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ORIGINAL SCIENTIFIC PAPER
Acute Coronary Syndromes

Trajectory and correlates of pulmonary congestion by lung ultrasound in patients with acute myocardial infarction: insights from PARADISE-MI

Elke Platz [1]*, Brian Claggett[1], Karola S. Jering[1], Attila Kovacs[2], Maja Cikes[3], Ephraim B. Winzer[4], Aria Rad[1], Martin P. Lefkowitz[5], Jianjian Gong[5], Lars Køber [6], John J.V. McMurray[7], Scott D. Solomon [1], Marc A. Pfeffer[1], and Amil Shah[1]

[1]Cardiovascular Division, Brigham and Women's Hospital, 360 Longwood Ave, 7th Floor, Boston, MA 02115, USA; [2]Heart and Vascular Center, Semmelweis University, Budapest, Hungary; [3]Department of Cardiovascular Diseases, University of Zagreb School of Medicine and University Hospital Centre Zagreb, Zagreb, Croatia; [4]Heart Center Dresden—University Clinic, Department of Internal Medicine and Cardiology, Technische Universität Dresden, Dresden, Germany; [5]Novartis Pharmaceutical Corporation, East Hanover, NJ, USA; [6]Rigshospitalet, Blegdamsvej, University of Copenhagen, Copenhagen, Denmark; and [7]BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

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Aim

PARADISE-MI examined the efficacy of sacubitril/valsartan in acute myocardial infarction (AMI) complicated by reduced left ventricular ejection fraction (LVEF), pulmonary congestion, or both. We sought to assess the trajectory of pulmonary congestion using lung ultrasound (LUS) and its association with cardiac structure and function in a pre-specified substudy.

Methods and results

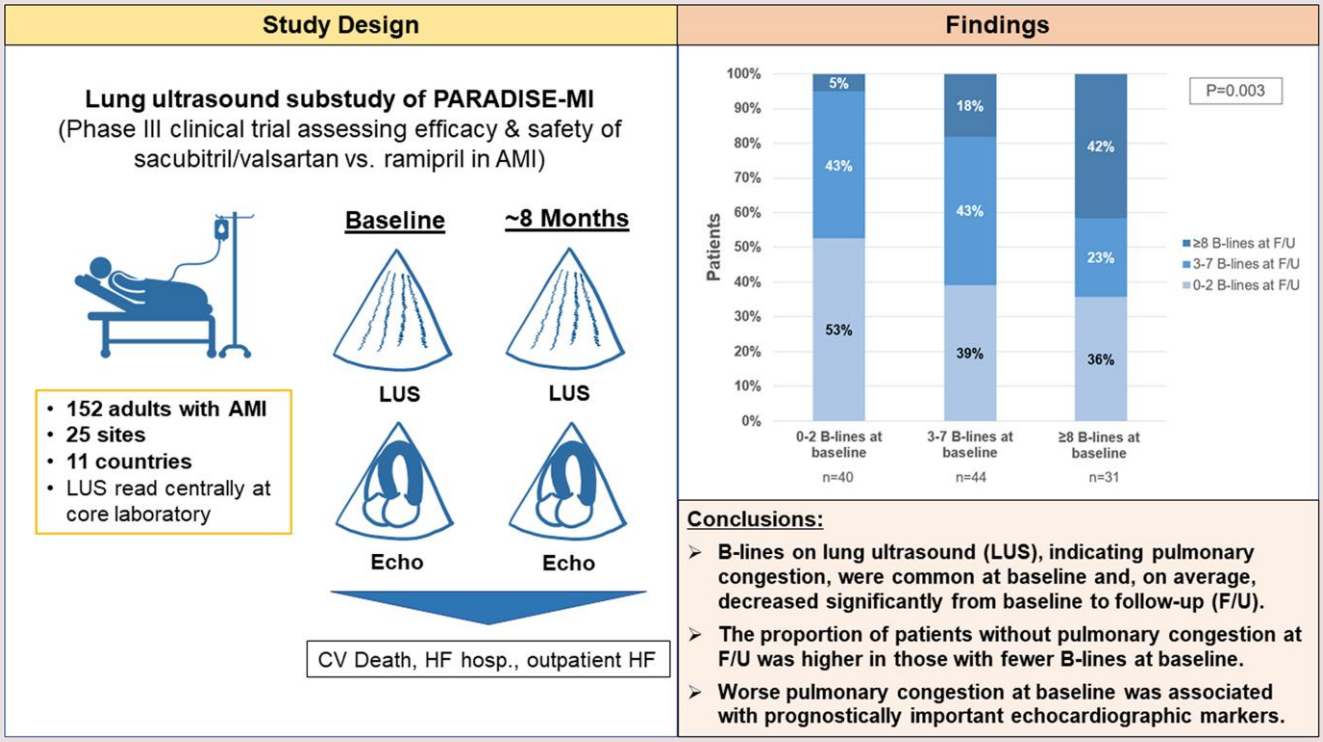
Patients without prior heart failure (HF) underwent eight-zone LUS and echocardiography at baseline (±2 days of randomization) and after 8 months. B-lines were quantified offline, blinded to treatment, clinical findings, time point, and outcomes. Among 152 patients (median age 65, 32% women, mean LVEF 41%), B-lines were detectable in 87% at baseline [median B-line count: 4 (interquartile range 2–8)]. Among 115 patients with LUS data at baseline and follow-up, B-lines decreased significantly from baseline (mean ± standard deviation: −1.6 ± 7.3; $P = 0.018$). The proportion of patients without pulmonary congestion at follow-up was significantly higher in those with fewer B-lines at baseline. Adjusted for baseline, B-lines at follow-up were on average 6 (95% confidence interval: 3–9) higher in patients who experienced an intercurrent HF event vs. those who did not ($P = 0.001$). A greater number of B-lines at baseline was associated with larger left atrial size, higher *E*/*e*′ and *E*/*A* ratios, greater degree of mitral regurgitation, worse right ventricular systolic function, and higher tricuspid regurgitation velocity (*P*-trend <0.05 for all).

