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Prognostic Value of Lung Ultrasound in Ambulatory Patients with Recently Diagnosed Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is highly prevalent and clinically diverse, with pulmonary congestion (PC) playing a central role in driving poor outcomes. Lung ultrasound (LUS) allows bedside detection of PC through B-line quantification, but its prognostic role in ambulatory HFpEF has not been fully established.

Objective: to compare the prognostic utility of LUS-derived B-lines with N-terminal pro-B-type natriuretic peptide (NT-proBNP) and echocardiographic measures, particularly left atrial reservoir strain (LASr), in patients recently diagnosed with HFpEF in the outpatient setting.

Methods: A total of 131 consecutive patients with suspected HFpEF underwent comprehensive echocardiography, LUS using a 28-zone protocol, and NT-proBNP testing. Following exclusion based on predefined criteria, 75 patients (mean age 70.3 ± 6.7 years; 56.0% women) were enrolled and monitored for a composite endpoint of heart failure hospitalization, diuretic intensification, or all-cause mortality over a median follow-up of 26 [22–32] months.

Results: Eleven patients (14.7%) experienced the composite outcome during follow-up. LUS was feasible in all patients, requiring 2.5 ± 0.47 minutes per scan. B-line counts correlated positively with NT-proBNP ($r = 0.330$, $p<0.001$) and inversely with LASr ($r = –0.418$, $p<0.001$). A threshold of >15 B-lines showed strong prognostic accuracy (AUC 0.863, 95% CI: 0.771–0.955), comparable to NT-proBNP (AUC 0.859, 95% CI: 0.765–0.952; $p=0.927$). Multivariable analysis confirmed >15 B-lines (HR 15.234, 95% CI: 1.864–124.530, $p=0.011$) and log-transformed NT-proBNP (HR 2.876, 95% CI: 1.187–6.967, $p=0.019$) as independent predictors. Event-free survival at 20 and 40 months was 100% and 97.3% in patients with ≤15 B-lines, compared to 72.0% and 58.2% in those with >15 (log-rank $\chi^2=16.804$, $p<0.001$).

Conclusions: LUS B-line quantification is a rapid, feasible, and reliable method for prognostic assessment in ambulatory HFpEF. A threshold of >15 B-lines identifies patients at higher risk of adverse events, with performance comparable to NT-proBNP, supporting its role in risk stratification and potential integration into outpatient management.

KEYWORDS: HFpEF; lung ultrasound; B-lines; pulmonary congestion; NT-proBNP; prognosis; risk stratification

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INTRODUCTION

Nearly 50% of heart failure cases are heart failure with preserved ejection fraction (HFpEF), and its incidence is rising rapidly

due in large part to related comorbidities such diabetes, obesity, and hypertension. In contrast to heart failure with reduced ejection fraction, HFpEF is a multifaceted condition characterized by abnormalities in diastolic relaxation, structural changes in the left atrium, and elevated filling pressures, making both diagnosis and risk prediction particularly complex. A hallmark of HFpEF is PC, which results from elevated left atrial and pulmonary capillary wedge pressures and is strongly linked to poor clinical outcomes [1][2].

Current diagnostic and prognostic strategies for HFpEF include the use of natriuretic peptides and advanced echocardiographic measures, such as the E/e′ ratio, left atrial volume index, and LASr. While NT-proBNP provides prognostic insight, its interpretation may be confounded by factors including age, renal dysfunction, body mass index, and the presence of atrial fibrillation. Similarly, LASr is a useful marker of atrial performance and correlates with invasive filling pressures, but its assessment is technically demanding and less reliable in patients with atrial fibrillation [3][4].

Lung ultrasound has gained attention as a non-invasive, radiation-free method for identifying B-lines—vertical artifacts reflecting PC. This tool has shown strong diagnostic and prognostic performance in both acute and chronic heart failure, independent of ejection fraction [11–13]. In hospitalized patients with HFpEF, quantifying B-lines has been associated with prediction of rehospitalization and mortality, with accuracy comparable to natriuretic peptide levels. However, limited evidence exists regarding the prognostic value of LUS performed at the time of HFpEF diagnosis in outpatient settings [5][6].

In a prospective cohort of ambulatory patients recently diagnosed with HFpEF, the study's goal was to assess the prognostic significance of LUS-derived B-line quantification in relation to NT-proBNP and echocardiographic parameters, including LASr. We hypothesized that B-line assessment would provide incremental prognostic information beyond traditional tools, enabling earlier and more precise risk stratification in this complex patient population.

METHODS

Study Design and Population

This prospective, single-center observational cohort research study was collaboratively conducted across multiple departments affiliated with prestigious medical institutions in Egypt from 1st June 2024 to July 2025. These included the Departments of Cardiology, Pulmonology, Radiodiagnosis and Interventional Radiology, and Internal Medicine at the Faculty of Medicine, Al-Azhar University, Assiut. Additional collaboration involved the Faculty of Medicine at Cairo University, which contributed statistical review expertise, Department of Cardiology, Faculty of Medicine, Minia University, and the Department of Radiology at the Faculty of Medicine, Ain Shams University, Cairo. All study procedures were carried out under the supervision of certified specialists in cardiology, pulmonology, radiology, and internal medicine from these participating institutions.

Patients referred from primary care with mild to moderate symptoms suggestive of heart failure and no prior HF diagnosis were consecutively screened. Eligibility criteria included: (1) age ≥18 years; (2) HFpEF diagnosis based on the 2016 ESC guidelines; (3) left ventricular ejection fraction ≥50% on echocardiography; (4) either sinus rhythm or atrial fibrillation with resting heart rate ≤80 bpm at enrollment; (5) absence of moderate/severe valvular disease; and (6) no history of cardiomyopathy or significant coronary artery disease. Exclusion criteria were: (1) asthma, pulmonary hypertension, moderate to severe chronic obstructive pulmonary disease, or prior interstitial lung disease; (2) advanced renal dysfunction (eGFR <35 mL/min/1.73 m²) or anemia (hemoglobin <100 g/L); (3) active malignancy (except localized basal cell carcinoma or prostate cancer); and (4) inability to provide informed consent [1].

