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# THE PROGNOSTIC VALUE OF LUNG ULTRASOUND IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION AND AORTIC STENOSIS

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**Ph.D. thesis**

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## The thesis is based on the following papers

**I.** Morvai-Illés B, Polestyuk-Németh N, Szabó IA, Monoki M, Gargani L, Picano E, Varga A, Ágoston G. The Prognostic Value of Lung Ultrasound in Patients With Newly Diagnosed Heart Failure With Preserved Ejection Fraction in the Ambulatory Setting. Front Cardiovasc Med. 2021 Dec 2;8:758147. doi: 10.3389/fcvm.2021.758147. PMID: 34926610; PMCID: PMC8674474.
Quartile: Q1 (2021)

**II.** Szabó IA, Gargani L, Morvai-Illés B, Polestyuk-Németh N, Frigy A, Varga A, Ágoston G. Prognostic Value of Lung Ultrasound in Aortic Stenosis. Front Physiol. 2022 Apr 5;13:838479. doi: 10.3389/fphys.2022.838479. PMID: 35480045; PMCID: PMC9037236.
Quartile: - Physiology (medical): Q1 (2022)
- Physiology: Q2 (2022)

## Further relevant papers

**I.** Morvai-Illés B, Ágoston G, Séllei Á, Kovács L, Varga A. Giant cell arteritis presenting with pericardial effusion, hoarseness, and amaurosis. Anatol J Cardiol. 2020 Mar;23(4):235-237. doi: 10.14744/AnatolJCardiol.2019.00502. PMID: 32235128; PMCID: PMC7163215.
Quartile: Q3 (2020)

**II.** Ágoston G, Morvai-Illés B, Pálinkás A, Varga A. The role of stress echocardiography in cardiovascular disorders. Kardiol Pol. 2019 Nov 22;77(11):1011-1019. doi: 10.33963/KP.15032. Epub 2019 Oct 24. PMID: 31647477.
Quartile: Q3 (2019)

**III.** Morvai-Illés B, Jdid MS, Csadi R, Varga A, Vágó H, Ágoston G. A felnőttkori autoimmun reumatológiai kórképek kardiológiai vonatkozásai. Cardiologia Hungarica. 2023; 53: 619–626. doi: 10.26430/CHUNGARICA.2023.53.6.619

## Quotable abstracts

**I.** Ágoston G, Morvai-Illés B, Bencsik P, Szabados T, Monoki M, Hulló D, Kovács L, Varga A. A terheléses echokardiográfia és a biomarkerek szerepe a szisztámás szklerózishoz kacsolódó kardiovaszkuláris szövődmények diagnózisában – Pilot tanulmány = The potential role of exercise echocardiography and biomarkers to assess cardiopulmonary complications in systemic sclerosis – a pilot study. Cardiologia Hungarica 52 : Suppl. C p. C303 (2022)

**II.** Morvai-Illes B, Burcsar SZ, Monoki M, Varga A, Kovacs L, Balog A, Agoston G, Assessment of the right ventricular-pulmonary circulation unit during stress in ankylosing

spondylitis and psoriatic arthritis patients, *European Heart Journal*, Volume 43, Issue Supplement_2, October 2022, ehac544.088. doi:10.1093/eurheartj/ehac544.088

**III.** Ladóczky-Hulló, D ; Morvai-Illés, B ; Bencsik, P ; Kovács, L ; Ágoston, G
Examination of exercise stress echocardiography and biomarkers in systemic sclerosis patients for the early detection of pulmonary arterial hypertension and myocardial involvement
Annals of the Rheumatic Diseases 82 : Suppl 1 pp. 1628-1629. , 2 p. (2023)

**IV.** Morvai-Illés, B ; Hulló, D ; Horváth, R ; Kovács, L ; Ágoston, G ; Varga, A. A terheléses echokardiográfia prognosztikus szerepe szisztémás szklerózisban [The prognostic role of exercise stress echocardiography in systemic sclerosis] Cardiologia Hungarica 53 : Suppl A p. A229 (2023)

## Abbreviations:

HFpEF: heart failure with preserved ejection fraction

AS: aortic stenosis

HF: heart failure

EF: left ventricular ejection fraction

HFrEF: heart failure with reduced ejection fraction

HFmrEF: heart failure with mildly reduced ejection fraction

LV: left ventricle/ left ventricular

CXR: chest X-ray

CT: computer tomography

TGF-B: transforming growth factor B

ECM: extracellular matrix

MMP: matrix metalloproteinase

TIMP: tissue inhibitors of metalloproteinases

EDP: end-diastolic pressure

PC: pulmonary congestion

NT-proBNP: N-terminal pro-B-type natriuretic peptide

VIC: valve interstitial cell

LDL: low-density lipoprotein

Lp(a): lipoprotein(a)

LUS: lung ultrasound

COPD: chronic obstructive pulmonary disease

eGFR: estimated glomerular filtration rate

Hgb: hemoglobin

AVA: aortic valve area

TTE: transthoracic echocardiography

ECG: electrocardiogram

ROI: region of interest

ROC: receiver operating curve

AUC: area under the ROC curve

LASr: left arterial reservoir strain

DCT: deceleration time

S': systolic myocardial velocity measured with tissue Doppler imaging at the tricuspid annulus

PASP: pulmonary artery systolic pressure

LAVI: left atrial volume index

AVR: aortic valve replacement

NYHA: New York Heart Association class

RV: right ventricular

TAPSE: tricuspid annular plane systolic excursion

PA: pulmonary artery

EVLW: extravascular lung water

PCWP: pulmonary capillary wedge pressure

LA: left atrial/left atrium

# Introduction

Both heart failure with a preserved ejection fraction (HFpEF) and aortic stenosis (AS) are common, chronically evolving diseases in everyday practice with considerable mortality and impact on patient's quality of life.

Despite the rising diagnostic possibilities, knowledge and the high prevalence of HFpEF, establishing its diagnosis and prognostication remained challenging. Polymorbidity is a typical characteristic of HFpEF patients, which makes the determination of independent, disease-specific prognostic factors reasonably difficult.

AS is the most common degenerative valve disease. The indication for surgery relies mainly on the quantitative assessment of the severity of stenosis. However, these measurements may not always show prognostic significance. Quantifying the cardiac damage caused by AS may result in a more reliable prognosis estimation.

## Heart failure with preserved ejection fraction (HFpEF)

According to the classical definition, heart failure (HF) is a group of diseases when the heart cannot "pump blood to the body at a rate commensurate with its needs or to do so only at the cost of high filling pressures"[1]. The classification of HF is based on the left ventricular ejection fraction (EF) but indicates different pathophysiologic and prognostic entities: if the EF is <40%, HF with reduced ejection fraction is present (HFrEF), in cases of 41-49% EF, HF with mildly reduced EF (HFmrEF) is diagnosed, and when the EF is ≥50%, HFpEF is the recommended terminology[2].

HFpEF is a heterogeneous, multifactorial disease. Estimating its prevalence depends on the HFpEF definition, which changes over time, and study settings. It is presumed that 19-55% of more than 64 million heart failure patients have a preserved EF based on several studies[3,4]. Since the prevalence of its common risk factors (ageing, hypertension, obesity, insulin resistance) is rising, HFpEF is expected to be diagnosed more often[5].

The exact pathophysiology is not fully understood. However, several studies suggest that focal or diffuse myocardial fibrosis is crucial in the disease's pathomechanism, contributing to increasing myocardial stiffness and, thus, diastolic dysfunction[6]. A common echocardiographic finding in HFpEF is left ventricular (LV)

hypertrophy, which may develop as a result of neurohumoral activation, mechanical overload, increased release of cytokines in response to arterial hypertension, chronic kidney disease, diabetes mellitus and other comorbidities[7]. These risk factors promote oxidative stress and consequential coronary and microvascular inflammation. This way, endothelial dysfunction develops with decreased nitric oxide bioavailability and protein kinase G activity, immune dysregulation and imbalance in anticoagulation evolve, and the inflammatory process propagates to the myocardium. Impaired bioavailability of nitric oxide and natriuretic peptide will lead to hyperphosphorylation of an elastic sarcomeric protein myofilament, called titin, and thus cardiomyocyte hypertrophy („titin-based stiffness")[8]. The inflammatory environment will also stimulate myocardial fibroblasts by transforming growth factor-β (TGF-β) to differentiate into myofibroblasts and upregulate the extracellular matrix (ECM) production. This maladaptive fibrotic remodelling in the perivascular and interstitial areas will cause increased myocardial stiffness, ischaemia and muscle failure. Furthermore, the overaction of TGF- β decreases the matrix metalloproteinase-1 (MMP-1) gene expression levels while increasing the tissue inhibitors of metalloproteinases (TIMPs), thereby promoting ECM deposition[9]. A schematic presentation of the proposed molecular mechanisms in HFpEF is shown in Figure 1.

In a healthy, compliant LV, diastolic suction enhances the inflow to the ventricle, and the volume increases without any relevant pressure rise, with the left ventricular end-diastolic pressure (EDP) remaining normal even during exercise. In HFpEF, volume changes lead to a larger EDP-rise, and together with the poor contractile reserve and chronotropic incompetence -which are also characteristic of HFpEF- leads to exercise intolerance and pulmonary congestion (PC) manifesting as dyspnoea. Non-cardiac mechanisms, such as peripheral vascular dysfunction leading to skeletal muscle dysfunction, are also presumed.

Notably, several underlying diseases may present as HFpEF (Table 1) [10].

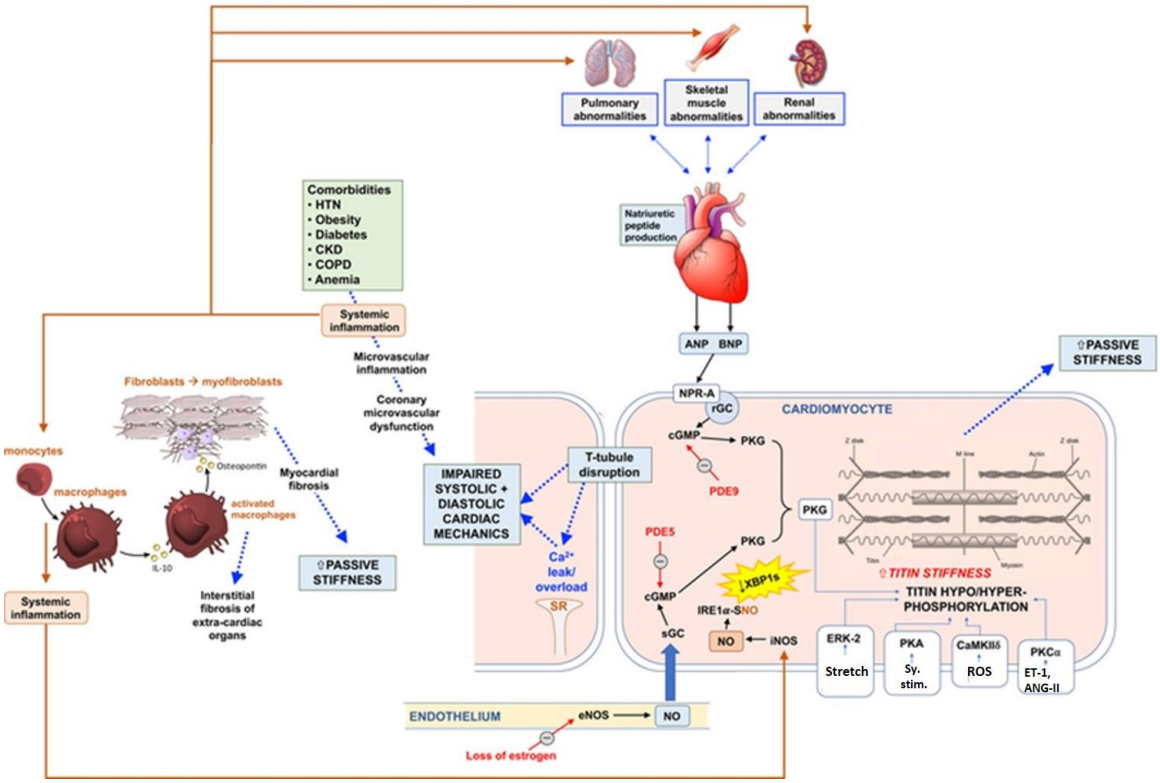



**FIGURE 1 |** Proposed molecular mechanism of HFpEF (modified from Shah et al., 2020)[11] (HTN-hypertension, CKD- chronic kidney disease, COPD- chronic obstructive pulmonary disease, SR- sarcoplasmic reticulum, eNOS- endothelial nitric oxide synthase, iNOS- inducible nitric oxide synthase, NO- nitric-oxide, ANP- atrial natriuretic peptide, BNP- brain natriuretic peptide, NPR-A- natriuretic peptide receptor-A, sGC- soluble guanylate cyclase, cGMP-cyclic guanosine monophosphate, PKG- protein kinase G, PDE- phosphodiesterase, XBP1- X-box-binding protein 1, IRE1α-SNO- S-nitrosylation of the endonuclease inositol-requiring protein 1α, ERK-2- extracellular signal-regulated protein kinase 2, Sy. stim.- sympathetic stimulation, MAPK- mitogen-activated protein kinase, PKA- protein kinase A, CaMKIIδ - Ca2+/calmodulin-dependent protein kinase II δ, ROS- reactive oxygen species, PKCα- protein kinase C-alpha, ET-1- endothelin-1, Ang-II- angiotensin II)