Conclusion

In this AMI cohort, B-lines, indicating pulmonary congestion, were common at baseline and, on average, decreased significantly from baseline to follow-up. Worse pulmonary congestion was associated with prognostically important echocardiographic markers.

* Corresponding author. Tel: +1 617 525 7932, Email: eplatz@bwh.harvard.edu

Graphical Abstract



AMI, acute myocardial infarction; CV, cardiovascular; F/U, follow-up; HF hosp., heart failure hospitalization; LUS, lung ultrasound.

Keywords Acute myocardial infarction • Pulmonary congestion • Lung ultrasound • Echocardiography

Introduction

Heart failure (HF) complicating acute myocardial infarction (AMI) early during the disease course is associated with a higher risk of subsequent death.[1] In patients with AMI, risk stratification is often performed by applying the Killip classification which includes the assessment of pulmonary congestion based on physical examination findings.[2] Pulmonary congestion is a common finding in acute HF and AMI but traditional tools such as auscultation and even chest X-ray are insensitive for its detection in patients presenting with undifferentiated dyspnoea.[3] Over the past two decades, lung ultrasound (LUS) has emerged as a sensitive tool for the detection and quantification of pulmonary congestion in patients with HF and has been integrated in the diagnostic algorithm for patients with known or suspected acute HF in the 2021 HF guidelines of the European Society of Cardiology.[4]

B-lines on LUS are vertical lines that can be quantified in pre-defined areas (or 'zones') across the chest and provide diagnostic and prognostic information in patients with acute or chronic HF.[5–8] In patients hospitalized for acute HF, the number of B-lines decreases with treatment for HF during the admission and patients with a higher number of B-lines prior to discharge are at increased risk for adverse outcomes.[8] Recent data also suggest that patients with acute coronary syndrome, including AMI, and a higher number of B-lines at baseline are at increased risk for in-hospital mortality.[9] Little is known, however, about the long-term trajectory of pulmonary congestion assessed by LUS among patients with AMI and the relationship between LUS findings and cardiac structure and function in this cohort.

Assessment of pulmonary congestion by LUS was pre-specified as an exploratory analysis in a subset of patients participating in the echocardiographic substudy of the PARADISE-MI trial. In this analysis, we describe the LUS findings at baseline and 8 months and their association with echocardiographic features of cardiac structure and function.

Methods

Patient population

The design, patient characteristics, and primary outcome of the PARADISE-MI trial have been previously published.[10,11] Briefly, PARADISE-MI was a multinational, double-blind, double dummy, randomized, active-controlled trial that tested the efficacy and safety of sacubitril/valsartan compared with ramipril in adults with AMI. The trial randomized 5661 patients in 41 countries between 2016 and 2020. Patients were required to have a left ventricular ejection fraction (LVEF) ≤ 40% and/or transient pulmonary congestion requiring intravenous treatment during the index hospitalization and at least one of the following eight pre-defined risk augmenting factors: (i) age ≥70 years; (ii) estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 at screening; (iii) diabetes mellitus; (iv) prior myocardial infarction; (v) atrial fibrillation associated with the index AMI; (vi) LVEF <30% associated with the index myocardial infarction; (vii) Killip Class III or IV associated with the index AMI requiring temporary intravenous treatment; or (viii) ST-segment elevation myocardial infarction (STEMI) without reperfusion therapy within the first 24 h after presentation. Key exclusion criteria were prior HF, clinical instability at

the time of randomization, eGFR <30 mL/min/1.73 m^2, serum potassium >5.2 mmol/L, history of angioedema, and intolerance to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. PARADISE-MI was approved by local ethics committees and all participants provided written informed consent. The PARADISE-MI trial is registered on ClinicalTrials.gov (NCT02924727).

Lung ultrasound substudy

To better characterize the degree of pulmonary congestion in a subset of the trial population participating in PARADISE-MI, patients were invited to take part in a pre-specified LUS substudy, which was optional. All sites participating in the echocardiographic substudy[12] were invited to submit LUS images at baseline (LUS1; ±2 days of randomization) and 8 months after randomization or at end of study (LUS2), per protocol. Patients with pulmonary fibrosis, interstitial lung disease, current pneumonia, pneumonitis, pneumothorax, or chest drain, prior lung resection or lung transplantation, or current or prior lung or pleural cancer at randomization were excluded from the LUS substudy. Patients with atrial fibrillation at baseline were excluded from the echocardiographic substudy and therefore also from the LUS substudy. A total of 25 sites from 11 countries participated in the LUS substudy. Sites underwent training in eight-zone LUS via an online video in addition to written instructions for standardized image acquisition and recording.[8,13]