Patient inclusion and exclusion were reported following CONSORT guidelines. Data were obtained through structured questionnaires administered by an investigator blinded to clinical records and imaging outcomes.

Echocardiographic Assessment

Transthoracic echocardiography was carried out using a Vivid-S70 ultrasound system (GE Vingmed, Horten, Norway) equipped with a 3S phased-array probe (1.5–3.6 MHz). All scans were performed by an experienced cardiologist accredited in transthoracic echocardiography by the European Association of Cardiovascular Imaging, in line with ASE/EACVI recommendations.

Standard echocardiographic parameters included left ventricular ejection fraction (Simpson’s biplane method), left ventricular dimensions, left atrial volume index, left ventricular mass index, relative wall thickness, mitral inflow velocities (E and A waves), tissue Doppler imaging of septal and lateral e′ velocities, E/e′ ratio, and tricuspid regurgitant velocity for estimating pulmonary artery systolic pressure.

Myocardial deformation was assessed using GE EchoPAC software (version v202). Left ventricular global longitudinal strain was analyzed with the QRS complex as the reference point. Left atrial strain parameters were retrospectively evaluated by two independent observers, following EACVI consensus guidelines. The R-wave upslope on ECG was used to define end-diastole. Apical four- and two-chamber views were acquired at 40–80 frames per second, with three cardiac cycles averaged. Endocardial borders were manually tracked to calculate longitudinal strain, and LASr was determined during the reservoir phase.

To ensure reproducibility, intra- and inter-observer variability was tested in 20 randomly selected patients. Variation was minimal, with coefficients <5% for ejection fraction and <10% for strain parameters.

Lung Ultrasound Protocol

LUS was carried out immediately after transthoracic echocardiography using the same imaging platform (Vivid-S70, GE

Vingmed, Horten, Norway) with a 3S phased-array transducer. All examinations were performed by a cardiologist with dedicated LUS training and prior experience, who remained blinded to both NT-proBNP concentrations and clinical data.

The scanning protocol adhered to established international standards, covering anterior and lateral thoracic regions on both sides. Imaging was obtained along the parasternal, midclavicular, anterior axillary, and midaxillary lines. The right lung was assessed from the second to fifth intercostal spaces, and the left lung from the second to fourth, resulting in a total of 28 predefined zones. A longitudinal probe position, perpendicular to the ribs, was used consistently.

B-lines were identified and quantified according to international consensus. They were defined as vertical, bright, comet-tail artifacts that originated from the pleural surface, extended to the far edge of the screen without fading, and moved in concert with lung sliding. The cumulative number of B-lines across all zones was recorded. When confluent B-lines occupied more than half of an intercostal space, they were counted as multiple individual lines based on visual estimation of spacing.

Image acquisition included optimization of gain and depth to ensure clear pleural visualization. For each zone, a 2-second video loop was stored to document lung sliding, and representative still frames were archived for subsequent review and quality control. Feasibility was defined as the proportion of patients in whom all 28 zones were successfully imaged. Examination time was measured from the initial probe placement until scanning of the final zone was completed.

Laboratory Analysis

Blood samples were collected from each participant within one hour after completion of the ultrasound examinations. NT-proBNP concentrations were determined using the Elecsys 2010 platform (Roche Diagnostics, Mannheim, Germany) in accordance with the manufacturer's recommendations. In addition, standard laboratory investigations were performed as part of routine clinical care, including complete blood count, metabolic panel, and calculation of estimated glomerular filtration rate.

Follow-up and Endpoint Definition

Patient follow-up was conducted in a structured manner, with telephone interviews scheduled every three months and outpatient clinic visits arranged every six months. The composite primary outcome consisted of three components: (1) death from any cause; (2) hospitalization for acute heart failure decompensation; and (3) worsening heart failure in the ambulatory setting requiring an escalation of loop diuretic therapy.

Outcome adjudication was based on review of hospital documentation, discharge reports, and, when required, direct consultation with the treating physician. Hospital admissions were classified as heart failure–related if acute heart failure was the principal diagnosis or the dominant clinical reason for hospitalization. Worsening heart failure requiring intensification of therapy was defined as either new initiation of loop diuretics or an increase in the pre-existing dose by ≥25%, prescribed specifically for symptomatic deterioration.

Follow-up ended at the occurrence of the first endpoint event, patient withdrawal or loss to follow-up, or at the predefined study closure date (July 31, 2025), whichever came first.

Statistical Analysis

The study, following STROBE guidelines, included about 70 patients based on power calculations and analyzed data using SPSS v22.0. Continuous and categorical variables were compared with appropriate parametric or non-parametric tests, while ROC analysis assessed prognostic accuracy of B-lines and NT-proBNP. Survival was evaluated with Kaplan–Meier and log-rank tests, and predictors were identified through Cox regression with checks for assumptions and multicollinearity. Missing data (<5%) were handled by complete case analysis, and significance was set at $p<0.05$.