**TABLE 1 |** Specific conditions may present as HFpEF (adapted from Gevaert AB et al.[10])

| Diseases affecting the myocardium | Diseases affecting the loading conditions |
|---|---|
| Coronary artery diseases | Hypertensive urgency |
| Amyloidosis | Valvular heart diseases |
| Sarcoidosis | Pericardial diseases |
| Storage disorders | Arrhythmias |
| Hypertrophic cardiomyopathies | High output state |
| Immune, inflammatory, metabolic and toxic cardiomyopathies | |

The diagnosis can be challenging partly because of the high prevalence of diastolic dysfunction in the elderly. It requires the fulfilment of the following three conditions: (1) Signs and/or symptoms of HF; (2) EF≥50%; (3) Evidence of cardiac structural and/or functional abnormalities caused by left ventricular (LV) diastolic dysfunction or raised left ventricular filling pressures (including raised natriuretic peptides)[2]. However, there is data that the left ventricular filling pressure can be normal at rest, so the HF signs and symptoms can be absent or subtle[2]. The gold standard of the diagnosis is the invasive diastolic stress test, which requires specific personal and equipment background. Its complication rate is also not negligible. Two diagnostic scores are accepted according to the guideline: the H2FPEF score, mainly based on clinical variables, such as age or comorbidities, and the HFA-PEFF score, which relies on more echocardiographic parameters and the natriuretic peptide levels[2]. However, up to 23% of patients were misclassified by both scores[12]. Additionally, there is a considerable dispersion of classification between the scores, and low scores do not exclude the presence of HFpEF[13]. Also, many patients cannot be classified by these scores, as a remarkable proportion of patients fall into the 'intermediate' category, which requires further testing, such as cardiopulmonary exercise testing, exercise testing or invasive haemodynamic testing[2].

Although the prognosis of HFpEF is better than that of HF with reduced ejection fraction (HFrEF), however the mortality and hospitalisation rates are very high[5,14]. Assessing the prognosis of HFpEF is challenging, as HFpEF may be overdiagnosed due to the high prevalence of diastolic dysfunction in the ageing groups, and symptoms may be consequences of comorbidities. Studies are also inconsistent with the definition of HFpEF, as sometimes patients with lower LV EFs were included. A large meta-analysis compared HFpEF's and HFrEF's prognosis: despite the lower mortality in HFpEF (HR 0.68, 95% CI 0.64-0.71), it remained remarkable (117 deaths / 1000 patient-years vs 141 deaths / 1000 patient-years in HFrEF)[15]. The best method for prognostication is debated. Several score systems have been devised to facilitate the diagnosis and assess the prognosis. The score systems were mainly validated on the hospitalised and acute HFpEF population[16–18]. Imaging parameters are included in the H2FPEF and HFA-PEFF scores, which were initially designed as diagnostic score systems. The diagnostic use of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in HFpEF is well-established[19], and the data are convincing about its predictive value[20]. However, several studies suggested its predictive value is still controversial[21–23].

Aortic stenosis (AS)

AS is the most frequent degenerative valvular heart disease in Western countries; its prevalence continuously increases with age [24–26]. In Europe, the primary cause of AS is a calcific valve disease, but a congenitally bicuspid valve is also an important etiologic factor. Rheumatic valve disease is not as prevalent in Europe and North America as in other sides of the world. The estimated prevalence of calcific AS, which increases with age, is 0.4% in the general population and 1.7% in the population over 65 years in developed counties[27].

Its common risk factors are shared with HFpEF or ischemic heart disease: the role of dyslipidaemia, obesity, hypertension, and diabetes was proved by several retrospective studies[28–34]. Chronic kidney disease has also been linked to the development of AS due to their common risk factors[35].

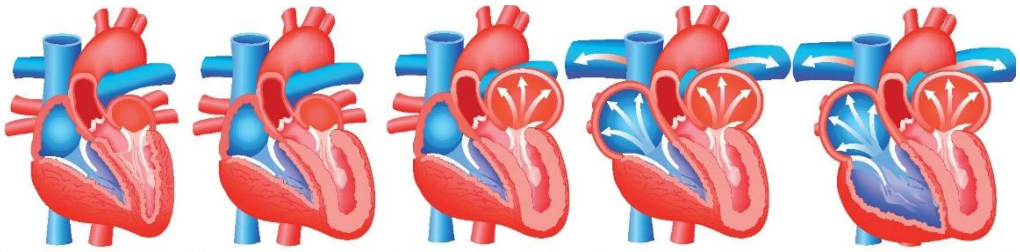
The exact pathogenesis of AS is unknown. In recent years, there has been a paradigm shift from the passive, degenerative perspective to a more active process manifesting in calcification, which may be similar to atherosclerosis[36]. Their shared risk factors may explain this observation.

The aortic valve has three leaflets and three layers as well. Its ventricular side is rich in circumferentially aligned elastin fibres responsible for flexibility. The aortic side consists of collagen and fibroblasts. Between these two layers lies the spongiosa layer with high proteoglycan content for lubrication. The main cell type of the aortic valve is the valve interstitial cell (VIC), and its role is to maintain the valve's structure. The calcification process begins with an initiating phase, which leads to atherosclerosis, most likely due to haemodynamic stress-induced endothelial damage, subendothelial low-density lipoprotein- (LDL-) cholesterol and lipoprotein(a) (Lp(a)) depose in the fibrosa layer. LDL becomes oxidised by reactive oxygen species, which will stimulate monocyte extravasation into the interstitium and differentiate into macrophages. The inflammatory cascade initiates at this point. Lp(a) is a carrier for oxidised phospholipids enhancing inflammatory process. During the propagation phase, the inflammation-activated VICs secrete matrix metalloproteinases, inducing fibrosis and microcalcification due to inflammation-induced VIC apoptosis. Lp(a) and the dysregulation of the osteogenic mediators will drive VICs to switch to osteoblast-like phenotype, leading to macrocalcification[37]. Macroscopically thickened valve leaflets will progress into

restricted valve motion and haemodynamic obstruction. Due to the increased afterload, increased left ventricular pressures are needed to maintain cardiac output. As a result, concentric left ventricular hypertrophy will develop. As a consequence of the constant outflow tract obstruction, the high intraventricular systolic pressure becomes persistent and contributes to myocardial fibrosis and myocyte death, manifesting in diastolic dysfunction. The high left ventricular filling pressure retrogradely elevates the left atrial (LA) pressure, which leads to PC. Finally, left ventricular dilatation and systolic dysfunction develop as the compensatory mechanisms burn out.

The diagnosis of AS relies on the transvalvular pressure gradients: the higher the mean gradient is, the more severe AS is possible. As the pressure gradients are highly flow-dependent, gradient-based diagnosis can be unreliable in hypertension, HFrEF or HFpEF cases. To bypass this limitation, the calculated aortic valve area has been introduced.[24,38] The manifestation of heart failure (HF) symptoms is a determinant factor in the survival of patients with AS[39]. The correlation between the severity of AS and the onset of symptoms is poor and depends mainly on the hypertrophic, compensatory response of the left ventricle (LV) to pressure overload[24].

The prognosis of severe symptomatic aortic stenotic patients is very poor: without surgery, the mortality is 49% at 1 year[40], but even in asymptomatic cases, the probability of death was 5.2% without and 4.7% with surgery [41]. According to several studies, the postoperative prognosis is more connected to the cardiac damage developed as a consequence of AS than to the preoperative valvular gradients or aortic valve area. Cardiac damage can be classified by echocardiographic parameters into 4 stages, with PC developing at more severe stages (Figure 2). The postoperative prognosis gradually worsens with the extent of the preoperative damage[42]. Postoperative reverse remodelling may have prognostic importance, too[43].



| Stages/Criteria | Stage 0 | Stage 1 | Stage 2 | Stage 3 | Stage 4 |
|---|---|---|---|---|---|
| | No Cardiac Damage | LV Damage | LA or Mitral Damage | Pulmonary Vasculature or Tricuspid Damage | RV Damage |
| Echocardiogram | | Increased LV Mass Index >115 g/m² (Male) >95 g/m² (Female) | Indexed left atrial volume >34mL/m² | Systolic Pulmonary hypertension ≥60 mmhg | Moderate-Severe right ventricular dysfunction |
| | | E/e' >14 | Moderate-Severe mitral regurgitation | Moderate-Severe tricuspid regurgitation | |
| | | LV Ejection Fraction <50% | Atrial Fibrillation | | |

**FIGURE 2 |** Stages of cardiac damage in aortic stenosis (adopted from Généreux et al., 2017)

Pulmonary congestion (PC)

PC is defined as fluid accumulation in the lungs, resulting in impaired gas exchange. It is a frequent and almost universal pathophysiological phenomenon in patients with heart failure. It is frequently seen in severe aortic stenosis patients, developing due to elevated capillary hydrostatic pressure. PC is responsible for the development of postcapillary pulmonary hypertension and, thus, the occurrence of dyspnea. PC is also connected with a worse prognosis in acute and chronic heart failure regardless of the EF[44–47].

PC's qualitative or quantitative examination is crucial because of its diagnostic and prognostic importance. The first approach used for that purpose is physical examination: rales by auscultation can detect heart failure with 51 % sensitivity and 81% specificity[48]. Although this is the broadest available method, the low sensitivity limits its utility. Chest X-ray (CXR) is also traditionally used for assessing PC. Its specificity is acceptable (76%-90%) and lacks high sensitivity (50%-73%)[48,49]. Furthermore, the interpretation of its radiological signs, such as vascular opacity redistribution and interstitial oedema, shows remarkable inter-observer variability[50]. Due to its affordability, relatively low radiation dose and value in differential diagnosis, CXR remained a first-line PC diagnostic method. Chest computer tomography (CT) can also be used to assess PC with the critical advantage of giving an excellent resolution of the pulmonary

parenchyma. Lung density measurements have been proven to correlate with invasively measured pulmonary artery wedge pressures and extravascular lung water[51,52] and are used as a reference method in more studies. Due to its costs and high radiation dose, CT is still not recommended for assessing PC in everyday practice. Tomographic perfusion lung scintigraphy for PC's quantitative assessment is an emerging modality with a sensitivity of 87% and specificity of 72% compared to right heart catheterisation[53]. However, its use for that purpose is still restricted to scientific research. The indicator dilution method is the gold standard for estimating extravascular lung water. Since it is expensive and may cause several potentially severe complications, it is not used outside of critical care[54].

Lung ultrasound (LUS)

Assessment of the lungs by ultrasound has been considered noninformative for a long. Ultrasonographic imaging relies on the acoustic similarity of the examined tissues, mainly due to their high water content. This similarity allows the ultrasound beam to reach the intended depth without significant scattering. Still, the moderate variations in the speed of the ultrasound enable the visualisation of the different tissues[55]. On the contrary, the air in the lungs determines a high acoustic mismatch with the surrounding tissues. Therefore, the ultrasound beam is completely reflected, making the imaging impossible[56]. The only visualisable anatomical structure of the healthy lung is the pleura, typically presenting as a hyperechogenic horizontal line, which moves synchronously with respiration in a horizontal plane (lung sliding). Whether it depicts the real pleura or a reverberation artefact remains debated. The lung parenchyma can be visualised only in pathological conditions when the air content decreases, and/or fluid or connective tissue accumulates in the lungs[57,58].