Lung ultrasound methods

LUS examinations were performed by investigators at each site trained in LUS and blinded to treatment assignment, using standard echocardiographic equipment with a phased-array transducer in sagittal orientation at an imaging depth of 18 cm with patients in sitting position (at 45–90°). Patients were assessed with an eight-zone imaging protocol (four zones on each hemithorax) with 6 s clips recorded for each zone.[7,8] Offline image analysis was performed on de-identified videos centrally at a core laboratory at Brigham and Women's Hospital by one experienced investigator (E.P.). The reader was blinded to clinical data, treatment assignment, timing of LUS (LUS1 vs. LUS2) and outcomes. The highest number of B-lines visualized in one intercostal space was quantified in a single frame after review of the entire clip for each zone and the sum of B-lines across eight zones was used for all analyses. This count-based approach to B-line quantification has been employed in several prior LUS studies in HF cohorts and in patients with AMI.[7,14,15] Inter- and intrareader agreements for this technique have been previously reported by our team and B-line imputation is described in Supplementary material.[8] Although the presence of pleural effusions was not separately assessed, large bilateral pleural effusions interfering with B-line analyses occurred in one patient for LUS1, requiring exclusion from the LUS analysis, and in no patients for LUS2. LUS data from patients in whom the LUS was not performed on the same day as the echocardiogram were excluded from the echocardiographic analyses (LUS2: $n = 7$). As this trial enrolled patients during the COVID-19 pandemic and B-lines are a common finding in patients with pulmonary COVID-19 infections, we analysed COVID-19-related adverse events in this substudy.[16] Data were reported according to the checklist for LUS studies in HF cohorts (see Supplementary material online, *Table S1*).[13]

Echocardiographic measurements

Echocardiographic studies were sent in digital format to the echocardiographic core laboratory, where quantitative measures were performed in accordance with American Society of Echocardiography (ASE) guidelines, unless otherwise specified, by dedicated analysts blinded to clinical information, treatment assignment, and study time point.[17] Each measure was performed by the same analyst for all study participants. LV volumes and LVEF were derived according to the modified biplane Simpson's rule. In cases in which the Simpson's method could not be used because of missing or poor-quality apical views, LVEF was calculated using the Teichholz method. LV mass was calculated using the ASE recommended formula for estimation of LV mass from LV linear dimensions and indexed to body surface area [LV mass index (LVMi)].[17] Left atrial (LA) volume was assessed using the modified biplane Simpson's method from apical two- and four-chamber views at end-systole and was indexed to body surface area (LA volume index). Peak early diastolic tissue velocity (e′) was measured from the septal and lateral aspects of the mitral annulus. Mitral inflow velocity was assessed using pulsed-wave Doppler from the apical four-chamber view. The severity of mitral regurgitation was based on the ratio of mitral regurgitation jet area to LA area from the apical four- and two-chamber views as follows: mild, < 0.20; moderate, 0.20–0.30; moderate to severe, 0.30–0.40; and severe, ≥ 0.40. Right ventricular (RV) functional measures included RV fractional area change (FAC) measured using the cavity area at end-diastole and end-systole, and s′. Peak tricuspid regurgitation (TR) velocity was measured from the continuous wave spectral Doppler envelope.

Long-term outcomes

Patients were followed for a median of 16 months. In addition to all-cause mortality, we report the composite long-term outcome as death from cardiovascular causes or incident HF, whichever occurred first based on investigator reports. Incident HF included hospitalization for HF and outpatient episodes of symptomatic HF treated with intravenous or sustained oral diuretic therapy as previously described.[10,11]

Statistical analyses

Patients were divided into three groups based on tertiles of B-lines at baseline (0–2; 3–7; ≥8 B-lines). Continuous variables are summarized using median (interquartile range, IQR) or mean (standard deviation, SD) and categorical variables as counts and percentages. We assessed trends in baseline characteristics across groups using Cuzick's non-parametric trend test and linear regression, respectively. Although B-lines demonstrated a skewed distribution at baseline, the changes in B-lines between baseline and follow-up were normally distributed and assessed via paired *t*-test (see Supplementary material online, *Figure S4*). In pre-specified, exploratory analyses we assessed the reduction in pulmonary congestion on LUS with sacubritril/valsartan compared with ramipril in patients with ≥3 B-lines at baseline. Of those congested at baseline, the proportion of patients who experienced de-congestion at follow-up in each treatment arm was compared by Pearson's χ^2 test.[14] For the analysis of clinical outcomes, patients were grouped according to baseline B-line tertiles and incidence of the composite from baseline to 240 days was reported as counts (percentages) and event rates, and compared using the log-rank test. In addition, regression analyses were used to examine the association between B-lines at follow-up and baseline in relation to intercurrent HF events. Results of these analyses were considered exploratory given the overall low event rate.

Echocardiographic measures were summarized according to (i) tertiles of B-line number at baseline, and (ii) B-line number at 8 months (0–2; 3–7; ≥8 B-lines), using analysis of variance or Kruskal–Wallis tests as appropriate.[14] Cubic spline models were used to estimate the potentially nonlinear associations between B-lines and key echocardiographic variables at baseline. The number of knots were selected according to the lowest values of Akaike information criterion (3–7 knots considered). We assessed the relationship between selected baseline characteristics, cardiac structure, and function (based on important predictors of HF outcomes in VALIANT: hypertension, prior MI, LA volume index, septal *E*/*e*′, MR grade, B-line count at baseline) and ≥8 B-lines at follow-up using logistic regression analyses.[18,19] Multivariate logistic regression with forward stepwise selection with a *P*-value of 0.1 was used to identify baseline characteristics and features of cardiac structure and function significantly associated with higher B-line count at follow-up. Two-sided significance levels of 0.05 were used for all analyses. No adjustments were made for multiple comparisons. Data were analysed using STATA SE 15.1 (StataCorp, TX, USA).