RESULT

Study Population and Patient Enrollment Between June 2024 and July 2025, 131 consecutive patients with suspected HFpEF were screened for study eligibility (Figure 1**).**

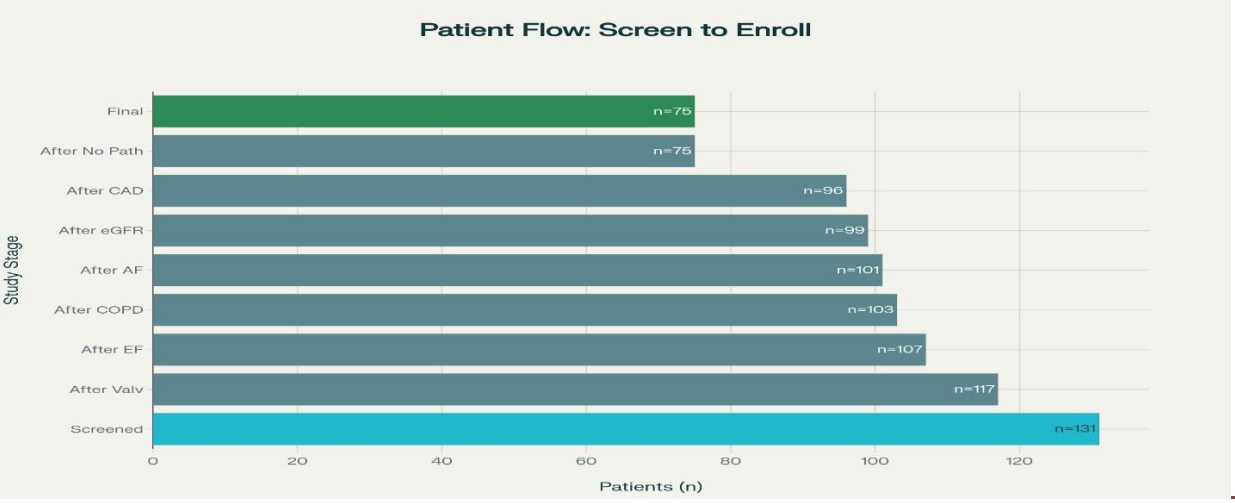

Figure 1: CONSORT flow diagram showing patient enrollment and exclusions

Following application of inclusion and exclusion criteria, 75 patients (57.3%) were enrolled in the final analysis. The primary reasons for exclusion were moderate or severe valvular disease (n=14, 25.0% of excluded), ejection fraction <50% (n=10, 17.9% of excluded), and absence of significant cardiac pathology supporting the referral diagnosis (n=21, 37.5% of excluded). Additional exclusions included moderate or severe pulmonary disease (n=4, 7.1%), atrial fibrillation with uncontrolled ventricular rate (n=2, 3.6%), severe renal impairment (n=2, 3.6%), and significant coronary artery disease confirmed on subsequent evaluation (n=3, 5.4%).

Baseline Patient Characteristics The final study cohort comprised 75 patients with a mean age of 70.3 ± 6.7 years, of whom 42 (56.0%) were female (Table 1). Ten patients (13.3%) presented with atrial fibrillation and controlled ventricular rate at enrollment, while the remaining 65 patients (86.7%) were in sinus rhythm. The most prevalent comorbidities included hypertension in 68 patients (90.7%), hyperlipidemia in 48 patients (64.0%), and diabetes mellitus in 26 patients (34.7%). Mean body mass index was 28.3 ± 3.5 kg/m², and mean estimated glomerular filtration rate was 71.5 ± 11.1 mL/min/1.73m².

Table 1: Baseline Characteristics of Study Population

Variable	Total (n=75)	Event (n=11)	No Event (n=64)	p-value
Age (years)	70.3 ± 6.7	72.3 ± 6.5	70.0 ± 6.8	0.290
Female sex, n (%)	42 (56.0)	6 (54.5)	36 (56.2)	1.000
Hypertension, n (%)	68 (90.7)	9 (81.8)	59 (92.2)	0.595
Hyperlipidemia, n (%)	48 (64.0)	10 (90.9)	38 (59.4)	0.094
Diabetes mellitus, n (%)	26 (34.7)	4 (36.4)	22 (34.4)	1.000
Atrial fibrillation, n (%)	13 (17.3)	2 (18.2)	11 (17.2)	1.000
Digoxin therapy, n (%)	15 (20.0)	5 (45.5)	10 (15.6)	0.061
LVEF (%)	58.7 ± 5.9	57.2 ± 6.2	58.9 ± 5.8	0.378
LAVI (mL/m²)	34.3 ± 7.1	41.7 ± 6.6	33.0 ± 6.4	<0.001
PASP (mmHg)	37.3 ± 9.8	43.7 ± 11.8	36.2 ± 9.1	0.019
LASr (%)	20.1 ± 8.9	10.6 ± 3.9	21.7 ± 8.6	<0.001
B-lines (count)	11.2 ± 6.0	21.6 ± 4.5	9.4 ± 4.1	<0.001
eGFR (mL/min/1.73 m²)	71.5 ± 11.1	67.7 ± 15.5	72.2 ± 10.2	0.216
BMI (kg/m²)	28.3 ± 3.5	29.9 ± 2.0	28.0 ± 3.6	0.105
NT-proBNP (pg/mL), median [IQR]	901 [529–1486]	1952 [1117–2378]	763 [514–1197]	0.002

Comparison between event and event-free groups revealed significant baseline differences (**Table 1**). During follow-up, patients who experienced adverse events more often presented with hyperlipidemia (90.9% vs. 59.4%, p=0.094) and diabetes mellitus (36.4% vs. 34.4%, p=1.000), and were more frequently treated with digoxin (45.5% vs. 15.6%, p=0.061). While these differences were not statistically significant, they suggested a higher overall cardiovascular risk profile among those with events.