Despite that, the lung parenchyma generally cannot be visualised, and enough information can be gained by assessing reverberation artefacts. Their evolvement results from the significant difference in acoustic impedance of the different surfaces, chest wall/aerated lung or gas/fluid film in this case. The meeting surface of these acoustically highly different substances will reflect the ultrasound beam. Reverberation artefacts occur when the ultrasound beam reflects back between these surfaces[59]. A-lines are hyperechogenic, horizontal lines occurring at regular intervals from the pleural line

(Figure 3. A). A-lines –when accompanied by lung sliding- represent normal (or higher) air content in the lungs. On the contrary, B-lines are „discrete laser-like vertical hyperechoic reverberation artefacts that arise from the pleural line, extend to the bottom of the screen without fading, and move synchronously with lung sliding"[60], and are present in lung interstitial syndrome (Figure 3. B). They typically erase the A-lines. Their presumed mechanism of formation is shown in Figure 4: the pathologic changes of the pulmonary parenchyma along with the surrounding air-rich tissue provide the basis of vertical reverberation artefact formation. Their presence is not specific to lung interstitial syndrome, though, as they can be found in the residual cavity of the post-pneumonectomy space or the bowel loops, too[59].

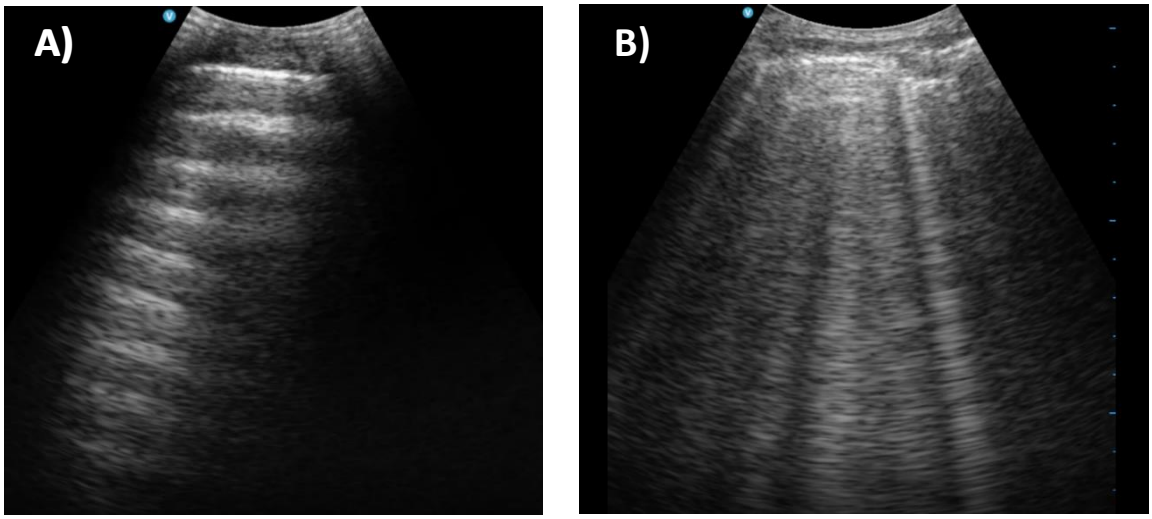



**FIGURE 3 |** A) Normal LUS finding showing pleura with A-lines; B) Alveolar-interstitial syndrome on LUS with multiple B-lines

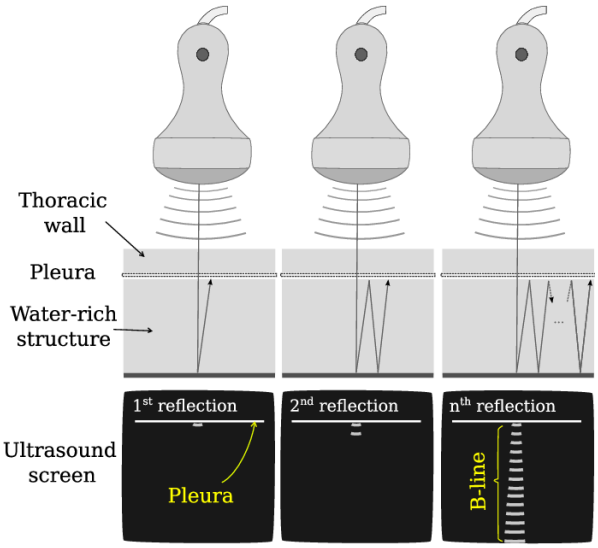



**FIGURE 4 |** The presumed generation of radial reverberation artefacts called B-lines (adapted from Moshavegh et al.[61])

The number of B-lines in the lung increases along with the decreasing air content and the increasing lung density. They can be confused with Z-lines, short-paths reverberations meeting none of those mentioned above criteria and having no clinical relevance[62] (Figure 5). Ultrasound interstitial syndrome is defined by more than 2 B-lines per intercostal space („lung rockets“)[63], as few B-lines can occur even in healthy lungs- especially at the bases, where the hydrostatic pressure is higher[59].

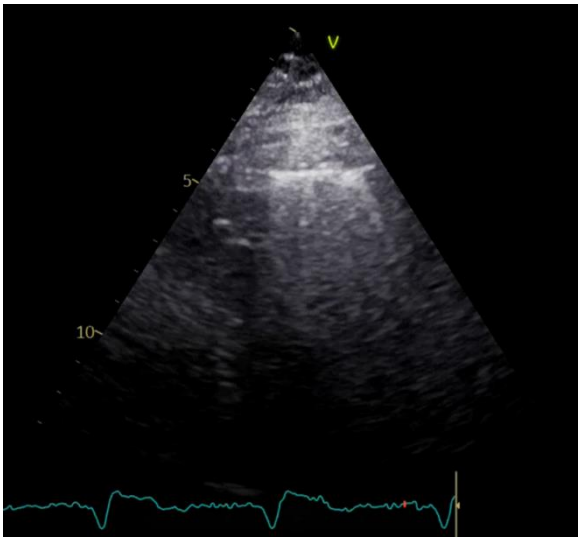



**FIGURE 5 |** Normal LUS finding with Z-lines

LUS can be performed with any ultrasound transducers, with the caveat that higher frequency probes provide a more detailed view of the pleura and the subpleural space, and lower frequency probes are more helpful in detecting pleural effusion and visualising deeper structures. The imaging is performed through the intercostal space with the probe positioned either sagittally or obliquely (Figure 6). The number of scanned regions depends on the clinical setting and suspected diagnosis. Therefore, more approaches are available: in the emergency setting, a 4- or 8-zone anterolateral examination may be sufficient, while in other situations, a more detailed 28-zone anterolateral method is more suitable with the possibility of adding posterior lung zones to the assessment, if needed[62].

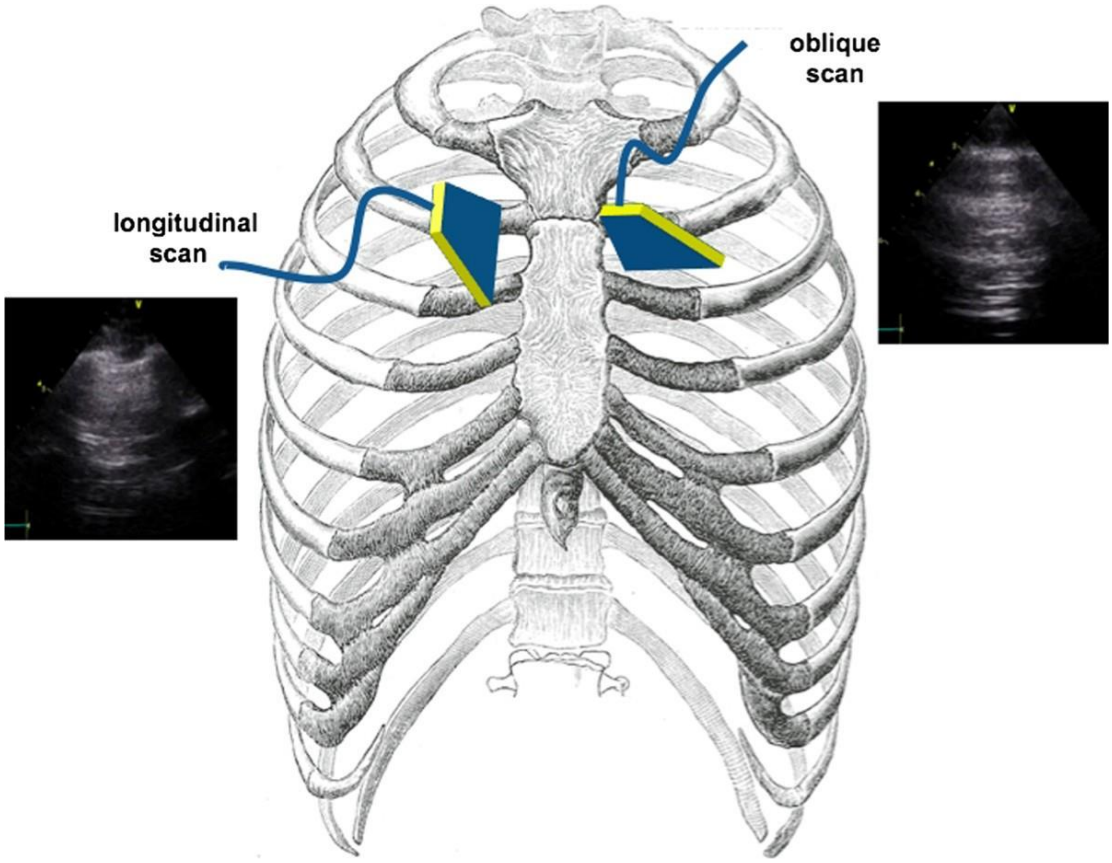



**FIGURE 6 |** Probe positions during lung ultrasound (adapted from Gargani et al., 2014)[62]

LUS evaluation of B-lines has been proposed as a simple, noninvasive, radiation-free, semi-quantitative tool to assess PC[57,60,64]. B-lines have been closely linked to the amount of extravascular lung water and pulmonary capillary wedge pressure in HF

patients[65]. LUS can identify clinically silent pulmonary oedema[65], suggesting that it can be utilised to assess hemodynamics and optimise treatment[64].

Aims

We aimed to assess how the number of B-lines correlates with symptoms, echocardiographic parameters, and how it affects the prognostication in newly diagnosed HFpEF patients and in patients with moderate and severe aortic stenosis.

# Methods

Study population for the HFpEF study

A total of 131 consecutive patients were screened at our cardiology outpatient clinic (University of Szeged, Hungary) between January 2018 and December 2019. General practitioners referred all patients with mild or moderate HF symptoms. None of the patients had a previous diagnosis of HF. Data collection was based on a standardised clinical questionnaire performed by a researcher blinded to clinical records. Our inclusion criteria were: (1) age ≥ 18 years; (2) diagnosis of HFpEF defined in the 2016 ESC guideline[66]. The following patients were excluded: (1) atrial fibrillation with > 80 beats per minute at rest; (2) prior history of interstitial lung disease, moderate or severe COPD (Chronic Obstructive Pulmonary Disease), bronchial asthma or pulmonary hypertension; (3) moderate or severe aortic or mitral valve disease on the screening echocardiogram; (4) history of cardiomyopathy; (5) severe kidney failure or anaemia (eGFR ≤ 35 ml/min, Hgb ≤ 100 g/l); (6) malignancy (except localised basal cell carcinoma of the skin or localised prostate cancer). Data handling and publication respected the Declaration of Helsinki. The registration number of ethical approval is 131/2019/SZTE.

Study population for the aortic stenosis study

75 consecutive patients with AS from two sites (University Of Szeged, Hungary, Clinical County Hospital Târgu Mures, Romania) were enrolled. The inclusion criteria were: (1) moderate degenerative AS with mean gradient of 20-40 mmHg and aortic valve area (AVA) 1–1.5 $cm^2$; or severe degenerative AS with mean gradient >40 mmHg and AVA <1 cm2; (2) age >18 years. We enrolled patients with severe symptomatic AS only if the patient refused surgery or it was contraindicated. The exclusion criteria were: (1) low flow-low gradient AS (mean gradient <40 mmHg, AVA <1 cm2, LVEF<50%); (2) concomitant moderate or severe aortic regurgitation; (3) concomitant moderate or severe mitral regurgitation; (4) severe, decompensated HF, requiring urgent hospitalisation (NYHA class IV); (5) severe interstitial lung disease; (6) active pneumonia or acute lung injury; (7) malignancy (except localised skin basal cell carcinoma or localised prostatic cancer); (8) cardiomyopathies—dilated, hypertrophic or infiltrative cardiomyopathy. All patients were evaluated in ambulatory settings in relatively stable conditions. None of the patients required hospitalisation at the time of transthoracic echocardiography (TTE) and LUS. The patients signed informed consent before inclusion in the study. Data handling and publication respected the Declaration of Helsinki. The registration number of ethical approval is 131/2019/SZTE.