Results

Baseline characteristics

Patients enrolled in the PARADISE-MI LUS substudy had ultrasound examinations performed between March 2018 and January 2021. Among eligible participants, 152 out of 185 (82%) had adequate LUS1 images and 141 out of 169 (83%) had adequate LUS2 images, with paired examinations in 115 patients (see Supplementary material online, *Figure S1*). In those with LUS1 images, 15% of patients were eligible for inclusion in PARADISE-MI based on clinical evidence of pulmonary congestion only (in the absence of a reduced ejection

fraction), whereas 36% were eligible based on a reduced ejection fraction without clinical evidence of pulmonary congestion at screening (see Supplementary material online, *Figure S2*). The mean age of all 152 participants with adequate LUS1 images was 65 years, 32% were women and 35% were obese [body mass index (BMI) ≥ 30 kg/m^2]. The median time from presentation for the index AMI to the LUS1 was 5 days (IQR 4–6). At randomization most patients received statins, beta-blockers and RAAS inhibitors. In addition, 55% received aldosterone antagonists (MRAs) and 59% oral diuretics at baseline. Compared with PARADISE-MI patients without LUS1 data, those with LUS1 data were more frequently Caucasian, less likely to have a history of atrial fibrillation, more likely to be current smokers, more likely to receive MRAs and diuretics and had a lower LVEF at screening (see Supplementary material online, *Table S2*).

Association between B-lines and clinical characteristics at baseline

The sum of B-lines across 8 zones ranged from 0 to 42 (median 4, IQR 2–8) at baseline with 132 (87%) of patients having any detectable B-lines. Baseline characteristics for this cohort according to tertiles of B-lines on LUS1 are summarized in *Table 1* and were similar across groups. Patients with a higher number of B-lines were more likely to have presented with a higher Killip class, have had pulmonary congestion documented by clinical signs or chest X-ray (CXR)/computed tomography (CT) requiring IV therapy, have a longer time from presentation to randomization, and lower haemoglobin, haematocrit, and albumin levels. However, 55% of patients with Killip Class I at screening had ≥3 B-lines at baseline (see Supplementary material online, *Figure S3*). Similarly, 56% of patients who qualified based on a reduced LVEF without evidence of pulmonary congestion on physical examination, CXR or CT at screening had ≥3 B-lines on LUS at baseline. There was no significant association between BMI or renal function with B-line tertiles.

Dynamic changes in B-lines from baseline to follow-up

Among 115 patients with baseline and 8-month LUS data, there was an overall decline in B-lines from baseline (mean ± SD: −1.6 ± 7.3; P = 0.018; see Supplementary material online, *Figure S4*). The proportion of patients without pulmonary congestion (<3 B-lines) at follow-up was higher in those with fewer B-lines at baseline when analysed by tertiles (53% vs. 39% vs. 36%, P = 0.003; *Figure 1*; *Graphical Abstract*). These results were similar when patients who had the LUS2 performed at end of the trial (n = 7) rather than at 8 months were excluded from the analyses. There was one patient with a reported COVID-19 infection between LUS1 (one B-line in eight zones) and LUS2 (one B-line in eight zones). In pre-specified, exploratory analyses among 75 patients with ≥3 B-lines at baseline, a decrease in B-lines to <3, indicating decongestion, occurred in 37% and was similar in the sacubitril/valsartan and ramipril groups (36 vs. 39%, P = 0.83). Whereas in 40 patients with <3 B-lines at baseline, an increase in B-lines occurred in 48%.

Long-term outcomes

In this LUS cohort of PARADISE-MI, 7 patients (5%) died, and 18 patients (12%) experienced a HF event or died due to CV causes within 8 months of randomization and 2 patients experienced the composite outcome between 8 months and the end of the trial. Although the 8-month event rates for the composite outcome were numerically higher among those with a higher B-line number at baseline, there was no statistically significant association: Tertile 1: 4 (8%), Tertile 2: 7 (13%), Tertile 3: 7 (16%; P = 0.50). However, adjusted for baseline, B-lines at follow-up were on average 6 (95% confidence interval: 3–9) higher in a patient who experienced an intercurrent HF event than a patient without a HF event (P = 0.001).

Association between B-lines and cardiac structure and function at baseline

Among participants with available LUS images, 126 (83%) had interpretable echocardiographic images at baseline. Patients with a higher number of B-lines had a larger LA size, higher *E*/*e*′ and *E*/*A* ratio, worse mitral regurgitation grade, lower FAC, and higher TR velocity (*Table 2*). The relationship between key echocardiographic measures and B-lines at baseline is illustrated by cubic spline plots in *Figure 2*.

Association between B-lines and cardiac structure and function at 8 months

Among participants with available LUS images, 130 (86%) had interpretable echocardiographic images at 8 months. Patients with a higher number of B-lines had significantly larger LA size, higher *E*/*e*′, *E*/*A* ratio, and RV systolic area (see Supplementary material online, *Table S3*). The range of B-line values associated with expected septal *E*/*e*′ values >15 (indicating elevated LV filling pressures) was estimated to be >12 B-lines at baseline and >6 B-lines at the 8-month visit. In multivariate logistic regression analyses, history of hypertension, prior MI, larger LA volume index and higher B-line count at baseline were independently associated with greater likelihood of ≥8 B-lines (Tertile 3) at 8 months.

Discussion

We investigated the prevalence and trajectory of pulmonary congestion by LUS and its relationship with cardiac structure and function in patients participating in the PARADISE-MI LUS substudy. Our results suggest that the majority of patients in this high-risk cohort of AMI patients had detectable B-lines at baseline, indicating pulmonary congestion. At baseline, worse pulmonary congestion on LUS was associated with prognostically important echocardiographic markers of LV filling pressure, pulmonary pressure, and RV function. In pre-specified, exploratory analyses we found no treatment effect of sacubitril/valsartan compared with ramipril on the degree of pulmonary congestion by LUS which is consistent with the primary results of the overall trial.[11]

The assessment of pulmonary congestion with LUS is increasingly being incorporated in the examination of patients with known or suspected HF, especially in the acute care setting. Although this is not routine practice yet in patients with AMI among the majority of cardiologists, recent data suggest that LUS can provide prognostic information beyond Killip class in patients with AMI when assessed on the day of admission.[20,21] Prior observational studies in patients with ACS or AMI employed 4-, 8-, or 28-zone imaging protocols using either phased array or curvilinear transducers and image analysis was performed by clinicians at the point of care.[9,22] The present study expands on these prior investigations by examining the trajectory of sonographic B-lines from baseline to 8 months following the index hospitalization in the context of a large Phase III clinical trial, and by assessing the association of pulmonary congestion by LUS with measures of cardiac structure and function at these two time points.