Echocardiographic and Imaging Findings

All participants maintained preserved left ventricular systolic function, with a mean ejection fraction of 58.7 ± 5.9% (Table 1). However, patients in the event group exhibited more advanced structural and functional abnormalities. Left atrial volume index was significantly greater in those with events compared to event-free patients (41.7 ± 6.6 vs. 33.0 ± 6.4 mL/m², p<0.001), consistent with marked atrial remodeling. Additionally, estimated pulmonary artery systolic pressure was elevated in the event group (43.7 ± 11.8 vs. 36.2 ± 9.1 mmHg, p=0.019), indicating higher right-sided pressures.

Left atrial reservoir strain analysis

Assessment of LASr was feasible in 69 of 75 patients (92%), with unsuccessful measurements primarily due to inadequate image quality in those with atrial fibrillation. Patients who experienced adverse outcomes showed markedly impaired atrial function, reflected by lower reservoir strain values compared with event-free individuals (10.6 ± 3.9% vs. 21.7 ± 8.6%, p<0.001). These findings are consistent with advanced diastolic dysfunction and elevated filling pressures.

Lung Ultrasound Feasibility and Findings

Lung ultrasound was successfully performed in all 75 patients (100% feasibility), with the procedure well tolerated and rapid, averaging 2.5 ± 0.47 minutes per examination.

Quantitative assessment of B-lines across the 28 standardized lung zones revealed a median of 12 [IQR: 6–18] in the total cohort. Event patients had a significantly greater B-line burden compared with event-free participants (median [IQR]: 22 [18–28] vs. 10 [5–15], p<0.001). The overall distribution ranged from 0 to 42, with clear separation between high- and low-risk groups.

Reproducibility testing in a random subset of 25 patients confirmed high reliability. Intra-observer agreement was excellent, with an intraclass correlation coefficient (ICC) of 0.94 (95% CI: 0.86–0.97). Inter-observer reliability was also strong, with an ICC of 0.89 (95% CI: 0.76–0.95). The mean difference in B-line counts between observers was 1.2 ± 2.8, with 95% limits of agreement ranging from –4.3 to +6.7, confirming robust measurement precision.

Laboratory Biomarkers:

NT-proBNP concentrations were markedly higher in patients who went on to experience adverse outcomes. Median values were almost threefold greater in the event group compared with those who remained event-free (1,952 [1,117–2,378] vs. 763 [514–1,197] pg/mL, *p*=0.002). This finding reinforces the well-established association between elevated natriuretic peptides and increased heart failure severity.

Correlation Analyses (*Figure 2)*

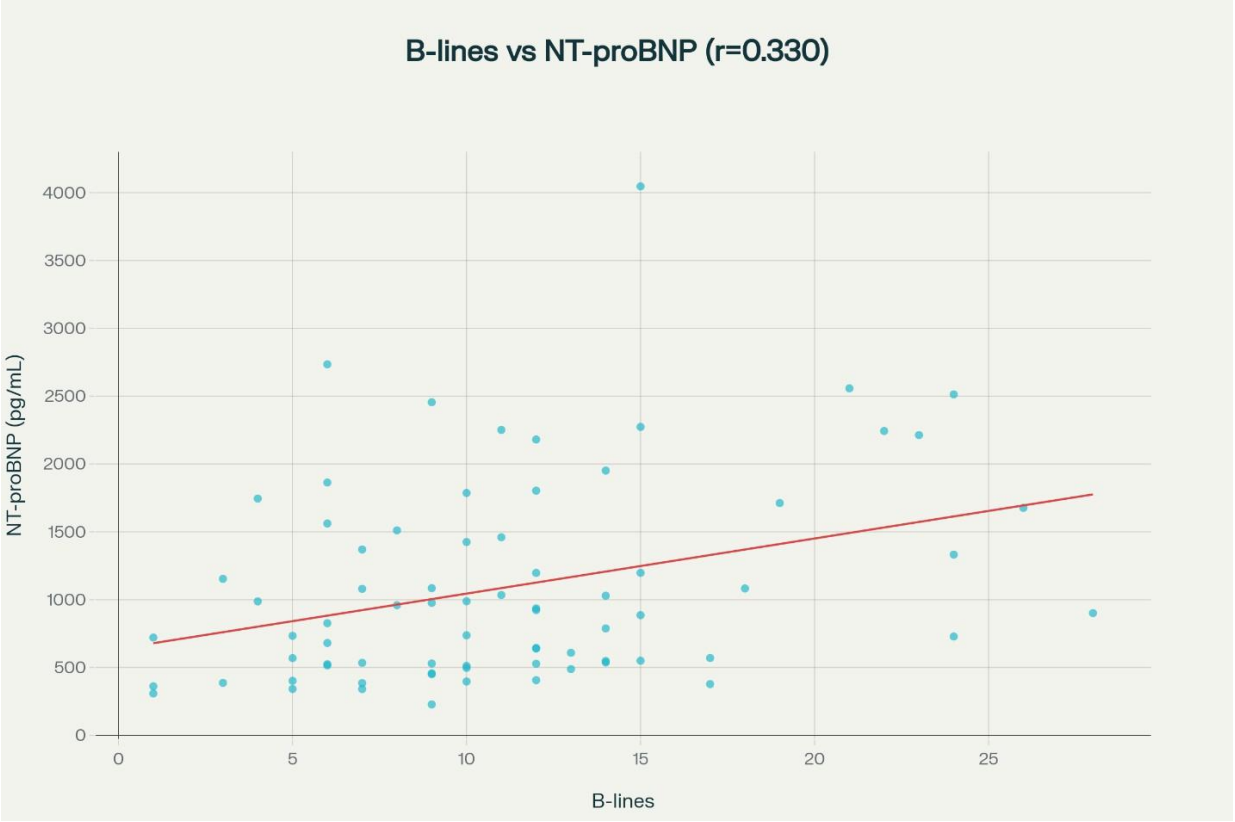

Figure 2: Correlation matrix showing relationships between B-lines, NT-proBNP, and LASr revealed several significant relationships. B-line counts demonstrated a moderate positive correlation with NT-proBNP concentrations (r=0.330,* p*<0.001), supporting the link between PC and neurohormonal activation. A moderate inverse correlation was found between B-lines and LASr (r=–0.418,* p*<0.001), suggesting that greater PC is accompanied by impaired atrial function. Additional correlations included a positive relationship between B-lines and estimated pulmonary artery systolic pressure (r=0.471,* p*<0.001), as well as with left atrial volume index (r=0.243,* p*=0.035).