Echocardiographic assessment

A comprehensive TTE was performed using a Vivid-S70 (GE Vingmed, Horten, Norway) ultrasound machine equipped with the 3S probe (1.5–3.6 MHz). An experienced cardiologist with EACVI-TTE certification performed all measurements according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging[67,68].

Myocardial deformation was analysed with GE EchoPAC (version v202) software. LV strain was measured according to EACVI recommendations[69]. QRS complex was used as a time reference. LA strain parameters were recorded as per the EACVI consensus document and were post hoc analysed by two experienced physicians[70]. An electrocardiography (ECG) trigger was used as a time reference, using the upslope of the R wave as a surrogate of end-diastole. In case of any uncertainty, the

strain pattern itself provided support (and mitral inflow pattern in patients with sinus rhythm). From apical four- and two-chamber views with a frame rate of 40–80 frames per second, three consecutive cardiac cycles were acquired and averaged in each patient. Region of Interest (ROI) was defined using a point-and-click approach for tracking the endocardial border. Longitudinal strains were calculated as strains in the direction tangential to the endocardial atrial border. Atrial strain values during the reservoir phase were evaluated (LASr).

LUS assessment

Immediately after transthoracic echocardiography, all patients underwent LUS performed by the same cardiologist, who obtained the echocardiographic measurements to assess B-lines using the same probe and echocardiography machine. We screened the anterior and lateral hemithoraces, scanning along the parasternal, midclavicular, anterior axillary and midaxillary lines from the second to the fifth intercostal space on the right hemithorax and the second to the fourth intercostal space on the left, adding up to a total of 28 zones (Table 2)[62]. A B-line was defined as a discrete, comet-like vertical hyperechoic reverberation artefact starting from the pleural line, extending to the bottom of the screen and moving synchronously with lung sliding[62]. An experienced operator who had completed a dedicated training previously and was blind to the NT-proBNP value, acquired and analysed all LUS studies.

**TABLE 2 |** Scanning sites for B-lines (adapted from Jambrik et al. 2004). B-lines were counted in every sector. The sum of them made the B-line score.

| | Mid-axillar | Anterior axillar | Mid-clavicular | Parasternal | Intercostal space | Parasternal | Mid-clavicular | Anterior axillar | Anterior axillar | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Right** | | | | | **II** | | | | | **Left** |
| | | | | | **III** | | | | | |
| | | | | | **IV** | | | | | |
| | | | | | **V** | | | | | |

NT-proBNP measurement

Within 1 hour of the cardiac and lung ultrasound, peripheral venous blood samples were obtained from each patient in the HFpEF study. NT-proBNP analysis was performed using the Elecsys 2010 analyser (Roche Diagnostics, Mannheim, Germany).

Follow-up data

Follow-up data were collected every three months via phone calls to monitor clinical status and adverse outcomes. Outpatient visits were performed 6-monthly when clinical status and adverse events were recorded. A composite HF endpoint was created, including death (any cause), hospitalisation for acute decompensation of HF, and worsening HF (defined as the intensification of loop diuretic therapy). Information about the endpoint events was retrieved from medical records.

Statistical analysis

Our data are expressed as number and percentage for categorical, and mean ± standard deviation or median with interquartile range for continuous variables. Univariate comparisons were made by chi-square or independent samples T-test, as appropriate. One-way analysis of variance (ANOVA) was used to compare continuous data of different NYHA functional classes. A p-value $< 0.05$ was accepted as statistically significant. Correlations between parameters were assessed with parametric Pearson or nonparametric Spearman correlation coefficient analysis, as appropriate. The prognostic performance was determined by means of receiver-operating characteristic (ROC) curves. Receiver-operating characteristic (ROC) curves were used to compare the predictive value of B-lines, LASr and NT-proBNP for the composite endpoint. The corresponding area under the curves (AUC) was reported. Univariate and multivariate (Backward LR method) Cox regression analysis was used to assess the prognostic capacity of parameters. Collinearity had been excluded using variance inflation factor <3 before the analysis. Results were reported as Hazard Ratios. Event-free survival was calculated

using Kaplan-Meier curves and the log-rank test to determine the significance between groups. Data were analysed using IBM SPSS 22 statistical software.

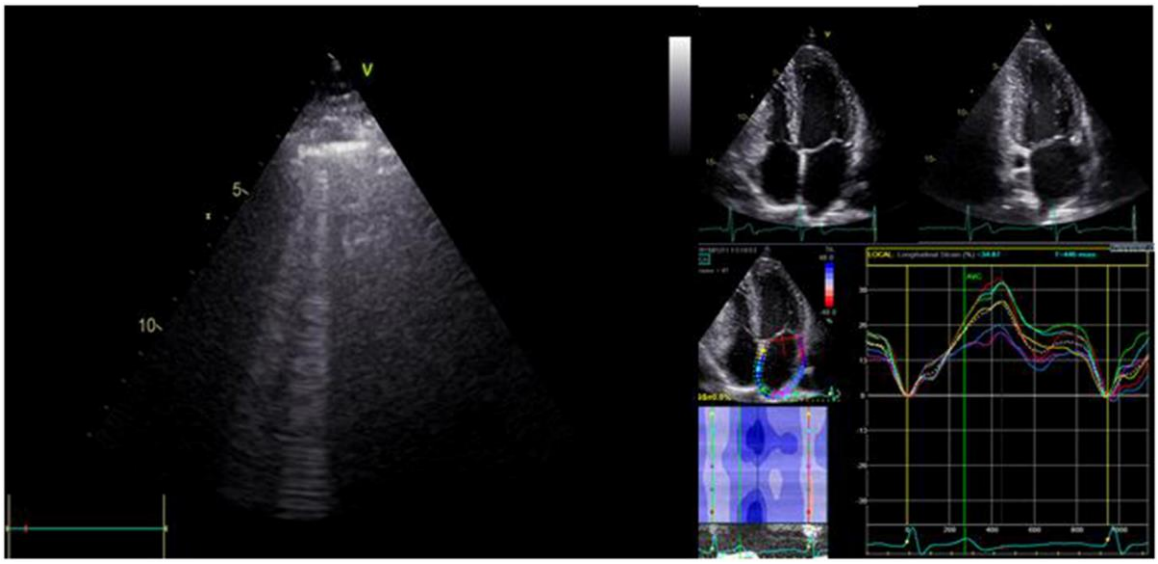


**FIGURE 7 |** Assessment of B-lines by lung ultrasound and determination of left atrial reservoir strain (LASr) in patients with HFpEF.

## Results

Results of the HFpEF study

131 consecutive patients were screened from January 2018. to December 2019. Fifty-six patients were excluded:14 patients had moderate or severe mitral and/or aortic valve disease, 2 patients had atrial fibrillation with heart rate above 80/min at rest, 10 patients had an EF below 50%, 4 patient had moderate or severe COPD or pulmonary disease, 2 patients had an estimated glomerular fitration rate (eGFR) below 35 mL/min/1.73 m², 3 patients had ischemic heart disease (where subsequent examinations were confirming significant coronary artery disease), and in 21 patients, we could not confirm any significant disorder that could support the referral diagnosis. Finally, 75 patients (age: 70.33 ± 6.85 years, 73.3% female) met our inclusion criteria. Ten patients had atrial fibrillation with normal ventricular rate during the enrollment, and others were in sinus rhythm. Patient characteristics are shown in Table 3.

During the 26 [22,32] months follow-up we detected 11 events: 4 patients were treated at an emergency department for an acute HF episode, 2 patients were admitted to the cardiology ward due to severe HF symptoms, 3 patients needed ambulatory intensification of loop diuretic treatment due to worsening of HF symptoms and 2 patients died (1 unknown cause, 1 patient during HF event). Patients with adverse clinical events more frequently had hyperlipidemia, diabetes mellitus, ongoing digoxin therapy, higher NT-proBNP levels, more B-lines, lower left atrial reservoir strain (LASr), deceleration time (DCT) and systolic myocardial velocity measured with tissue Doppler imaging at the tricuspid annulus (S') than the event-free group (Table 3).

**TABLE 3 |** Baseline demographic and echocardiographic parameters.

| **Parameters** | **Overall n=75** | **HF event free group n=64** | **HF event group n=11** | **Significance** |
|---|---|---|---|---|
| **Demographic parameters** | | | | |
| Age (years) | 70.33±6.85 | 70.02±7.02 | 72.18 ±5.67 | - |
| Gender (female, n,%) | 55 (73.3%) | 49 (76.56%) | 6 (54.54%) | - |
| Body Mass Index (kg/m$^2$) | 30.15±4.89 | 29.96±4.64 | 31.13 ±6.20 | - |
| **Clinical parameters** | | | | |
| Systolic blood pressure (mmHg) | 134.24±15.05 | 134.91±15.60 | 130.33±11.15 | - |
| Diastolic blood pressure (mmHg) | 79.00±9.35 | 79.57±9.70 | 75.67±6.40 | - |
| Heart rate (beats/min) | 68.48±10.55 | 67.65±9.73 | 72.82±13.81 | - |
| NYHA I. (n,%) | 3 (4%) | 3 (4.69%) | 0 (0%) | |
| NYHA II. (n,%) | 60 (80%) | 53 (82.81%) | 7 (63.64%) | |
| NYHA III. (n,%) | 11 (14.67%) | 7 (10.77%) | 4 (36.36%) | |

| | | | | |
|---|---|---|---|---|
| NT-proBNP level (pg/ml) | 406.60 [165.00, 772.00] | 376.95 [163.00,640.00] | 904.00 [668.00,2156.00] | 0.01 |
| eGFR (ml/min) | 71.45±17.54 | 73.12±17.16 | 63.59±18.32 | - |
| Haemoglobin (g/l) | 130.33±14.83 | 130.57±12.80 | 129.22±22.80 | - |
| **Comorbidities** | | | | |
| Hypertension (n,%) | 65 (86.67%) | 56 (84.50%) | 9 (81.82%) | - |
| Diabetes mellitus (n,%) | 21 (28.00%) | 15 (23.44%) | 6 (54.54%) | 0.025 |
| Atrial fibrillation (n,%) | 21 (28.00%) | 16 (25.00%) | 5 (45.45%) | - |
| Hyperlipidaemia (n,%) | 27 (36.00%) | 19 (29.69%) | 8 (72.72%) | 0.006 |
| **Treatment** | | | | |
| Beta-blocker (n,%) | 55 (73.33%) | 48 (75.00%) | 7 (63.64%) | - |
| Angiotensin convertase enzyme inhibitor (n,%) | 30 (40.00%) | 27 (42.19%) | 3 (27.27%) | - |
| Angiotensin receptor blocker (n,%) | 28 (37.33%) | 21 (32.81%) | 7 (63.64%) | - |
| Calcium channel blocker (n,%) | 20 (26.67%) | 16 (25.00%) | 4 (36.36%) | - |
| Digoxin (n,%) | 4 (5.33%) | 2 (3.12%) | 2 (18.18%) | 0.045 |
| Loop diuretic (n,%) | 44 (58.67%) | 36 (56.25%) | 8 (72.73%) | - |

| | | | | |
|---|---|---|---|---|
| Aldosterone antagonist (n,%) | 5 (6.67%) | 4 (6.25%) | 1 (9.09%) | - |
| Statin (n,%) | 34 (45.33%) | 27 (42.19%) | 7 (63.64%) | - |
| Anticoagulant (n,%) | 23 (30.67%) | 18 (28.12%) | 5 (45.45%) | - |
| Proton pump inhibitor (n,%) | 32 (42.67%) | 25 (39.01%) | 7 (63.64%) | - |
| **Echocardiographic parameters** | | | | |
| EF (%) | 67.56±8.32 | 68.92±7.39 | 62.82±6.69 | 0.013 |
| LV GLS (%) | -16.67±6.38 | -17.21±6.52 | -13.26±4.27 | - |
| IVS (mm) | 11.35±1.30 | 11.30±1.11 | 11.64±2.16 | - |
| PW (mm) | 11.20±1.41 | 11.16±1.21 | 11.45±2.34 | - |
| LVmass index ($g/m^2$) | 114.22±26.07 | 112.70±22.43 | 112.13±40.66 | - |
| RWT | 0.45±0.07 | 0.45±0.07 | 0.44±0.08 | - |
| LAVI (ml/m2) | 43.85±16.22 | 45.57±16.25 | 43.65±16.81 | - |
| LASr (%) | 19.76±8.83 | 20.71±8.84 | 14.46±6.98 | 0.038 |
| E/A | 1.04±0.56 | 1.02±0.56 | 1.18±0.52 | - |
| DCT (ms) | 223.24±69.08 | 231.45±65.42 | 177.30±74.89 | 0.021 |
| E/E'mean | 10.82±3.81 | 10.61±3.62 | 12.28±4.93 | - |
| S' | 8.41±2.76 | 8.73±2.82 | 6.54±1.37 | 0.014 |
| PASP (mmHg) | 37.50±14.97 | 36.21±14.10 | 45.10±18.34 | - |
| TAPSE (mm) | 25.14±5.42 | 25.31±5.46 | 24.18±5.31 | - |
| No of B-lines | 11 [5,20] | 9 [4,15] | 21[17,33] | <0.001 |
| B-lines>30 (n, %) | 50 (66.70%) | 7 (10.94%) | 3 (27.27%) | - |
| B-lines>15 (n, %) | 25 (33.30%) | 15 (23.44%) | 10 (90.91%) | <0.001 |

