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Prognostic impact of lung ultrasound detected B-lines on hospitalised ischaemic heart failure with mildly reduced ejection fraction patients

Hui Zhang,[1,2] Yuying Zhou,[1,2] Fangqun Cheng,[3] Yunlong Zhu ,[1,4] Na Li,[1,2] Xin Peng,[1,2] Mingxin Wu,[1] Haobo Huang,[1] Lingling Zhang,[1] Min Liao,[1] Sha Xiao,[1] Yongliang Chen,[1,2] Sihao Chen,[1,2] Zhican Liu ,[1] Liqing Yi,[1] Jie Fan,[1] Jianping Zeng [3]

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HZ, YZ and FC contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Jianping Zeng; xhjiang2@hnust.edu.cn

Yunlong Zhu; zhuyunlong@stu.cpu.edu.cn

ABSTRACT

Objectives Prognostic impact of lung ultrasound-derived B-lines (LUS-BL) in heart failure with mildly reduced left ventricular ejection fraction (HFmrEF) patients remains elusive. We evaluated the correlation between LUS-BL and prognosis in HFmrEF patients.

Methods This is a subgroup analysis based on our previously published retrospective study with 1691 HFmrEF patients. This subgroup analysis involved 574 patients with LUS-BL results at admission. After discharge, patients underwent clinical follow-up for a minimum of 1 year through telephone, clinical visits or community visits. The primary endpoint was defined as cardiovascular (CV) event, including CV-related mortality or HF hospitalisation at 90 days and 1 year after discharge.

Results CV event at 90 days was significantly increased with higher LUS-BL number (0, 1–2, 3–9 and ≥10: 20%, 14%, 18% and 33%, p=0.008), while CV event rate at 1 year was similar among groups (45% vs 45% vs 42% vs 50%, p=0.573). Older age, hypertension (HR=2.06, 95% CI 1.31 to 3.25), higher right ventricular diameter (>23 mm, HR=2.008, 95% CI 1.37 to 2.94), increased ratio of early transmitral flow velocity to early mitral annular velocity (>24, HR=1.79, 95% CI 1.11 to 2.26) and higher LUS-BL number (>11, HR=1.510, 95% CI 1.01 to 2.26) were identified as independent determinants associated with increased risk of CV event at 90 days after discharge. The Harrell's C-Statistic analysis, based on the Cox regression models, demonstrated a significant improvement in the predictive ability of the model that incorporated both clinical and echocardiographic risk factors along with LUS-BL (areas under the curve (AUC)=0.72) compared with the model comprising only clinical risk factors and LUS-BL (AUC=0.69, p=0.036), or to the model with echocardiographic risk factors and LUS-BL (AUC=0.68, p=0.025).

Conclusion In HFmrEF patients with ischaemic heart disease, admission LUS-BL>11 is independently associated with an increased risk of CV event at 90 days following discharge.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The prevalence of heart failure with mildly reduced left ventricular ejection fraction (HFmrEF) patients among HF patients is estimated to be between 10% and 25%. Existing research on HFmrEF consistently demonstrates that the characteristics of these patients fall between those of heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. The Framingham Heart Study highlights that hypertension is the leading contributing factor to HF onset, taking precedence over other conditions such as myocardial infarction, coronary artery disease and diabetes. Additionally, a significant note is that 75% of individuals had hypertension before manifesting symptoms of chronic HF. Research led by Butler J and colleagues shows a direct correlation between increasing blood pressure and heightened HF risk, with hypertension nearly tripling the likelihood of developing HF. This current study explores the general health profiles of HF patients and examines the prognostic implications of underlying conditions.

WHAT THIS STUDY ADDS

⇒ Our findings further underscore the detrimental effects of hypertension and pulmonary congestion on the prognosis of HFmrEF patients. Notably, those with ischaemic heart disease and more than 11 B-lines present a poorer 90-day prognosis. In addition to B-lines, older age, hypertension, an enlarged right ventricle and the diastolic function index ratio of early transmitral flow velocity to early mitral annular velocity are all associated with cardiovascular event in this ischaemic HFmrEF cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study confirm the pronounced influence of elevated blood pressure and pulmonary congestion on the outcomes for HF patients. To further substantiate our findings, future prospective studies are recommended.