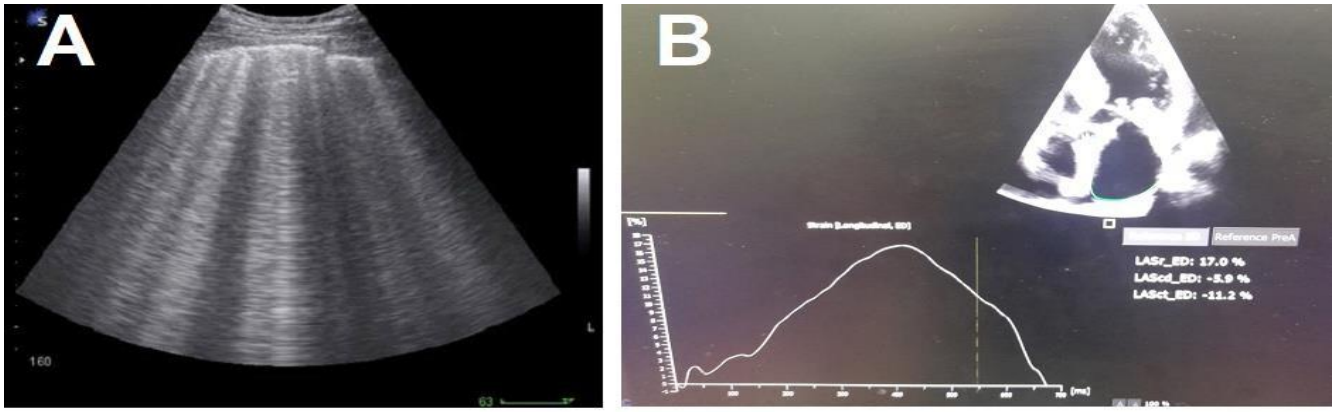

Figure 4: A) Ultrasound evaluation of lung shows confluent B-lines of longitudinal white lines appearance and B) determination of left atrial reservoir strain in patients with HFpEF.

Diagnostic Performance Analysis *Receiver operating characteristic analysis* ***(****Figure 3)***

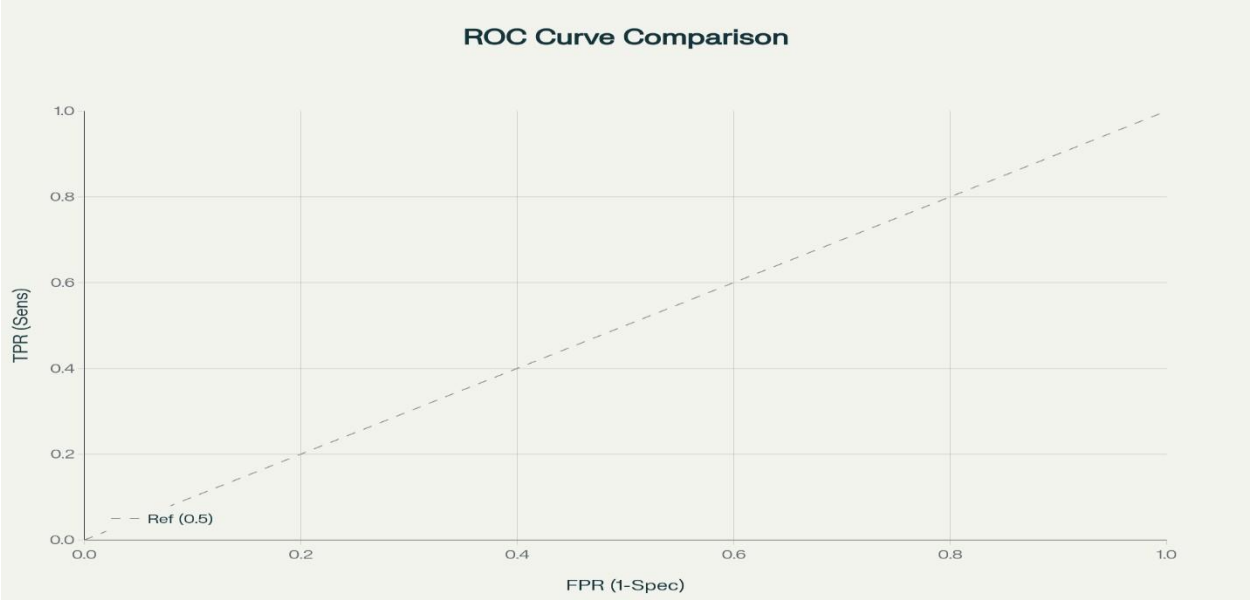

Figure 3: ROC curves comparing prognostic performance of B-lines, NT-proBNP, and LASr

Revealed excellent prognostic performance for B-line quantification. B-lines achieved an area under the curve (AUC) of 0.863 (95% CI: 0.771-0.955) for predicting the composite endpoint, which was statistically comparable to NT-proBNP performance (AUC 0.859, 95% CI: 0.765-0.952; p=0.927 for comparison). The optimal cut-off value for B-lines was >15, determined by Youden's index, yielding sensitivity of 90.9%, specificity of 78.1%, positive predictive value of 41.7%, and negative predictive value of 98.0%.