Prevalence, correlates, and trajectory of pulmonary congestion

The majority of patients in the current substudy had detectable B-lines at baseline which is not surprising considering that PARADISE-MI targeted a high-risk cohort of patients with recent AMI. While the presence of transient pulmonary congestion was part of the inclusion

Table 1 Baseline characteristics by B-line tertiles ($n = 152$)

	0–2 B-lines ($n = 51$)	3–7 B-lines ($n = 56$)	≥8 B-lines ($n = 45$)	*P* trend
Median B-line count across 8 zones	1 (0–2)	5 (3–6)	12 (9–19)	—
Mean B-line count across 8 zones	0.9 (0.8)	4.5 (1.4)	16.0 (8.7)	—
Age (years)	65 (12)	64 (12)	65 (12)	0.72
Female sex (%)	16 (32)	17 (30)	16 (36)	0.67
Race				0.55
Caucasian	48 (94)	55 (98)	41 (91)	
Other	3 (6)	1 (2)	4 (9)	
Medical history (%)				
Hypertension	31 (61)	31 (55)	28 (62)	0.91
Diabetes	16 (31)	27 (48)	16 (36)	0.63
Prior atrial fibrillation	3 (6)	6 (11)	3 (7)	0.86
Prior myocardial infarction	4 (8)	10 (18)	7 (16)	0.26
Prior PCI/CABG	5 (10)	13 (23)	10 (22)	0.11
Prior stroke	1 (2)	1 (2)	3 (7)	0.21
Current smoker	15 (29)	14 (25)	14 (31)	0.88
COPD	4 (8)	2 (4)	2 (4)	0.42
Cancer	3 (6)	4 (7)	2 (4)	0.74
Medications at randomization (%)				
Beta-blocker	44 (86)	50 (89)	39 (87)	0.94
ACEi/ARB	43 (84)	47 (84)	37 (84)	0.79
Aldosterone antagonist	30 (59)	27 (48)	26 (58)	0.88
Statin	51 (100)	54 (96)	42 (93)	0.07
Oral diuretic	30 (59)	31 (55)	28 (62)	0.76
Oral anti-diabetes agent	12 (24)	17 (30)	5 (11)	0.17
Insulin	3 (6)	11 (20)	7 (16)	0.16
Examination findings				
BMI (kg/m^2)	28 (5)	29 (5)	30 (6)	0.49
Heart rate (b.p.m.)	74 (9)	72 (10)	71 (11)	0.23
Systolic blood pressure (mmHg)	121 (11)	119 (13)	119 (15)	0.13
Diastolic blood pressure (mmHg)	74 (9)	71 (10)	71 (11)	0.18
Worst Killip class				0.052
I	22 (45)	14 (25)	13 (30)	
II	13 (27)	23 (41)	12 (27)	
III	12 (25)	16 (29)	13 (30)	
IV	2 (4)	3 (5)	6 (14)	
Pulmonary congestion by clinical examination, CXR or CT requiring IV therapy	27 (53)	38 (68)	33 (73)	0.035
IV diuretics	33 (65)	36 (64)	32 (71)	0.52
IV vasodilators	5 (10)	7 (13)	10 (22)	0.09
IV inotropes	2 (4)	2 (4)	4 (9)	0.29
IV vasopressors	2 (4)	2 (4)	4 (9)	0.29
Qualifying MI characteristics				
MI type				0.49
STEMI	36 (71)	34 (61)	35 (78)	
NSTEMI/other	15 (29)	22 (39)	10 (22)	
Location of MI				0.58
Anterior MI	33 (65)	32 (57)	34 (76)	
Inferior MI	13 (26)	11 (20)	3 (7)	

Continued

Table 1 *Continued*

	0–2 B-lines ($n = 51$)	3–7 B-lines ($n = 56$)	≥8 B-lines ($n = 45$)	*P* trend
Other MI	5 (10)	13 (23)	8 (18)	
LVEF at screening (%)	34 (8)	36 (11)	34 (10)	0.77
Time: presentation to randomization (days)	3.8 (1.6)	4.0 (1.7)	4.6 (1.6)	0.023
Laboratory results at randomization				
Sodium (mmol/L)	139 (4)	139 (3)	139 (4)	0.95
Potassium (mmol/L)	4.4 (4.0–4.6)	4.3 (4.1–4.5)	4.3 (3.9–4.5)	0.15
Creatinine (mg/dL)	1.06 (0.3)	1.05 (0.3)	1.02 (0.3)	0.33
eGFR (mL/min/1.73 m^2)	69 (19)	71 (21)	73 (21)	0.28
Haemoglobin (g/dL)	14.1 (1.4)	13.8 (1.9)	13.0 (1.6)	0.006
Haematocrit (%)	44 (5)	43 (6)	41 (5)	0.004
AST (U/L)	37 (26–57)	42 (27–64)	37 (26–51)	0.82
ALT (U/L)	30 (21–44)	34 (22–64)	41 (26–53)	0.06
Albumin (g/dL)	4.3 (0.4)	4.1 (0.4)	3.9 (0.3)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CXR, chest X-ray; eGFR, estimated glomerular filtration rate; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-elevation MI.