INTRODUCTION

Heart failure (HF) is the fastest growing cardiovascular (CV) disease and related with high mortality and rehospitalisation.[1] Ischaemic heart disease is one of the most frequent causes of HF.[2] In a previous study, we reported that higher uric acid, creatinine, N-terminal pro-B type natriuretic peptide (NT-proBNP) and lower haemoglobin levels at baseline are valuable serum biomarkers for risk stratification of short-term and long-term CV outcomes of HF with mildly reduced left ventricular ejection fraction (HFmrEF) patients.[3]

The main symptoms of HF are dyspnoea and fatigue and may be accompanied by signs such as increased jugular vein pressure, alveolar sound and peripheral oedema.[4 5] Increased left ventricular end-diastolic filling pressure, which might lead to pulmonary congestion, is the usual mechanism responsible for the main symptoms of HF patients. Lung ultrasound (LUS) is a helpful tool to detect pulmonary congestion and can be used to guide the diagnosis, treatment and to define prognosis of acute or chronic HF patients with reduced ejection fraction (HFrEF), with preserved ejection fraction (HFpEF) and HFmrEF.[6–9] The number of LUS detected B-lines (LUS-BL) associated with the severity of pulmonary congestion. Previous single-centre prospective study showed that the number of LUS-BL assessed early during hospitalisation and at discharge was an independent risk factor for adverse in-hospital and after discharge outcomes in acute HF patients.[7]

Although the concept of HFmrEF has been known for many years, related clinical report on the prognostic impact of LUS-BL in these patients cohort is still scanty. A previous study assessed the prognostic impact of LUS-BL in 71 HFmrEF patients after reversing acute decompensated HF, semiquantitative evaluation of LUS-BL was performed at 5+2 days after hospitalisation and on discharge from the hospital. Results showed that the presence of LUS-BL was associated with rehospitalisation up to 2 years after discharge.[10] In this subgroup analysis, we evaluated the prognostic impact of LUS-BL on CV outcome at 90 days and 1-year after discharge in enrolled HFmrEF patients with LUS results at admission.[3]

METHODS

Study population and protocol

This subgroup analysis is based on our established database focused on HFmrEF, encompassing both de novo, acute presentations and decompensation of chronic conditions. This database comprised 1691 consecutive HFmrEF patients who were admitted to our hospital between January 2015 and August 2020.[3] The inclusion criteria for this study required patients to have LUS records available within 24 hours after admission. Out of the 610 patients with complete LUS data, 574 individuals with ischaemic HF were selected for further analysis, while 36 patients with non-ischaemic HF were excluded from the study (see figure 1). All patients completed clinical follow-up at 90 days and at 1 year after discharge by means of a clinical visit or telephone interview. Definitions of hypertension, coronary artery disease, diabetes, renal insufficiency and the primary endpoint (ie, CV event, defined as a composite of CV death or HF hospitalisation at 90 days and 1 year after discharge) were the same as our previously published study.[3] All patients underwent standard transthoracic echocardiography examination (GE, Norway) as previously described.[3]

LUS and B-lines assessment

LUS examinations were carried out for decision-making for HF medication, especially diuretics use, and the results were obtained from medical records. The examinations were conducted by trained cardiologists of our department, following a standardised imaging protocol using the GE Versana Premier ultrasound system (GE, USA) equipped with an M5Sc probe. Patients were in a sitting or semirecumbent position during the examination. A three-second ultrasound loop was recorded for each of the eight LUS zones, with four on each hemithorax, as recommended by an international guideline (see figure 2).[11] Offline image analysis was performed by the trained cardiologists, with experience in LUS analysis. The highest number of B-lines (vertical lines arising from the pleural line) visualised in a single intercostal space was recorded for each zone. The sum of B-lines in all eight zones was reported.

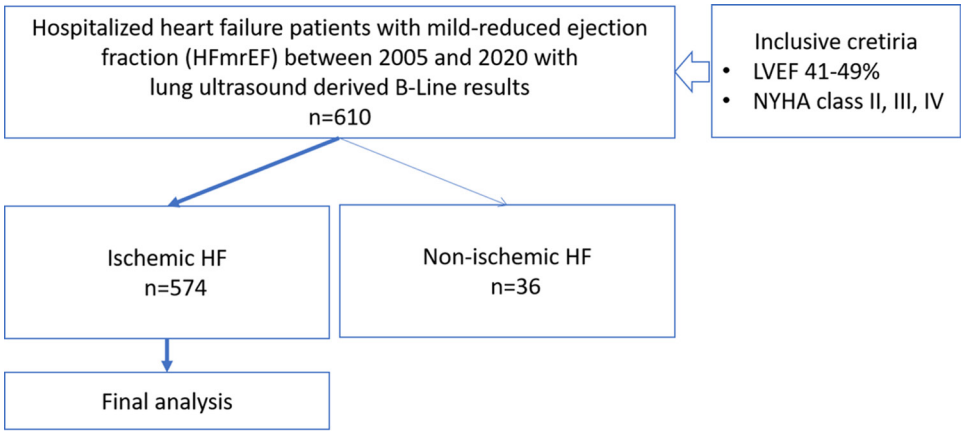

Figure 1 Study flowchart.