Data are expressed as mean±SD or median [IQR1,IQR3], or number and percentage. NYHA: New York Heart Association classification to stages of heart failure; NT-proBNP: N 468 -terminal (NT)-prohormone B type natriuretic peptide; eGFR: estimated Glomerular Filtration Rate; LV EF: Left Ventricular Ejection Fraction, LV GLS: Left Ventricular Global Longitudinal Strain; IVS: Interventricular Septum Thickness; PW: Posterior Wall Thickness; LV mass index: Left Ventricular Mass Index; RWT: Relative Wall Thickness; LAVI: Left Atrial Volume Index; LASr: Left Atrial Reservoir Strain; DCT: E wave deceleration time; E/E'mean: the relationship between maximal values of passive mitral inflow (E, PW-Doppler) and the average of lateral and septal early diastolic mitral annular velocities (E', TDI), TDI: Tissue Doppler

Imaging; S': systolic myocardial velocity measured with TDI at the tricuspid annulus; PASP: pulmonary artery systolic pressure; TAPSE: Tricuspid annular plane systolic excursion

The feasibility of lung ultrasound was 100%, and the mean duration of the examination was 2.5±0.47 min. We found a strong correlation between the number of B-lines and NT-proBNP levels and a moderate correlation between B-lines and LASr (Figure 8). B-lines significantly correlated with estimated pulmonary artery systolic pressures (PASP; r = 0.471, p < 0.001) and left atrial volume index (LAVI; r = 0.243, p < 0.05), too.

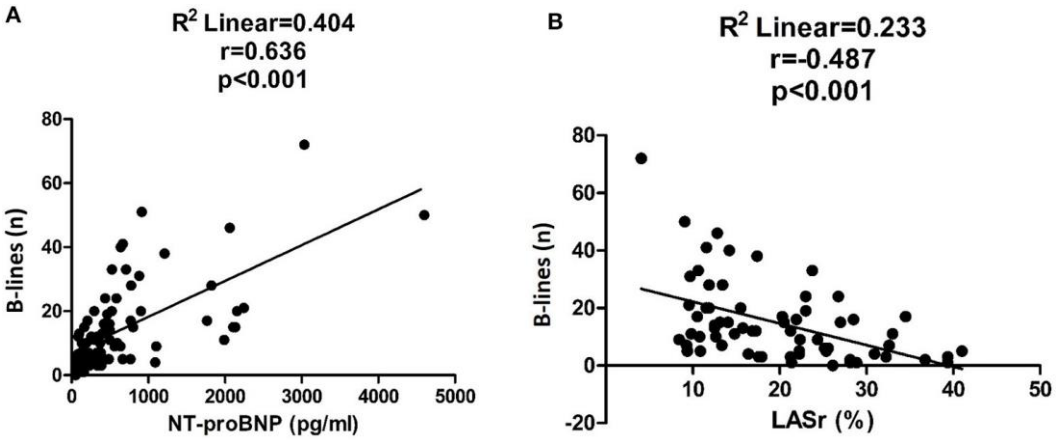



**FIGURE 8 |** Correlation between the number of B-lines and NT-proBNP levels (A) and LASr values (B).

The performance of the number of B-lines in the prediction of HF events was similar to the performance of NT-proBNP levels (Figure 9), with the best cut-off value at 16 B-lines (sensitivity 91%, specificity 79%), which corresponds with the widely used cut-off for moderate PC[71]. LASr's predictive value was weaker (Figure 9), with the best cut-off at 13.75% (sensitivity 71.4%, specificity 70%). The feasibility of the LASr measurements was 92%. Having >15 B-lines significantly increased the risk of the endpoint events, and during the multivariate analysis, proved it to be an independent predictor of endpoint events (Table 4).

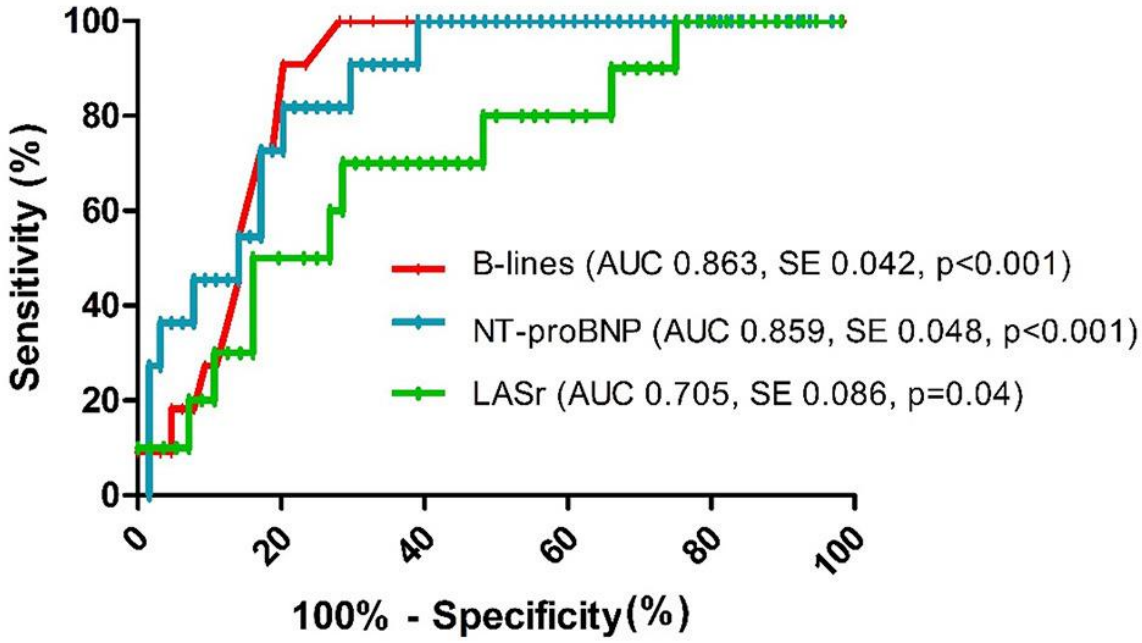



**FIGURE 9 |** Receiver operating curves (ROC) for the prediction of endpoint events (AUC: area under the curve; SE:standard error).

**TABLE 4 |** Cox regression analysis demonstrating the prognostic capacity of the predictor parameters.

| Parameters | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | p | Hazard Ratio | p | Hazard Ratio |
| **Diabetes mellitus** | - | - | - | - |
| **Hyperlipidemia** | 0.024 | 5.96 | - | - |
| **Digoxin** | - | - | - | - |
| **NT-proBNP** | 0.008 | 1.001 | - | - |
| **LASr** | - | - | - | - |
| **S'** | 0.029 | 0.769 | - | - |
| **DCT** | 0.023 | 0.986 | - | - |
| **B-lines>15** | 0.004 | 20.956 | 0.01 | 15.473 |

NT-proBNP: N 468 -terminal (NT)-prohormone B type natriuretic peptide; LASr: Left Atrial Reservoir Strain; DCT: E wave deceleration time; S': systolic myocardial velocity measured with TDI at the tricuspid annulus

The event-free survival was significantly worse among patients with >15 B-lines ($p < 0.001$, Log Rank: 16.804). The probability of cumulative event-free survival at 20 and 40 months in patients with ≤15 B-lines was 100 and 97.3%, respectively, while in patients with >15 B-lines it was 72% at 20 and 58.2% at 40 months (Figure 10).

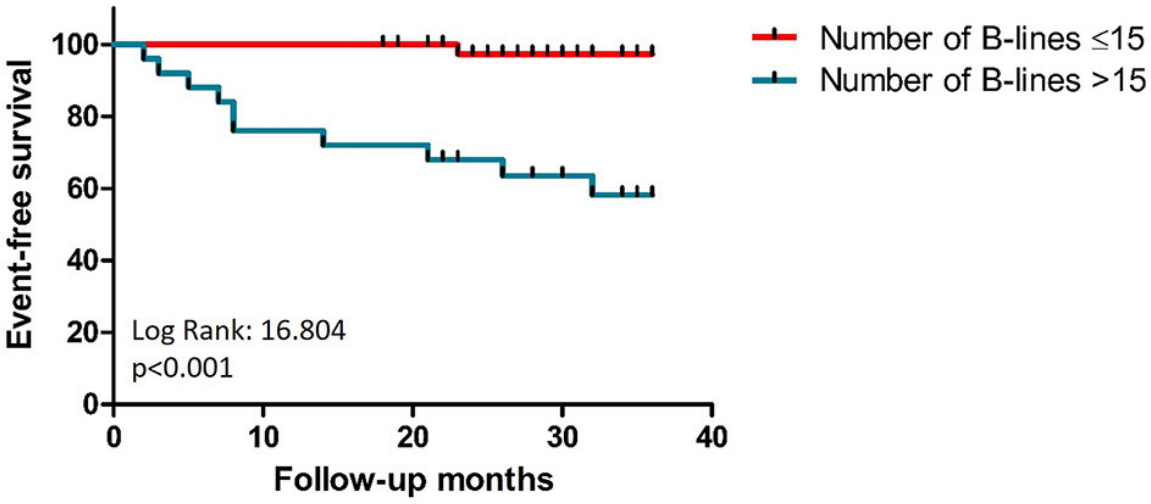



**FIGURE 10 |** Comparison of Kaplan-Meier curves for patients with and without B-lines >15.

Results of the AS study

97 patients were screened from May 2019. to October 2020. 22 patients were excluded from the initial population (4 patients had concomitant moderate aortic regurgitation, 6 patients had concomitant moderate or severe mitral regurgitation, 4 patients had dilated cardiomyopathy with moderate AS, 4 patients had low-flow, low-gradient AS, 3 patients had severe chronic obstructive pulmonary disease, and 1 patient had active lung cancer). Finally, 75 patients (39 women, mean age 73.85±7.7 years) were enrolled in the study. According to the 2021 ESC guideline categorization[24], the enrolled patient population included 30 patients with high-gradient AS, 22 patients with low-flow, low-gradient AS with a preserved EF, 8 patients with normal-flow, low-gradient AS with preserved EF, and 15 patients with moderate AS. During the 13.4±6 months follow-up, we detected 28 events: 19 patients had hospitalisations due to HF (2 of them underwent

urgent aortic valve replacement (AVR), 7 of them required ambulatory intensification of loop diuretic therapy. 2 patients died (the exact cause of death is unknown). Baseline characteristics of the study population and the comparisons between those with and without events are shown in Table 5.