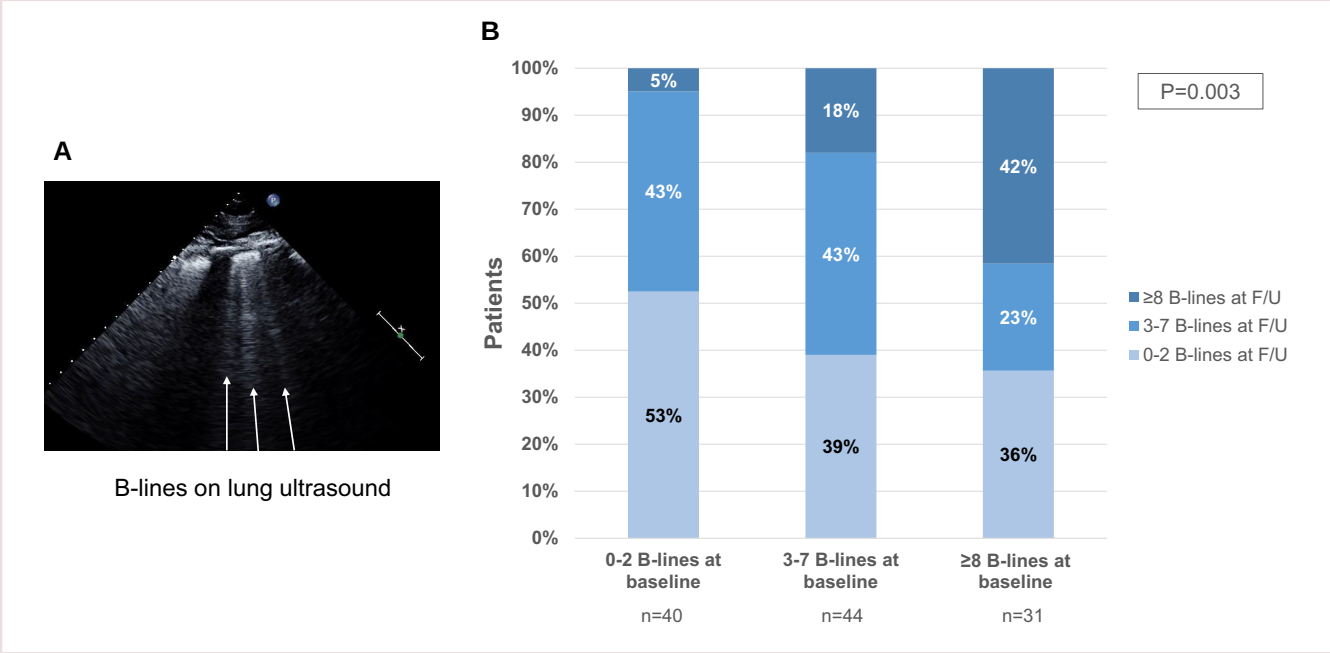


Figure 1 Trajectory of B-line number in patients with acute myocardial infarction from baseline to follow-up. (*A*) Lung ultrasound image with B-lines indicated by arrows. (*B*) Trajectory of B-line number from baseline to follow-up ($n = 115$). Percentages may not add up to 100% due to rounding. F/U, follow-up.

criteria of this trial, a third of patients in the LUS substudy qualified based on ejection fraction alone without pulmonary congestion detected by traditional methods. However, among patients with Killip Class I at screening, more than half had ≥3 B-lines at baseline indicating subclinical pulmonary congestion. These findings are consistent with two prior observational studies in patients with AMI from Brazil and China in which 32–55% of patients with Killip Class I had evidence of pulmonary congestion on LUS.[20,21] In these studies, the addition of LUS to the Killip class assessment improved the prediction of inpatient and 30-day adverse outcomes. The small sample size and overall low event rate in our study did not allow for adequately powered outcome analyses of B-lines as a predictor beyond traditional risk markers in this cohort.

Prior studies in patients hospitalized for AHF have demonstrated a significant reduction in B-line number with decongestive therapy between baseline and hospital discharge or after as few as 3 h of diuretic therapy.[8,23] Prior data on the trajectory of pulmonary congestion by

Table 2 Association between B-lines on lung ultrasound and cardiac structure and function at baseline