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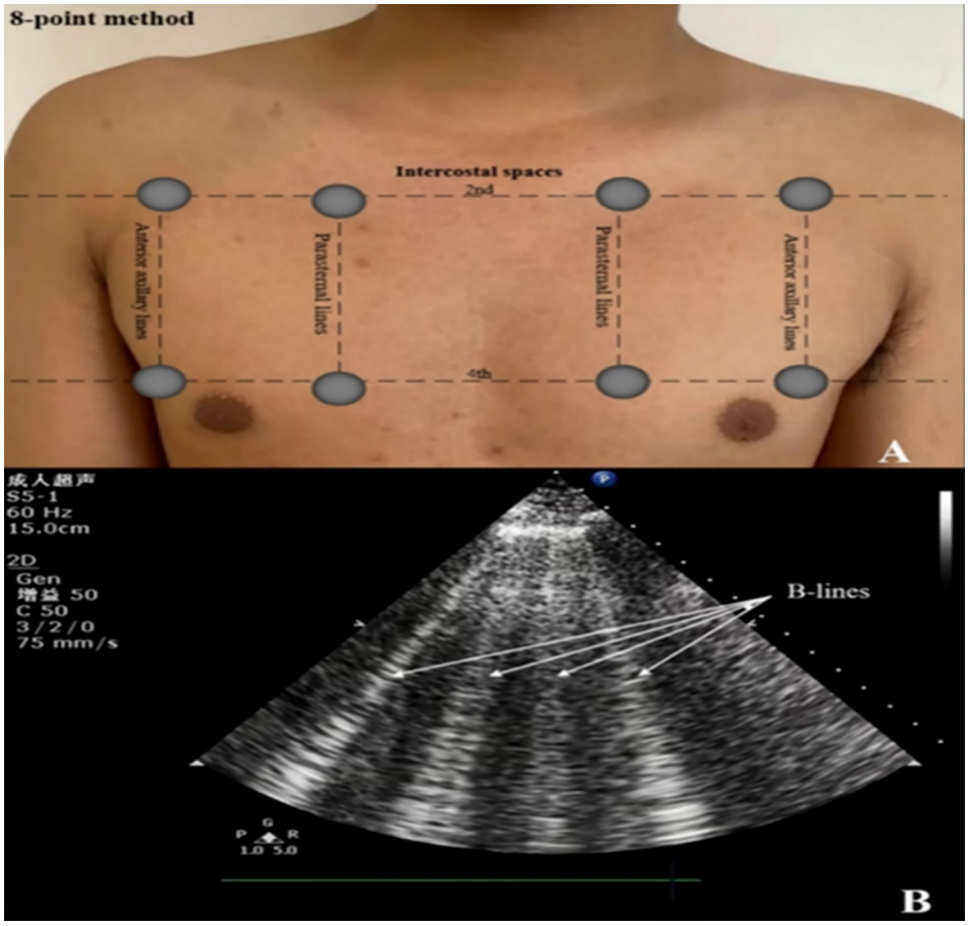

Figure 2 Detection of B-lines by lung ultrasound.

Statistical analysis

Continuous variables were presented as mean±SD or median (IQRs). Differences on continuous data with normal distribution across groups were compared using one-way analysis of variance followed by either Tukey's or Games-Howell multiple comparison post hoc tests, as appropriate. Variables with skewed distribution were compared using the Kruskal-Wallis test and the Dunn post hoc method, if applicable. Categorical variables were presented as numbers (percentages) and compared using the Pearson χ^2 tests or Fisher's exact test.