Left atrial reservoir strain demonstrated more modest but still significant prognostic value (AUC 0.713, 95% CI: 0.567-0.858) with an optimal cut-off of ≤13.75%, providing sensitivity of 71.4% and specificity of 70.3%. (**Figure 4).**

Clinical Outcomes and Follow-up During a median follow-up period of 26 months [IQR: 22-32], 11 patients (14.7%) experienced the composite primary endpoint. *Event distribution* ***comprised emergency department visits for acute heart failure (n=4, 36.4% of events), inpatient cardiology admissions for severe heart failure symptoms (n=2, 18.2% of events), ambulatory intensification of loop diuretic therapy for worsening symptoms (n=3, 27.3% of events), and death (n=2, 18.2% of events). Of the two deaths, one occurred during a heart failure hospitalization and one was attributed to unknown cause in the setting of advanced heart failure.***

Event timing analysis revealed a median time to first event of 18.5 months [IQR: 12.3-24.7]. Notably, all 11 events occurred exclusively in patients with >15 B-lines at baseline, while no events were recorded among the 63 patients with ≤15 B-lines during the entire follow-up period.

Survival Analysis *Kaplan-Meier survival analysis* ***(Figure 5)***

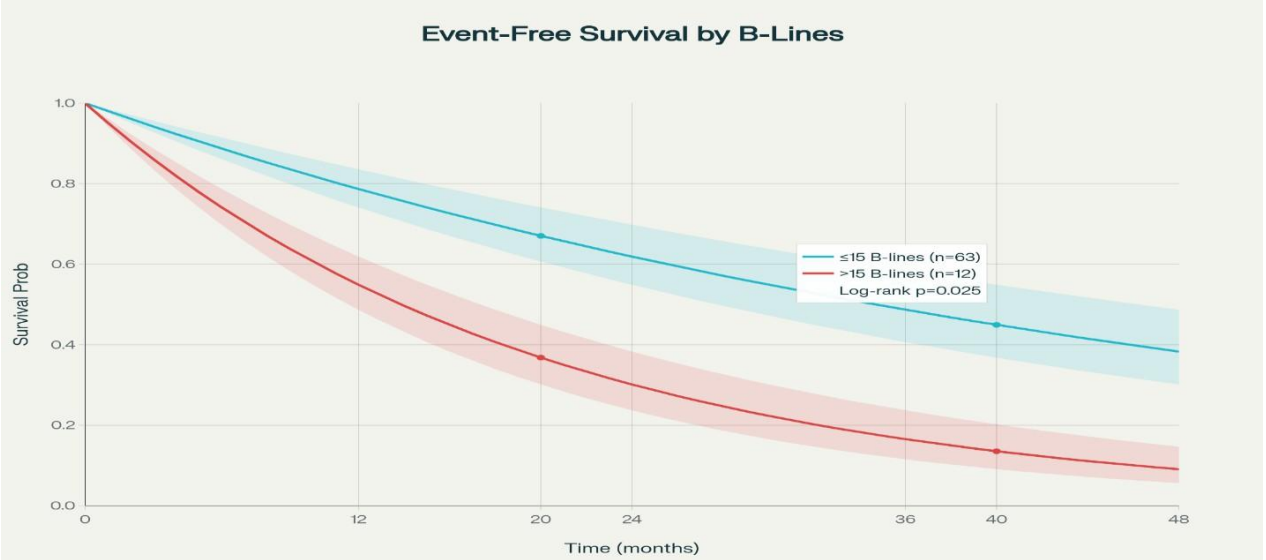

Figure 5: Kaplan-Meier event-free survival curves stratified by B-line threshold (≤15 vs >15)

Demonstrated striking differences in event-free survival stratified by B-line threshold. Patients with >15 B-lines experienced significantly worse outcomes compared to those with ≤15 B-lines (log-rank $\chi^2 = 16.804$, $p<0.001$). The cumulative probability of event-free survival at 20 months was 100% in patients with ≤15 B-lines versus 72.0% in those with >15 B-lines. At 40 months, these proportions were 97.3% versus 58.2%, respectively, representing a clinically meaningful absolute risk difference of 38.9%.

Multivariable Risk Assessment *Univariable Cox proportional hazards analysis (Table 2)* ***identified several significant predictors of the composite endpoint. B-lines >15 emerged as the strongest predictor with a hazard ratio (HR) of 20.956 (95% CI: 2.654-165.342, p=0.004). Other significant univariable predictors included log-transformed NT-proBNP (HR 3.891, 95% CI: 1.745-8.680, p=0.001), hyperlipidemia (HR 5.714, 95% CI: 1.224-26.674, p=0.026), diabetes mellitus (HR 3.529, 95% CI: 1.036-12.024, p=0.044), and digoxin therapy (HR 5.926, 95% CI: 1.742-20.154, p=0.004).***

Table 2: Univariable and Multivariable Cox Regression Analysis

Variable	Univariable HR	95% CI	p-value	Multivariable HR	95% CI	p-value
B-lines >15	20.956	2.654–165.342	0.004	15.234	1.864–124.530	0.011
Age (per year)	1.043	0.962–1.130	0.307	–	–	–
Female sex	0.914	0.268–3.120	0.885	–	–	–
Hyperlipidemia	5.714	1.224–26.674	0.026	2.147	0.418–11.033	0.364
Diabetes mellitus	3.529	1.036–12.024	0.044	1.892	0.513–6.974	0.339
Atrial fibrillation	1.127	0.252–5.044	0.875	–	–	–
Digoxin therapy	5.926	1.742–20.154	0.004	2.683	0.704–10.228	0.148
LVEF (per %)	0.931	0.850–1.020	0.125	–	–	–
LAVI (per mL/m²)	1.098	1.021–1.181	0.012	1.032	0.945–1.126	0.489
PASP (per mmHg)	1.052	1.008–1.098	0.020	1.021	0.968–1.077	0.445
LASr (per %)	0.877	0.804–0.956	0.003	0.932	0.836–1.039	0.205
log NT-proBNP	3.891	1.745–8.680	0.001	2.876	1.187–6.967	0.019
eGFR (per mL/min/1.73 m²)	0.968	0.928–1.009	0.125	–	–	–
BMI (per kg/m²)	1.147	0.969–1.357	0.108	–	–	–