	All ($n = 126$)	0–2 B-lines ($n = 42$)	3–7 B-lines ($n = 47$)	≥8 B-lines ($n = 37$)	*P* trend
LVEF (%)	41 (11)	41 (10)	42 (11)	40 (11)	0.70
LVEDD (cm)	4.9 (0.7)	4.8 (0.6)	4.8 (0.7)	4.9 (0.7)	0.42
LVESD (cm)	3.4 (0.9)	3.3 (0.8)	3.6 (1.0)	3.5 (0.9)	0.37
LVED volume index (mL/m^2)	63 (56–73)	65 (53–72)	62 (51–67)	68 (59–87)	0.16
LVES volume index (mL/m^2)	37 (29–48)	37 (29–46)	37 (27–40)	39 (31–58)	0.28
Relative wall thickness	0.42 (0.09)	0.41 (0.08)	0.42 (0.08)	0.42 (0.10)	0.66
LV mass index (g/m^2)	91 (79–105)	94 (79–108)	88 (77–102)	96 (81–114)	0.83
LV mass index (g/height$^{2.7}$)	42 (36–49)	42 (37–50)	42 (34–47)	44 (35–52)	0.89
LA width (cm)	3.7 (0.6)	3.6 (0.5)	3.6 (0.6)	3.9 (0.6)	0.16
LA volume index (mL/m^2)	23 (19–29)	21 (19–27)	22 (18–29)	27 (21–30)	0.044
MR grade ≥2 (*n*, %)	8 (6.7%)	0	3 (6.5%)	5 (13.9%)	0.017
E wave (cm/s)	66 (52–84)	57 (49–71)	71 (53–85)	75 (54–98)	0.001
A wave (cm/s)	71 (55–83)	67 (55–79)	76 (62–84)	70 (53–81)	0.92
e′ lateral (cm/s)	6.7 (5.2–8.5)	6.2 (5.2–7.9)	7.1 (5.9–8.9)	6.7 (4.8–8.0)	0.75
e′ septal (cm/s)	5.3 (4.2–6.5)	5.1 (3.9–6.5)	5.3 (4.3–6.5)	5.3 (4.2–6.4)	0.37
E/e′ lateral	9.8 (8.0–12.7)	9.2 (6.9–10.8)	9.8 (7.8–12.8)	10.8 (8.7–15.1)	0.011
E/e′ septal	12.7 (10.1–15.6)	12.3 (9.4–14.5)	12.9 (9.9–15.7)	13.2 (11.8–17.9)	0.036
E/*A*	1.0 (0.7–1.4)	0.8 (0.5–1.2)	1.0 (0.7–1.3)	1.2 (0.7–1.7)	0.008
RV diastolic area (cm^2)	19 (5)	19 (5)	19 (5)	20 (6)	0.95
RV systolic area (cm^2)	11 (3)	10 (3)	11 (3)	11 (3)	0.25
FAC (%)	44 (7)	46 (7)	44 (8)	42 (5)	0.017
s′ (cm/s)	11.8 (2.8)	11.6 (3.3)	11.9 (2.4)	11.8 (2.7)	0.50
TR velocity (cm/s) $n = 50$	256 (219–292)	219 (207–244)	274 (242–301)	274 (231–298)	0.001

FAC, fractional area change; LA, left atrial; LVEDD, LV end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, LV end-systolic diameter; MR, mitral regurgitation; RV, right ventricular; TR, tricuspid regurgitation.

LUS in patients with AMI who are at risk for developing HF are sparse. One study from China examined short-term changes in B-lines in a subset of 39 patients with anterior STEMI. Patients who developed HF during the hospitalization (3–4 days after the initial LUS) demonstrated a significant increase in B-lines whereas those who did not develop HF did not.[24] While transient pulmonary congestion (assessed with traditional methods) can occur during the index hospitalization following an AMI, it is well recognized that only a subset of patients subsequently develop chronic HF.[18] To the best of our knowledge no other study has previously reported on the long-term trajectory of pulmonary congestion detected by LUS following AMI. Accordingly, B-line number at follow-up was higher in patients who developed symptomatic HF in our cohort. This finding highlights the opportunity of using LUS to monitor for the development of pulmonary congestion and the potential to use LUS findings to adjust HF therapy earlier in the disease course.

Pulmonary congestion and cardiac structure and function

The ability to compare the findings of the current study to prior observational studies reporting LUS and echocardiographic data is limited by the heterogeneity in patient cohorts, reporting, and imaging protocols.[9] However, consistent with prior reports we found a close relationship between B-line number and measures of elevated filling pressures and diastolic function both at baseline and follow-up. Raised LV end-diastolic pressure (LVEDP) is associated with LV dysfunction, increased pulmonary capillary wedge pressure and pulmonary congestion. In a recent observational study from Brazil, the number of B-lines just prior to left heart catheterization was associated with invasively measured LVEDP in patients with STEMI.[25] In the setting of AMI, *E*/e′ >15 (indicating elevated filling pressures) is an important prognostic marker for adverse outcomes.[26,27] Similarly, LA dilation has also been identified as an important predictor of mortality and adverse outcomes post-MI.[19,28] In the PARADISE-MI LUS substudy, larger LA size was associated with a higher number of B-lines both at baseline and after 8 months indicating a higher degree of pulmonary congestion. This was despite the fact that LA size overall was smaller than that reported in prior observational studies, possibly due to the exclusion of patients with concurrent atrial fibrillation in this substudy.[15,29]

Our findings are largely consistent with data from a recent observational study in patients with AMI who underwent LUS and echocardiography during the index hospitalization which reported associations between B-lines and *E*/e′, as well as inverse correlations with LVEF and RV systolic function, assessed by TAPSE.[24] The lack of a significant association between LVEF in PARADISE-MI is perhaps not surprising as pulmonary congestion can occur irrespective of LVEF and the entire spectrum of LVEF may not have been represented in PARADISE-MI due to the inclusion criteria.[8,30] Furthermore, we found an association between RV systolic function, as assessed by FAC, and markers of pulmonary pressure at baseline. RV dilation and impaired RV systolic function likely reflect the acute rise in LVEDP after AMI and are known and