**TABLE 5 |** Clinical characteristics of the study population and comparisons between patients with and without events.

| **Parameters** | **Overall (n=75)** | **HF event-free group (n=47)** | **HF event group (n=28)** | **Significance** |
|---|---|---|---|---|
| **Age (years)** | 73.85±7.7 | 72.04±8.1 | 76.89±6.3 | 0.008 |
| **Gender (female)** | 39 (52%) | 26 (55.3%) | 13 (46.4%) | - |
| **BMI ($kg/m^2$)** | 27.11±3.8 | 26.99±4.19 | 27.22±3.4 | - |
| **SBP (mmHg)** | 127.82±12 | 126.85±11 | 129.00±14.7 | - |
| **DBP (mmHg)** | 76.66±8 | 76.71±6 | 76.71±10.8 | - |
| **HR (BPM)** | 70.11±9.4 | 69.60±9.9 | 70.43±9.1 | - |
| **NYHA I** | 16 (19.2%) | 16 (31.4%) | 0 (0%) | <0.001 |
| **NYHA II** | 43 (57,3%) | 24 (51.0%) | 19(67.8%) | - |
| **NYHA III** | 15(20%) | 6 (12.7%) | 9 (32.1%) | 0.047 |
| **Peripheral oedema** | 10 (13.3%) | 5 (10.6%) | 5 (17.8%) | - |
| **Syncope** | 5 (6.67%) | 2 (4.2%) | 3 (10.7%) | - |
| **Rales** | 12 (16%) | 4 (8.5%) | 8 (28.5%) | 0.048 |

Data are expressed as mean±SD or number and percentage. BMI: body mass index, SBP: Systolic blood presure, NYHA: New York Heart Association classification to stages of heart failure.

All patients with events were already in NYHA class II-III, but only 66.67% of the event-free group were symptomatic. More patients in the event group had pulmonary rales, whereas the presence of peripheral oedema was not different.

Pressure gradients measured above the aortic valve differed significantly between the two groups (Table 4), and LV EF was significantly worse in the event group. PASP was significantly higher, and the tricuspid annular plane systolic excursion (TAPSE) was lower in the event group. RV-pulmonary artery (PA) coupling, expressed by TAPSE/PASP ratio, was also significantly different in patients with and without events (Table 6).

**TABLE 6 |** Baseline echocardiographic characteristics of the study population and comparisons between patients with and without events.

| Parameters | Overall (n=75) | HF event-free group (n=47) | HF event group (n=28) | Significance |
|---|---|---|---|---|
| **Peak Ao Gradient (mmHg)** | 59.61±22 | 54.74±19.3 | 67.79±24 | 0.012 |
| **Mean Ao Gradient (mmHg)** | 37.60±13.4 | 34.45±12.6 | 42.89±13.2 | 0.008 |
| **AVA ($cm^2$)** | 0.78±0.2 | 0.83±0.3 | 0.71±0.2 | - |
| **LAVI ($ml/m^2$)** | 34.23±19.5 | 35.34±17.1 | 44.64±21.5 | - |
| **LASr %** | 23.55±12.7 | 24.93±12.9 | 16.22±9.5 | - |
| **LA stiffness** | 0.75±1.1 | 0.57±0.4 | 1.01±0.9 | - |
| **EDV (ml)** | 114.80±29 | 115.40±27.5 | 113.57±32.5 | - |
| **ESV (ml)** | 40.97±20.4 | 36.83±15.8 | 49.43±26 | 0.041 |
| **EF (Simpson) %** | 63.32±10.6 | 67.67±7.4 | 56.02±11.2 | <0.001 |
| **IVS (mm)** | 12.33±1.5 | 12.11±1.2 | 12.71±1.9 | - |
| **PW (mm)** | 11.97±1.3 | 11.94±1.2 | 12.04±1.5 | - |
| **LV GLS (%)** | -17.03±8.5 | -17.08±9.8 | -16.90±4.3 | - |

| | | | | |
|---|---|---|---|---|
| **PASP (mmHg)** | 36.59±15.7 | 31.00±11.5 | 45.79±17.4 | <0.001 |
| **E (cm/s)** | 83.21±31.6 | 81.46±28.3 | 85.69±36.1 | - |
| **A (cm/s)** | 98.86±27.5 | 105.44±28.1 | 88.57±23.7 | 0.020 |
| **E/A** | 0.87±0.4 | 0.78±0.2 | 1.00±0.5 | - |
| **DCT (ms)** | 229.29±63.5 | 238.79±64.2 | 215.05±60.4 | - |
| **Lateral E' (cm/s)** | 8.55±3.5 | 8.72±3.1 | 8.27±4.2 | - |
| **E/e' (cm/s)** | 11.35±6.2 | 10.83±5.2 | 12.17±7.6 | - |
| **RV basal diameter (mm)** | 35.55±4.1 | 34.77±3.3 | 36.44±4.7 | - |
| **TAPSE (mm)** | 23.20±4.9 | 24.54±4.7 | 21.25±4.6 | 0.006 |
| **Lung ultrasound** | | | | |
| **Total number of B-lines (n)** | 22±22 | 18±23 | 29±18 | 0.028 |
| **≥15 B-lines** | 38 (50.6%) | 17 (36.1%) | 21 (75%) | 0.001 |
| **≥30 B-lines** | 22 (29.33%) | 8 (17.%) | 14 (50%) | 0.002 |

Data are expressed as mean±SD or number and percentage.

Ao Peak Gradient: estimated peak pressure gradient across the aortic valve, Ao mean gradient: estimated mean gradient across the aortic valve, AVA: calculated aortic valve area, LV EF: left ventricular Ejection Fraction, LV GLS: left ventricular Global Longitudinal Strain, IVS: intraventricular septum thickness, PW: posterior wall thickness, LAVI: left atrial volume index, LASR: left atrial reservoir strain, LA stiffness: left atrial stiffness, E: early mitral inflow peak velocity, A: late mitral peak inflow velocity, DCT: E wave deceleration time, E/E'mean: relationship between maximal values of passive mitral inflow (E, PW-Doppler) and lateral early diastolic mitral annular velocities (Lateral E', TDI), PASP: pulmonary artery systolic pressure, TAPSE: tricuspid annular plane systolic excursion.

We found severe degree of PC (B-lines≥30) in 29.33% of all patients. Significantly more B-lines occured in the event group (p=0.028) and in this group more patients had 30 or more B-lines (p = 0.002). The number of B-lines increased significantly

along with the worsening of NYHA functional classes (Figure 11), from 13±12 in NYHA Class I, through 19±15 in Class II, to 43±34 in Class III ($p<0.05$, rho=0.383).

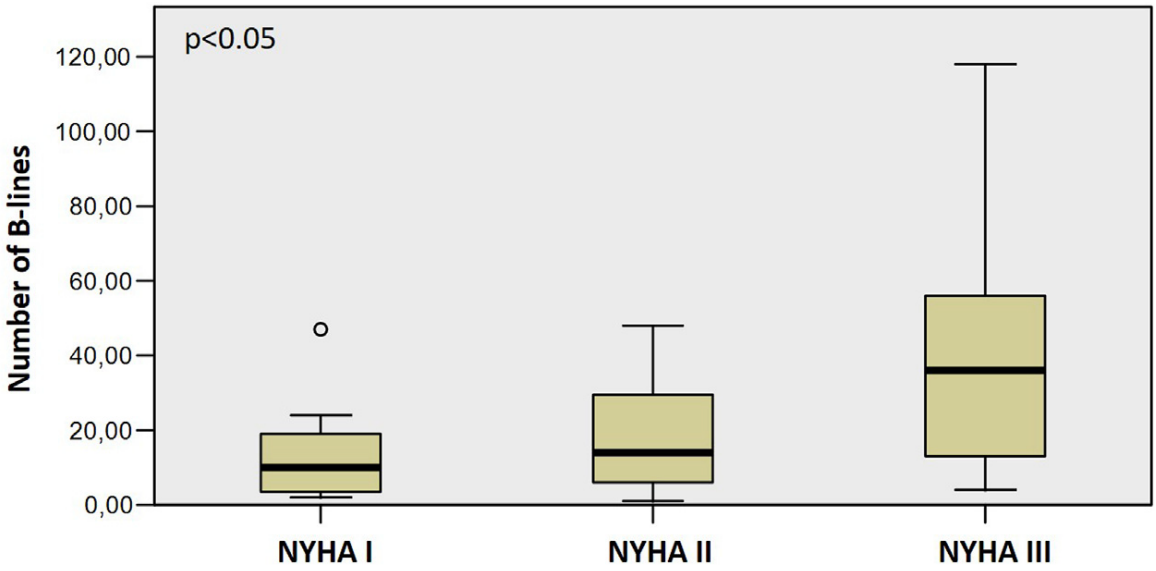



**FIGURE 11 |** The increasing number of B-lines with worsening NYHA functional class.

Patients with severe AS had significantly more B-lines than patients with moderate AS (14±13 vs. 25±24; $p<0.05$). We also found that the number of B-lines was correlated (Figures 12 A, B) with LVEF ($R=-0.325$, $p<0.05$) and PASP ($R=0.574$, $p<0.001$). We did not find a significant correlation between E/e' and B-lines or LAVI and B-lines.

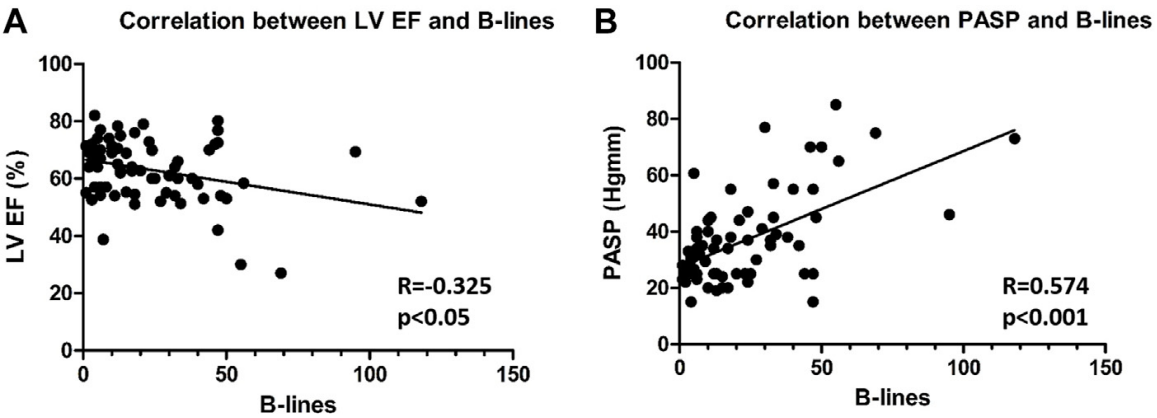



**FIGURE 12 |** Correlation between B-lines and LVEF (A) and PASP (B) (LVEF: Left ventricular ejection fraction, PASP: Pulmonary arterial systolic pressure).

Having ≥30 B-lines meant lower event-free survival (Log rank 8.619; p<0.05) (Figure 13) and significantly increased the risk of endpoint events [(hazard ratio B-lines CI: 2.79 (1.03–7.54), p<0.05)]. During multivariable modelling, B-lines and mean aortic gradient were the independent predictors of events (Table 7).