Multivariable analysis using backward likelihood ratio selection retained two independent predictors in the final model (**Table 2**). B-lines >15 remained the dominant prognostic factor with an adjusted HR of 15.234 (95% CI: 1.864-124.530, p=0.011). Log-transformed NT-proBNP also maintained independent prognostic significance with an adjusted HR of 2.876 (95% CI: 1.187-6.967, p=0.019). The final model demonstrated excellent discrimination with a C-statistic of 0.891 (95% CI: 0.793-0.989) and explained 45.2% of the variation in time to event occurrence ($R^2 = 0.452$).

Model validation confirmed that proportional hazards assumptions were satisfied for all covariates (global test p=0.312), and no significant multicollinearity was detected with all variance inflation factors <2.0.

DISCUSSION

Our study demonstrates that B-line quantification by LUS provides powerful prognostic information in ambulatory patients with recently diagnosed HFpEF, with prognostic performance comparable to NT-proBNP. The optimal threshold of >15 B-lines identifies patients at substantially increased risk for adverse outcomes, with a hazard ratio exceeding 20-fold in multivariable analysis. Importantly, LUS achieved 100% feasibility with a brief examination time of 2.5 minutes, supporting its practical implementation in routine clinical care. These findings position LUS as a valuable addition to current risk stratification approaches in this challenging patient population.

The prognostic utility of LUS in heart failure has been increasingly recognized across diverse clinical settings [19-21]. Our findings extend this evidence base by demonstrating the specific value of B-line assessment in ambulatory HFpEF patients, a population where diagnostic and prognostic challenges are particularly pronounced. The >15 B-line threshold identified in our study aligns remarkably well with established cut-offs for moderate PCongestion in broader heart failure populations, suggesting biological consistency across heart failure phenotypes. [7][8]

Miglioranza et al. previously reported the prognostic value of B-lines in outpatient HFrEF, finding 15 B-lines as the optimal threshold. Our study confirms this threshold's relevance extends to HFpEF, supporting the notion that PC assessment transcends ejection fraction categories. This consistency strengthens the evidence for standardized B-line interpretation protocols across heart failure phenotypes, potentially facilitating broader clinical adoption. [9]

Recent investigations have similarly demonstrated the prognostic importance of B-lines at hospital discharge in both HFpEF and HFrEF populations. Palazzuoli et al. found that ≥22 B-lines at discharge predicted adverse outcomes regardless of ejection fraction, while Rueda-Camino et al. confirmed the 15 B-line threshold using the same 28-zone protocol employed in our study. Our findings uniquely contribute by demonstrating prognostic value in the ambulatory diagnostic setting, before clinical decompensation occurs. [10][11]

The strong correlation between B-lines and LASr observed in our study provides novel mechanistic insights into HFpEF pathophysiology. Left atrial dysfunction represents a fundamental feature of HFpEF, reflecting elevated filling pressures and contributing to symptom development. The inverse relationship between B-lines and LASr ($r=-0.418$, $p<0.001$) suggests that PC detected by LUS directly reflects the hemodynamic consequences of diastolic dysfunction. [12][13]

This mechanistic understanding has important clinical implications. Unlike NT-proBNP, which can be influenced by multiple factors including age, gender, renal function, and atrial fibrillation[14-15], B-lines provide a direct visualization of the pathophysiological endpoint—PC. Our observation that B-lines maintained prognostic significance even in patients with atrial fibrillation, while LASr did not, further supports the robustness of LUS assessment. [16-17]

The excellent negative predictive value of 98.0% for the >15 B-line threshold has particular clinical significance. This finding suggests that patients with ≤15 B-lines have an extremely low probability of experiencing adverse events during medium-term follow-up, potentially identifying a group suitable for less intensive monitoring. Conversely, the substantial hazard ratio associated with >15 B-lines indicates the need for enhanced therapeutic intervention and closer surveillance in this high-risk subset. [18-19][20]

The comparable prognostic performance between B-lines and NT-proBNP (AUC 0.863 vs. 0.859) represents a significant finding given NT-proBNP's established role in heart failure management. However, our multivariable analysis revealed that B-lines and NT-proBNP provide complementary prognostic information, with both parameters retaining independent significance. This suggests that LUS adds incremental value to biomarker-based risk assessment rather than simply duplicating existing information. [21, 22]

Current HFpEF diagnostic and prognostic scores, including H2FPEF and HFA-PEFF, incorporate multiple echocardiographic parameters requiring comprehensive examinations and expert interpretation [23-24]. While these scores have shown diagnostic utility, recent validation studies have questioned their prognostic performance. In contrast, LUS offers a simple, rapid assessment that directly visualizes the pathophysiological consequences of heart failure—PC. [25-26]

The practical advantages of LUS are particularly relevant in contemporary healthcare delivery. The technique requires minimal training, can be performed with standard ultrasound equipment, and provides immediate results. These characteristics support point-of-care implementation across diverse clinical settings, potentially improving access to prognostic assessment in resource-limited environments. [27-28]

Our findings support the integration of LUS into routine HFpEF management pathways. The ability to rapidly identify high-risk patients using a bedside technique could facilitate earlier therapeutic intensification and more frequent monitoring. The technique's high feasibility and short examination time make it particularly suitable for serial assessments during follow-up visits, potentially enabling personalized therapeutic adjustments based on changing congestion status.

