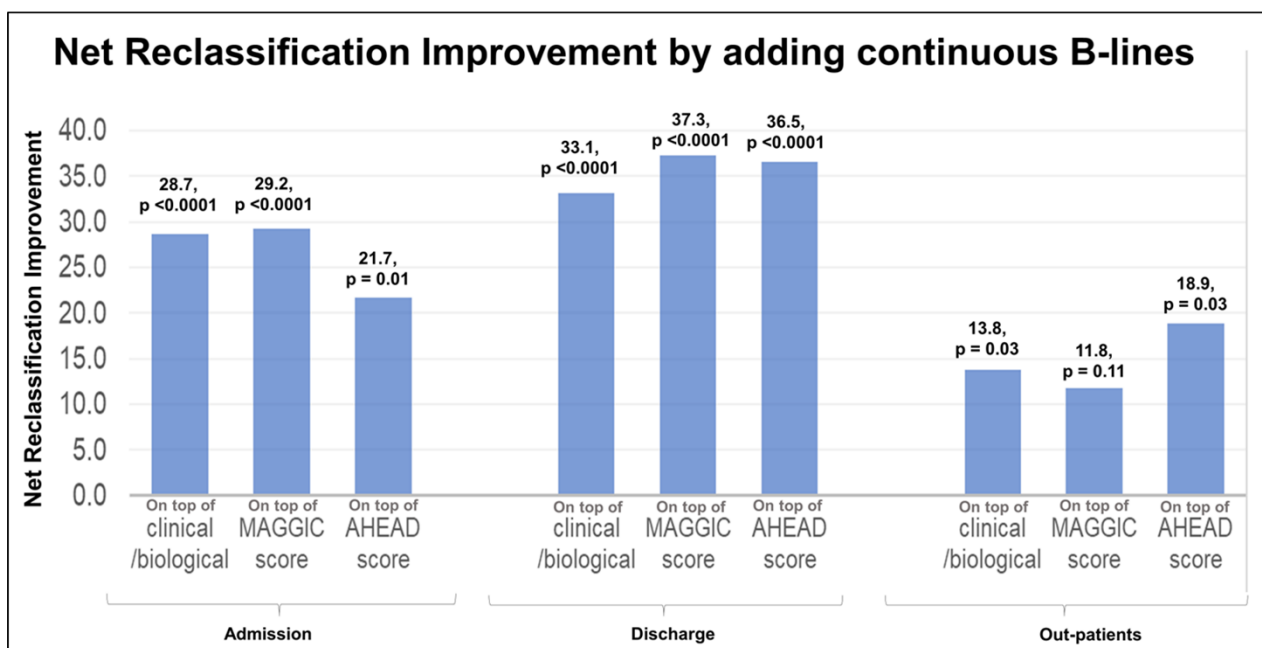


Figure 2: (a) KM curves for primary outcome and (b) association of B-lines with primary outcome according to clinical variables in admission, discharge and out-patient cohorts



Inset: magnified view of KM curves in the plot for out-patients.

Figure 3: Net Reclassification Improvement for risk of primary outcome in clinical



model, MAGGIC score and AHEAD score by adding continuous B-lines

Legends on the bar present the net reclassification improvement and the p-value.

Figure: Graphical abstract

Prognostic implication of Lung UltraSound in Heart Failure in different clinical settings

Prognostic value of B-line count on Lung UltraSound in HF

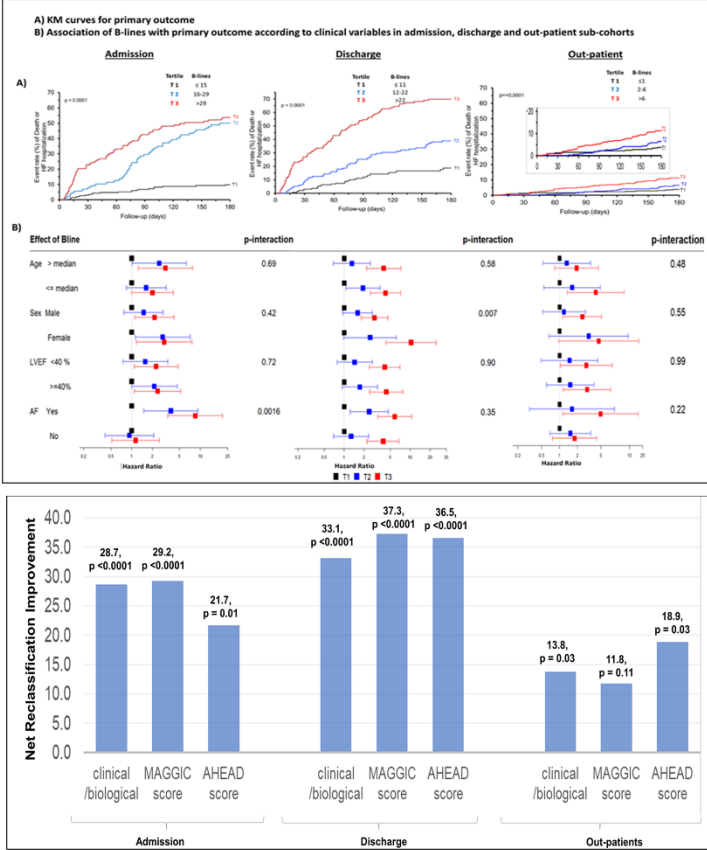
➔

- Higher risk of hospitalization for HF or death in patients with higher B-line count
- In all 3 clinical setting
- Regardless of age or LVEF

Added prognostic value of B-line count On top of risk scores

➔

- Improved net reclassification (%) in all 3 clinical setting



Data availability statement:

The data that supports the findings of this study are available on reasonable request to corresponding authors.

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