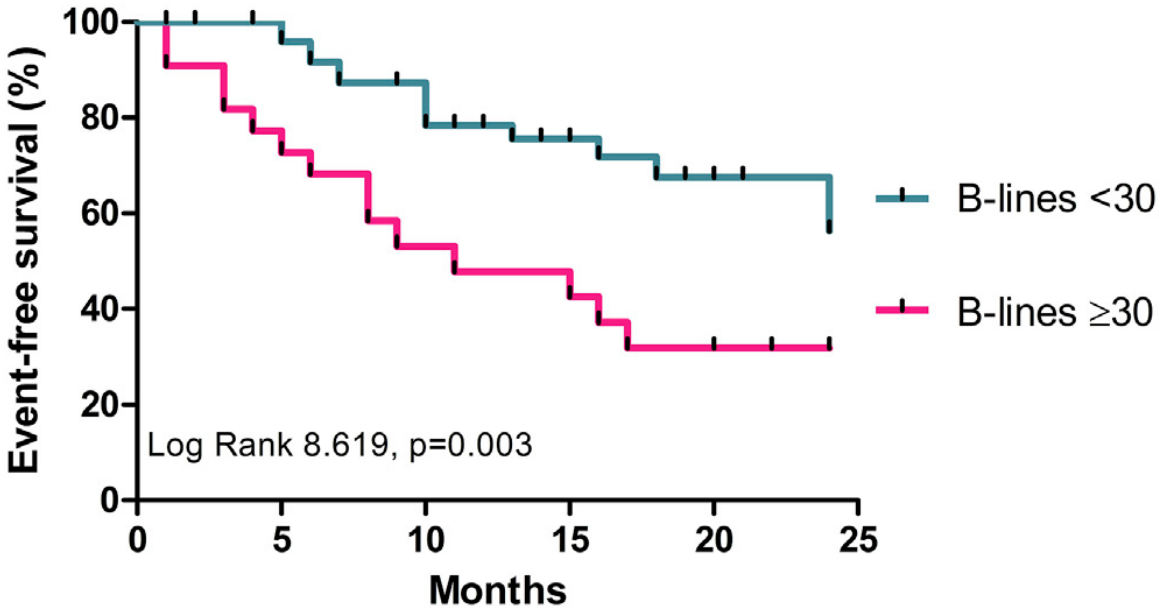



**FIGURE 13 |** Comparison of HF endpoints among patients with ≥30 and <30 B-lines.

**TABLE 7 |** Cox regression analysis.

| **Parameters** | **Univariate analysis** | | **Multivariate analysis** | |
|---|---|---|---|---|
| | HR (95% CI) | p<0.05 | HR (95% CI) | p<0.05 |
| **Age** | 1.06 (1.01-1.11) | 0.018 | 1.03 (0.98-1.08) | - |
| **Aorta mean gradient** | 1.044 (1.02-1.07) | <0.001 | 1.04 (1.01-1.07) | 0.004 |
| **PASP** | 1.04 (1.02-1.06) | <0.001 | 1.01 (0.98-1.04) | - |
| **B-lines≥15** | 2.61 (1.10- 6.19) | 0.029 | - | - |
| **B-lines≥30** | 2.86 (1.36-6.03) | 0.006 | 2.79 (1.03-7.54) | 0.043 |

# Discussion

## Utility of LUS

Lung ultrasound was firstly introduced more than 40 years ago, as a potential diagnostic method for pneumonia[72–77]. Then „lung comets" (B-lines) arrived as an excellent alternative for bed-side CXR for diagnosing alveolar-interstitial syndrome in the intensive care unit in the '90s[78].

Since LUS' first description, an enormous body of evidence has assisted the raison d'être of B-lines in the everyday practice, so nowadays LUS is included in practical guidelines wordwide[2,79–82]. Its efficacy has been compared to widely accepted methods for assessing PC. The good correlation of the number of B-lines with PC on CXR has been established long ago in both acute and chronic conditions[83,84]. It has also been described that LUS' sensitivity in assessing extra-vascular lung water (EVLW) is comparable to CXR[84] or computer tomography[85] and is better than auscultation[86]. The number of B-lines correlates well with thoracic fluid content estimated by impedance measurements[87,88]. B-lines' number is also associated with pulmonary capillary wedge pressure (PCWP)[89–91] and EVLW measured with thermodilution[90,92].

According to Frassi et al., New York Heart Association (NYHA) class, LV EF and the degree of diastolic dysfunction are independently associated with the number of B-lines in hospitalised patients (11% of them had acute HF)[91]. Among routinely measured echocardiographic parameters, PASP also showed a good correlation with LUS in a patient population with undifferentiated dyspnoe[89].

NT-proBNP has a prominent place both in the diagnosis and prognosis of HF[2]. BNP significance is marked by none less than their rule-in/rule-out role in the diagnostic workup.

LUS can help clinicians to differentiate easier and faster between the causes of dyspnoe[93,94], leading to faster achievement of adequate therapy. In a study including severe acute dyspneic HF or COPD patients, Zanatta et al. described that pre-hospital lung ultrasound had a 94.4% specificity and 100% sensitivity for identifying alveolar interstitial syndrome[95]. Gargani et al. found that LUS performed similarly in predicting the cardiac origin of acute dyspnoe as NT-proBNP: ROC analysis showed an AUC of 0.893 for B-lines and 0.978 for proBNP ($p=0.001$)[96]. Another study described a better

distinctive ability of LUS compared to proBNP among acutely dyspneic patients[97]. LUS can help clinicians easily and quickly differentiate between the causes of dyspnoea in emergency and ambulatory circumstances, leading to faster achievement of adequate therapy[93,95].

The significance of B-lines lies not just in their diagnostic utility; their use in therapy monitoring and determination of the prognosis is also widely studied. In acute HF their number can change within 3 hours after HF treatment[98]. Due to the dynamic characteristics of B-lines, LUS could be the ultimate method to guide HF therapy. However, studies investigating that opportunity reached conflicting results[99,100].

The learning curve for acquiring B-lines is very short[101,102]. With handheld ultrasound machines, this diagnostic tool could aid general practitioners as a point-of-care test. The length of the examination depends on the chosen method, but in the case of PC estimation, it usually takes under 3 minutes[83,103].

However, there are still gaps in our knowledge, which impede the maximum use of the benefits of this fast, achievable and radiation-free method. The main problem is the divergence of methods for B-lines quantification, making the establishment of exact cut-off values more difficult. Most data are available from studies counting B-lines on both anterolateral hemithoraces using 28 intercostal zones, which provides a more complete examination of the lungs but is more time-consuming than simplified methods. This method is recommended for non-critical patients, especially for follow-up[62].

## The prognosis of chronic HFpEF

In spite of its heterogeneity, HFpEF is a distinct entity with its characteristic patient population, pathogenesis, treatment responsiveness and prognosis. Although the morbidity outcomes (hospitalisation and symptomatic status as measured by quality of life indicators) of HFpEF and HFrEF are similar[104–106], a large prospective study observed lower mortality in HFpEF compared to HFrEF[16]. Independent predictors of mortality were older age, male sex, higher NYHA class, the severity of coronary artery disease and diastolic dysfunction, lower LV EF, right ventricular dysfunction, pulmonary hypertension, elevated BNP, diabetes mellitus, impaired renal function and increased red blood cell distribution width[107–112]. Some of these parameters may not readily available

in the ambulatory setting, and there is still no established system for prognostication in case of HFpEF.

In our study of newly diagnosed HFpEF patients, having more than 15 B-lines at the time of diagnosis was highly suggestive of a worse prognosis and performed better in predicting HF events than NT-proBNP and the other clinical and echo parameters. We also found that the number of B-lines has a relationship with LA volume and estimated systolic pulmonary artery pressures. In our study, B-lines showed a close relationship with LA dysfunction represented by decreased LASr, which is a new observation.

Assessing the number of B-lines is a simple, radiation-free and easily accessible method to estimate PC with 100% feasibility and short examination time[71,113]. Due to its advantages, a lot of data have been gathered until now about its potential use in different clinical settings. B-lines correlate with several clinical and echocardiographic parameters[65,92,96].

The commonly used cut-off value is >15 for moderate and >30 B-lines for severe congestion summing B-lines from 28 anterolateral lung areas[71]. Examining HFrEF outpatients, Miglioranza et al. found the best cut-off value to be at 15 B-lines[65]. Another study with pre-discharge HF patients confirmed this cut-off irrespective of EF[114].

B-lines also have an exceptional prognostic value, shown in patients with HF[114–119]. After a 1-year follow-up in dyspneic patients, an increased number of B-lines was associated with a higher hospitalisation rate with a best cut-off at 6 B-lines (8 sector LUS)[120]. Measurement of PC at discharge provides prognostic information for patients with either HFpEF[121,122] or HFrEF[122]. Rueda-Camino et al. found significantly more hospital readmissions and HF deaths among patients with at least 15 B-lines (using the 28-segment LUS method)[121]. According to Palazzuoli et al., B-lines ≥22 at discharge and ≥25 at admission was associated with higher HF rehospitalisation rate and all-cause mortality, and that prognostic value was similar in both HFpEF and HFrEF patients[122,123]. The studies, which are related to B-lines' prognostic utility in HF are summarized in Table 8.

**TABLE 8 |** Lung ultrasound in the prognostication of HF

| Study (first author, date of publication) | HF patients | LUS method | LUS timing | LUS at rest/peak stress | Follow-up length (months; median) | Main finding | Proposed cut-off for the number of B-lines |
|---|---|---|---|---|---|---|---|
| Frassi, 2007 | acute, mixed | 28 | at admission | rest | 16 | B-profile predicts events. | 30 |
| Coiro, 2015 | acute, mixed | 28 | pre-discharge | rest | 3 | B-profile predicts events. | 30 |
| Gargani, 2015 | acute, mixed | 28 | pre-discharge | rest | 6 | B-profile predicts readmission. | 15 |
| Gustafsson, 2015 | non-acute, mixed | 5 | - | rest | 17 | B-profile and pleural effusion predicts events. | 3 |
| Cogliati, 2016 | acute, mixed | 8 | pre-discharge | rest | 3 | B-profile predicts events. | - |
| Platz, 2016 | non-acute, mixed | 8 | - | rest | 6 | B-profile predicts events. | 3 |
| Miglioranza, 2017 | non-acute HFrEF | 28 | - | rest | 4 | B-profile predicts hospitalisation. | 30 |
| Scali, 2017 | non-acute, HFrEF | 28 | - | exercise | 8 | B-profile predicts events. | 30 |
| Palazzuoli, 2018 | acute, mixed | 8 | pre-discharge | rest | 6 | B-profile predicts events. | 22 |
| Domingo, 2021 | non-acute, mixed | 8 | - | rest | 6 | B-profile predicts events. | 8 |
| Gargani, 2021 | acute HFpEF and HFrEF / non-acute, mixed | 28 | at admission / - | rest | 14,4 | B-profile had a strong predictive value in HFpEF and non-AHF, but not in HFrEF. | 30 |
| Rueda-Camino, 2021 | acute HFpEF | 28 | pre-discharge | rest | 3 | B-profile predicts events. | 15 |
| Morvai-Illés, 2021 | non-acute HFpEF | 28 | - | rest | 26 | B-profile predicts events. | 15 |
| Pugliese, 2023 | acute, HFpEF, HFrEF, HFmrEF | 28 | pre-discharge | rest | 6 | B-profile predicts events. | 15 |
| Palazzuoli, 2024 | acute, HFpEF, HFrEF and HFmrEF | 8 | at admission | rest | 6 | B-profile was significantly associated with events. | 25 |

Natriuretic peptides are frequently used biomarkers for diagnosis, risk stratification and therapeutic decision making in HF; but even in currently used guidelines their cutoff value for HF diagnosis varies[2]. HFpEF is a very heterogeneous disease, which makes both setting up the diagnosis and estimating prognosis more difficult. BNP and NT-proBNP are recognized outcome-predicting factors in acute HF regardless of EF[124]. However, many studies suggested that their prognostic value remains controversial. According to a study by Salah et al, the discharge NT-proBNP levels predict outcomes similarly in HFpEF and HFrEF; however, in the HFpEF group the NT-proBNP levels were lower. The authors concluded, that the comorbidities may contribute more to prognosis than proBNP in patients with HFpEF[22]. Another pitfall of natriuretic peptide-based prognosis estimation is that its cut-off may depend on gender, age, body mass index, presence or absence of atrial fibrillation and renal failure[125–128]. Eriksson et al. described significantly higher NT-proBNP values among HFmrEF (heart failure with mildly reduced EF) and HFpEF patients in the event cohort for all-cause mortality, but the standard deviations were very high at 1, 3, and also at 5 years (for HFpEF patients the means±SD were 5035.9±5630.3; 3785.1±4647.7; 3493.2±4365.5 ng/l), which reduces the prognostic utility of NT-proBNP in clinical practice[129]. The levels are generally higher in patients presenting with acute HF than in patients with chronic HF[130]. Additionally, the thicker myocardial wall, which is commonly seen in HFpEF, can normalize the wall stress, so even in the case of invasively proven HFpEF, the natriuretic peptide levels can be below the widely used threshold[131]. These weaknesses are not characteristic of B-lines because PC is a frequent and almost universal pathophysiological phenomenon in patients with HF. It is not influenced by age, gender or body mass index. B-lines have diagnostic and prognostic utility without being affected by comorbidities except for diseases that involve lung parenchyma.