Future research should address several important questions raised by our findings. First, the dynamic nature of PC suggests that serial B-line assessments may provide superior prognostic information compared to single-time-point evaluations. Second, the therapeutic implications of B-line findings require investigation—specifically, whether treatment decisions guided by LUS improve clinical outcomes. Third, the integration of LUS with other emerging technologies, including handheld devices and artificial intelligence-enhanced interpretation, could further enhance accessibility and standardization [29-30]

Exercise LUS represents another promising avenue for future investigation. Previous studies have demonstrated that stress-induced B-line development may reveal subclinical congestion in patients with normal resting assessments. This approach could potentially improve diagnostic accuracy in early-stage HFpEF and identify patients at risk for symptom progression.

Several limitations warrant consideration when interpreting our findings. The single-center design and relatively small sample size (n=75) limit generalizability, particularly given the heterogeneity of HFpEF populations across different healthcare settings. The limited number of events (n=11) affects the precision of our risk estimates, though the consistency with larger studies supports the robustness of our findings.

The selection of a 28-zone LUS protocol, while comprehensive, may limit practical implementation compared to simplified approaches. However, our examination time of 2.5 minutes suggests that comprehensive assessment remains feasible in clinical practice. Future studies should evaluate whether simplified protocols maintain comparable prognostic performance while further reducing examination time.

The composite endpoint, while clinically relevant, encompasses events of varying severity. The inclusion of outpatient diuretic intensification alongside hospitalization and death reflects real-world clinical decision-making but may introduce variability in endpoint adjudication. Nevertheless, the clear separation in outcomes between B-line groups supports the clinical relevance of our findings.

The practical implications of our findings extend beyond risk stratification to potentially influence therapeutic decision-making in HFpEF. The ability to directly visualize PC could guide diuretic optimization, inform decisions regarding device therapy, and enhance patient education regarding symptoms and treatment adherence. The technique's accessibility suggests potential

applications in primary care settings, where early identification of high-risk HFpEF patients could facilitate timely specialist referral.

Healthcare system implementation of LUS for HFpEF management would require standardized training protocols, quality assurance measures, and integration with existing clinical workflows. The development of automated B-line quantification systems could further reduce operator dependence and improve reproducibility, supporting broader clinical adoption. [11]

CONCLUSIONS

Our study establishes LUS B-line quantification as a powerful prognostic tool in ambulatory HFpEF, with performance comparable to established biomarkers. The >15 B-line threshold effectively identifies high-risk patients requiring intensified management, while the excellent feasibility and rapid assessment time support clinical implementation. These findings position LUS as a valuable addition to contemporary HFpEF management, offering direct visualization of the pathophysiological process underlying symptoms and adverse outcomes. Future investigations should focus on therapeutic applications, simplified protocols, and integration with emerging technologies to optimize the clinical utility of this promising technique.

List of Abbreviations

Abbreviation	Full Term
HFpEF	Heart Failure with Preserved Ejection Fraction
LUS	Lung Ultrasound
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
LASr	Left Atrial Reservoir Strain
PC	Pulmonary Congestion
B-lines	Bright reverberation artifacts in lung ultrasound indicating congestion
LVEF	Left Ventricular Ejection Fraction
PASP	Pulmonary Artery Systolic Pressure
LAVI	Left Atrial Volume Index
BMI	Body Mass Index
eGFR	Estimated Glomerular Filtration Rate
ROC	Receiver Operating Characteristic
AUC	Area Under the Curve
HR	Hazard Ratio
ICH-GCP	International Council for Harmonisation – Good Clinical Practice
WHO	World Health Organization

Ethical Considerations

Ethical approval for the study was obtained from the Research Ethics Committee of the Faculty of Medicine, Al-Azhar University, Assiut under code number:

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All participants provided written informed consent before enrollment. Patient confidentiality and data privacy were maintained throughout the research, and all procedures were performed with full ethical oversight and minimal risk.

Author Contributions

- **Mahmoud M. Ibrahim:** Conceptualization; study design; supervision; cardiological assessment; writing – original draft; corresponding author.
- **Ahmed Mostafa Abd Ellatif Farghal, Mohamed Khedrawy, Tarek A. H. Bakr, Mona Sallam Esmail, Ahmed Mostafa Abd Ellatif Farghal**: Patient recruitment; clinical data acquisition; cardiological evaluation.
- **Mohamed Elqlyee, Ahmad M. Omar, Montaser Farag**: Pulmonological evaluation; lung ultrasound execution and interpretation.
- **Tarek Mohamed M. Mansour, Yasser Abd El Aal Ahmed Abdellah, Ahmed Abd Elrady Ahmed Teleb, Osama Mohamed Mohamed Elsabrout, Nabil Ibrahim Fayad, Ahmed M. AbdelHakam, Mohamed Mattar, Islam Ahmed Abo Shady, Maged M. A. Ataky**: Echocardiographic and radiological assessment; LASr analysis; imaging protocol design.
- **Wael Shaibat Alhamd Mohamed**: Internal medicine support; clinical comorbidity management and stratification.
- **Mohamed I. Shalaby, Mostafa A. Rakha**: Statistical analysis; methodology; validation; data interpretation.
- **Sherif N. A. Hegazy**: Critical review and final manuscript editing; radiology consultation.

All authors contributed to manuscript review and approved the final version for submission.

Conflicts of Interest

The authors declare no conflicts of interest related to this study.

Confidentiality of Data

All patient information was handled in strict confidentiality. Data were anonymized before analysis, stored securely, and used solely for the purpose of this research in compliance with institutional and national data protection policies

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