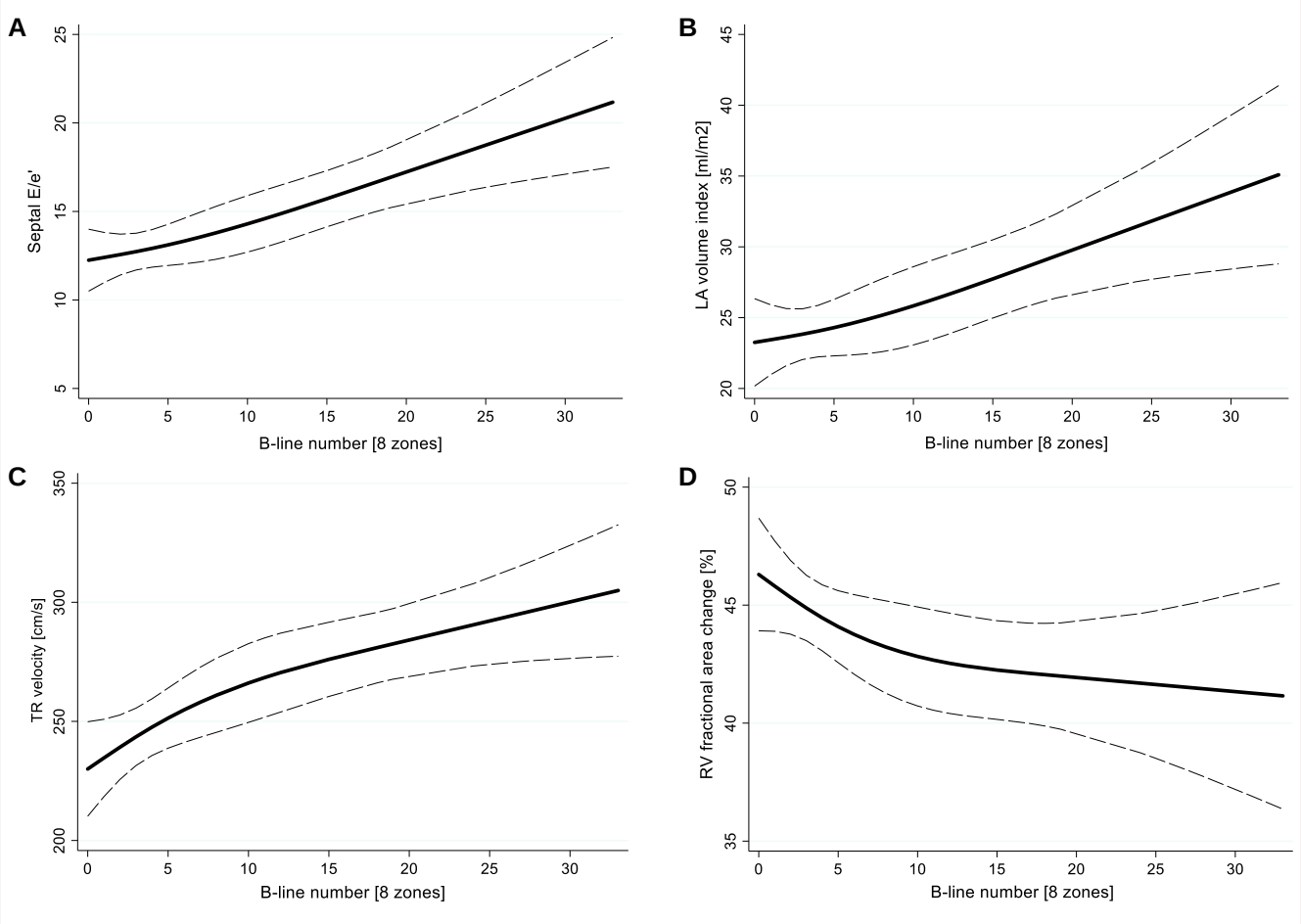


Figure 2 Relationship between B-line number and key echocardiographic variables in cubic spline models at baseline. Restricted cubic spline analysis illustrating the relationship between (*A*) septal *E*/*e*′ ($n = 121$, $P < 0.001$), (*B*) left atrial volume index ($n = 118$, $P = 0.003$), (*C*) tricuspid regurgitant velocity ($n = 50$, $P < 0.001$), and (*D*) right ventricular fractional area change ($n = 111$, $P = 0.034$) with B-line number at baseline. None of the four associations were significantly nonlinear.

important risk markers for the development of HF or death in patients following an AMI.[19,31]

Clinical perspective

The qualitative assessment of pulmonary congestion with traditional methods both in the clinical setting and in trials remains subjective and variable. LUS is a non-invasive tool that allows for the detection and quantification of subclinical pulmonary congestion in patients following an AMI. This technique could enable earlier initiation of therapy directed at decongestion in the acute care setting and potentially facilitate the identification of patients with AMI at high risk for adverse outcomes. Finally, in the research context, LUS is emerging as a feasible, complementary measure for assessing the efficacy and safety of novel therapies.

Strengths and limitations

Several strengths and limitations of our publication are worth noting. To our knowledge, this is the first LUS substudy of a large, multicentre, randomized, Phase III clinical trial in which the feasibility of employing this technique has been demonstrated. In addition, all ultrasound image analyses were performed centrally, at a core laboratory, with blinding to clinical data, time point, therapy, and outcomes. Given that pulmonary infections (including pneumonia due to COVID) can present with B-lines, patients with concurrent pneumonia were not eligible for this LUS substudy. Despite the importance of the COVID pandemic worldwide, we do not believe that the number of B-lines significantly impacted our study results as only one patient was reported to have developed COVID between LUS1 and LUS2. Our analyses are limited by the small sample size and the number of events which may impact the generalizability of our findings and did not allow for adequately powered outcome analyses. Moreover, natriuretic peptides were only available in a small number of patients ($n = 10$). Since clinical examinations and radiologic data (CXR, CT) were not collected concomitantly with LUS assessment, this may have impacted the association between worst reported Killip class and B-line number. However, our findings are consistent with those from a prior study in which Killip class and LUS were assessed on the same day.[20]

Conclusions

In this AMI cohort, sonographic B-lines, indicating pulmonary congestion, were common at baseline and, on average, decreased significantly from baseline to follow-up. Worse pulmonary congestion was associated with echocardiographic markers of elevated filling pressures,

elevated pulmonary pressure and worse RV function at baseline. Lung ultrasound has the potential to facilitate the early detection, quantification, and monitoring of pulmonary congestion in patients following AMI who are at risk for developing HF.

Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care*.

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Data availability

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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