In the last 10 years, LA deformation imaging has become more and more widespread in research and in daily routine. The LA is closely connected with the pulmonary venous system, and its dysfunction may play an essential role in the pathophysiology of PC. LA pressure increases to augment LV filling, resulting in pulmonary and systemic venous congestion. The LASr is an easy to measure and reproducible parameter, and it is now widely recognized that it has diagnostic and prognostic value regardless of EF[132,133]. LASr correlates well with diastolic dysfunction[134,135] and the invasively measured LV filling pressure[136,137], which plays a leading role in the pathophysiology of HFpEF, and it may have a prognostic value,

too[133,138]. In patients with chronic HFrEF, LASr ≤ 12.9% showed a much worse outcome than higher strain values[132]. In another study enrolling posthospitalized HFpEF patients, LASr was an independent predictor of cardiovascular events, and LASr < 31.2% was associated with significantly worse event-free survival[133]. In our current study, the LASr was significantly reduced in the event group compared to those without any events (14.46±6.98% vs. 20.71±8.84%). It correlated well with both NT-proBNP and the number of B-lines. Still, we could not prove it to be an independent prognostic factor in HFpEF. The possible explanation is that we also included patients with atrial fibrillation. Park et al. found in 3,818 patients that the lowest tertile of the peak atrial longitudinal strain is predictive in acute HF patients regardless of EF; however, when subgroup analysis was performed, LASr did not show predictive value in the AF population [139]. These results also emphasize the advantage of B-lines, which are not influenced by atrial fibrillation.

Finally, several score systems exist to estimate the risk of HFpEF patients, but until now, none of them has been recommended by guidelines. The widely used H2FPEF and HFA-PEFF scores were designed as diagnostic tools[19,140]. They also performed well in the prognostication of HFpEF caused by amyloidosis regardless of the clinical setting[141]. The H2FPEF score might be a potentially useful marker for the prediction of cardiovascular and HF-related events in HFpEF patients[18,142]. Sotomi et al. found that the HFA-PEFF score is an excellent diagnostic tool, and it also has a practical prognostic value[17]. Parcha et al. concluded that HFA-PEFF and the H2FPEF scores are reliable diagnostic tools; however, their prognostic utility requires further validation[143]. The MEDIA echo score is the only system by now, which was originally designed for prognostication purposes in HFpEF. It provides an improved risk stratification if added to BNPs and clinical variables[144], and was validated in both hospitalized and ambulatory cohorts[145]. The mentioned score systems incorporate echocardiographic parameters like EF, tissue doppler echocardiography (TDI) measurements, estimated systolic pulmonary pressure, left atrial volume index, relative wall thickness, and left ventricular mass index. Measurement of these parameters needs a comprehensive echocardiographic examination, which is time-consuming, requires an expert and might not be readily available. On the other hand, B-line assessment is simple and feasible, takes only a few minutes, and allows to visualize PC, which is the main pathophysiological change and the direct cause of symptoms in HF.

The prognosis of AS

To the best of our knowledge, this is the first study to address the prognostic value of B-lines for the prediction of adverse events in patients with AS. Our results show that the assessment of B-lines in AS adequately reflects patients functional class and the haemodynamic consequences caused by AS. Presence of severe congestion marked by B-lines ≥30 strongly predicts adverse events.

Current guidelines advise valve replacement when an integrative evaluation of pressure gradients, AVA, the extent of valve calcification, and flow indicates severe AS, and there is evidence of LV decompensation evaluated by echocardiographic measurements or appearance of symptoms. The guidelines also pointed out some additional prognostic markers, which also help decide on AVR[24]. Exercise stress echocardiography can unmask symptoms, pathologic blood pressure responses or low flow-low gradient AS and may provide prognostic information in asymptomatic patients: an elevation of 18 to 20 mmHg or higher in the mean aortic pressure gradient, or a decrease or no change in LVEF and induced pulmonary hypertension (≥60 mmHg) are markers of poor prognosis[146–149]. Cardiac magnetic resonance enables to assess myocardial fibrosis[150,151]. Moreover, natriuretic peptides have been shown to predict symptom-free survival and outcome in normal and low-flow severe AS[152]. These predictors, especially stress echocardiography and cardiac magnetic resonance, are not always available, and the repeated measurements are not feasible.

LV hypertrophy is a mechanism of accommodation in AS to restore wall stress and maintain cardiac output under increasing pressure afterload caused by the stenotic valve. However, the progressive cardiomyocyte death and consequent fibrosis that accompanies LV hypertrophy may lead to the development of LV systolic and diastolic dysfunction and finally to HF. Historical data have shown that the time from the onset of symptoms to death is about 2 years in patients who develop HF[39]. Besides the prognostic importance of HF in recent years, the data supports that cardiac damage also holds prognostic significance after AVR. Stages of cardiac damage in patients with severe AS have been defined from stage 1 to stage 4. These are: LV dysfunction, left atrial enlargement, pulmonary hypertension, and RV dysfunction (Figure 2). Each stage is associated with an increased mortality risk within one year, ranging from 4% in stage 0 (no damage) up to 25% in stage 4[42]. Our results are consistent with these data, showing that patients with HF events have lower EF, lower TAPSE, and higher PASP.

However, the worsening LVEF is a late and insensitive marker of myocardial dysfunction[42]. LV systolic and diastolic dysfunction and mitral regurgitation result in PC, which is a common finding in patients with HF. LUS assessment of PC by B-lines has been demonstrated to be an excellent diagnostic tool[64,78,83,153,154]. Decompensation is clinically silent in most patients and is often not recognized until developing rapid progression that requires urgent hospitalisation. LUS can assess lung oedema noninvasively in real-time, even at an early subclinical stage. B-lines are helpful for the differential diagnosis of acute HF syndromes from noncardiac causes of acute dyspnoea in the emergency setting, with high sensitivity and specificity[155].

We did not find a significant correlation between E/e' or LAVI and B-lines. Previous studies have shown this correlation, especially when assessing B-lines during exercise. However, this relation has never been tested in patients with significant aortic stenosis. Reddy and colleagues simultaneously performed stress tests, lung ultrasound, and right heart catheterization in HFpEF. B-lines' increase during exercise was associated with lower RV systolic velocity and RV fractional area change, worse RV-PA coupling, higher PCWP, and higher PASP. However, baseline E/e' was not higher in patients who increased B-lines during exercise[156]. Simonovic et al. enrolled HFpEF patients and performed exercise stress echocardiography and B-lines assessment; again, the resting E/e' value was not higher in patients with ≥10 B-lines at exercise[157]. Hubert and colleagues performed direct measurements of LV filling pressure and B-lines assessment on patients with different cardiovascular patients undergoing coronary angiography, and found that the total number of B-lines was significantly higher in the elevated LV EDP group (≥20 mmHg). They underline that the diagnostic capacity of B-lines to identify elevated LV EDP is higher than that of classical echocardiographic strategies[158].

We also found a significant correlation between B-lines and RV-PA coupling, expressed by TAPSE/PASP ratio ($r$ −0.443, $p < 0.001$). RV-PA coupling refers to the relationship of RV contractility and RV afterload. Its constitutients, contractility and afterload are interdependent: a rise in afterload should be followed by a similar elevation in contractility. In cases of elevation of the pulmonary pressures and decreased RV contractile reserve, RV-PA uncoupling is present, which indicates worse prognosis compared to patients with preserved RV-PA coupling in pulmonary hypertension, severe AS, HFpEF and HFrEF, too[159–162]. A meta-analysis by Kobayashi et al. also confirmed that worse RV function and RV–PA coupling were associated with higher B-line counts on admission and at discharge regardless of LVEF[163].

B-lines also have an exceptional prognostic value, shown in patients with HF, as mentioned above[114–118]. The predictive value is independent and additive over conventional clinical, imaging, and laboratory markers[116,118,119,164]. Our results are consistent with these previous findings: patients with AS-related PC have significantly more B-lines, and patients with ≥30 B-lines have significantly more HF-related events and death. In line with previous studies, we chose ≥30 B-lines in 28 scanning sites to determine severe congestion[44,117].

The determination of B-lines in AS is a promising method because establishing symptomatic status in this population is challenging due to their usually sedentary lifestyle and high prevalence of co-morbidities[165], as ageing and concomitant medical problems can cause symptoms similar to AS or conceal them by restricting physical activity. Even though angina and syncope are easily detectable symptoms, HF can be indolent. Therefore, there is a rationale for using additional methods to detect HF early. Several attempts were made to improve the prognostic stratification of AS patients. CAIMAN-ECHO score is an echocardiography based tool for asymptomatic, moderate or severe AS patients. It takes into account the calcium score of the aortic valve, inappropriate LV mass, and peak gradient across the aortic valve to predict the risk of cardiovascular events (all-cause mortality, AVR, hospitalisation for myocardial infarction and HF)[166]. Monin et al. developed a scoring system for patients with asymptomatic severe AS, including gender, BNP level, and peak aortic jet velocity. It can be used for the prediction of midterm risk of death and AVR[167]. Kearney et al. followed up AS patients older than 60 years of age (mild to severe valvular disease) for 18 years, and he found that age-adjusted Charlson co-morbidity index and grade of LV dysfunction were risk factors of all-cause mortality while having an AVR acted as a protective factor[168]. The predictive role of apical rotation was also assessed in a group of patients with symptomatic and asymptomatic severe AS and preserved EF. It was found that increased apical rotation was linked to worse survival[169]. According to two further studies, raised BNP and troponin I are also markers of adverse prognosis in asymptomatic patients with moderate-to-severe AS[170,171].

The assessment of B-lines has several advantages in patients with moderate and severe AS. The expansion of regular, standard TTE by LUS could improve risk stratification of patients. Cardiac damage, especially LV, mitral valve and LA dysfunction, results in PC and, consequently in HF signs and symptoms. Hence, early detection by LUS holds incremental prognostic and diagnostic possibilities. A more

accurate PC assessment might optimize the timing of valve surgery or help tailor HF therapy. It may identify high-risk AS patients whose concomitant heart disease aggravates PC, for example ischemic LV dysfunction, cardiomyopathies, and mitral valve disease. B-line assessment before surgery (transcatheter aortic valve replacement or open-heart surgery) may influence postoperative events; however, further studies are needed to confirm these hypotheses.

Limitations

The studies' populations were relatively small, and the number of events was limited (n=11 in HFpEF study and n=28 in AS study). However, our results are consistent with previous studies on larger populations demonstrating the prognostic value of B-lines in patients with HFpEF and in patients with dyspnea and all spectrum of resting EF[172,173].

Our series may not represent the average patient with moderate or severe AS, as low flow-low gradent aortic stenosis patients have been excluded.

PC is a dynamic variable, and in a considerable number of patients with HFpEF[174] or HFrEF[175] without B-lines at rest will develop PC during exercise. The number of B-lines during stress outperforms the prognostic value of B-lines at rest in patients with HFpEF[172,174], in patients with HFrEF[175] and in consecutive patients with the full range of underlying resting ejection fraction[176]. Therefore, our current study protocol has been adapted and currently includes a dynamic evaluation of B-lines also during stress in the framework of Stress Echo 2020 and 2030 multicenter study[173].

Many diseases which could have had an impact on the number of B-lines, the echocardiographic findings or the patient's heart failure symptoms were excluded at screening. The studies' population still remained quite heterogeneous; however, this heterogeneity reflects the circumstances under which the prognosis is estimated in everyday practice. The detection of B-lines does not necessarily imply their cardiogenic origin since pulmonary fibrosis and non-cardiogenic pulmonary oedema may also result in the presence of B-lines; however, we were applying strict exclusion criteria, so our study population did not have the mentioned etiological backgrounds.

The 28-zone protocol was used, which is more time-consuming than the simplified protocols, but performing the lung ultrasound still took only a few minutes.

# Conclusion

LUS is a radiation-free, fast, highly feasible and non-invasive method, and seems to be an excellent aid for prognostication in chronic HFpEF and moderate-to-severe AS as well.

Since the methods for the LUS-HFpEF studies varies, and chronic HFpEF patients are underrepresented (Table 7), more research is needed to define the best cut-off values. Literature is also divided according to which LUS method was used, which also stands in the way of wide dispersive use of LUS for prognostication. As our study was the first to assess the prognostic value of B-lines in AS, more studies are necessary to confirm our results.

Several recent studies[177] suggest, that the estimation of B-lines with artificial intelligence may be the way of the future by shortening the time of examination and training. This would strengthen LUS's position in the everyday practice not just in prognostication, but during diagnostic workup and tailored patient management as well.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