For survival analysis, Kaplan-Meier curves were plotted and log-rank tests were used for comparison. Univariable and multivariable Cox proportional hazard regression models were used to determine independent risk factors associated with CV event at 90 days and 1 year after discharge. Unadjusted and adjusted HRs and 95% CI were calculated. Variables of p value<0.05 in univariable Cox regression models were incorporated into the multivariable model, and likelihood ratio test statistics were used to determine independent factors. Potential clinical and echocardiographic parameters with a p value<0.05 in univariable Cox regression models, defined as clinical and echocardiographic covariates, were added into Cox regression models with an 'Enter' method. Classification tree with chi-square automatic interaction detection (CHAID) was used to determine the potential cut-off point of LUS-BL associated with CV event and to assess accuracy of the estimated model for CV event at 90 days or 1 year after discharge. The Harrell's C-statistic was used to assess the discriminative ability of the multivariable Cox models. The areas under the curve (AUC) of receiver operating characteristics base on the C-index were compared derived from the different models. P value<0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics V.28.0.0.

RESULTS

The mean age was 68±12 years, 67.2% were men. The proportion of New York Heart Association (NYHA) class II, III and IV was 43.4%, 31.7% and 24.9%, respectively. CV mortality and CV event rate were 2.6% and 22.1% at 90 days and were 7.7% and 45.5% at 1 year, respectively. The median number of LUS-BL was 2 (0–9) with a skewed distribution (online supplemental fiugre 1). Patients were divided into four groups according to the median value and IQR of LUS-BL: group 1, LUS-BL 0; group 2, LUS-BL 1–2; group 3, LUS-BL 3–9; group 4, LUS-BL≥10 (table 1). In proportion with increased number of LUS-BL, the proportion of NYHA class IV, obesity, hypertension, NT-proBNP, troponin T, creatinine and

Table 1 Baseline characteristics in ischaemic HFmrEF patients with and without LUS-BL

	Total	Group 1 LUS-BL 0	Group 2 LUS-BL 1–2	Group 3 LUS-BL 3–9	Group 4 LUS-BL≥10	P value
n (%)	574 (100)	250 (43.6)	42 (7.3)	147 (25.6)	135 (23.5)	
Male (n (%))	386 (67.2)	175 (70.0)	31 (73.8)	88 (59.9)	92 (68.1)	0.147
Age (years)	68±12	65±12	71±11	69±11	69±11	0.003
BMI (kg/m²)	25.8±4.3	26.5±4.5	24.4±3.8	25.2±4.0	25.6±3.9	0.002
Systolic blood pressure (mm Hg)	133±27	131±26	132±25	133±26	136±30	0.415
Diastolic blood pressure (mm Hg)	80±17	79±16	78±14	80±16	82±19	0.492
Heart rate (beats/minute)	82±19	81±20	84±24	82±16	84±17	0.743
NYHA functional class (n (%))						<0.001
II	249 (43.4)	153 (61.2)	15 (35.7)	48 (32.7)	33 (24.4)	
III	182 (31.7)	75 (30.0)	23 (54.8)*	69 (46.9)	15 (11.1)†‡	
IV	143 (24.9)	22 (8.8)	4 (9.5)	30 (20.4)*	87 (64.4)†‡	
Cardiac risk factors and comorbidities (n (%))						
Obesity	147 (25.6)	74 (29.6)	9 (21.4)	24 (16.3)	40 (29.6)‡	0.016
Currently smoking	228 (39.7)	110 (44.0)	19 (45.2)	51 (34.7)	48 (35.6)	0.174
Hypertension	501 (87.3)	149 (59.6)	33 (78.6)	95 (64.6)	98 (72.6)	0.018
Diabetes	407 (70.9)	72 (28.8)	13 (31.0)	51 (34.7)	57 (42.2)	0.063
Hyperlipidaemia	2 (0.3)	248 (99.2)	41 (97.6)	145 (98.6)	131 (97.0)	0.411
Previous atrial fibrillation	375 (65.3)	27 (10.8)	5 (11.9)	8 (5.4)	15 (11.1)	0.266
Stroke	193 (33.6)	27 (10.8)	4 (9.5)	19 (12.9)	15 (11.1)	0.900
COPD	565 (98.4)	14 (5.6)	6 (14.3)	14 (9.5)	14 (10.4)	0.146
Renal insufficiency	55 (9.6)	30 (12.0)	10 (23.8)	27 (18.4)	28 (20.7)	0.060
Blood test (median (IQR))						
NT-proBNP (pg/mL)	1634 (357–5334)	701 (300–3000)	2799 (1700–7500)	1790 (787–3600)	3915 (213–10 200)	<0.001
TnT (ng/mL)	0.70 (0.13–3.48)	0.92 (0.13–4.65)	1.76 (0.27–4.07)	0.68 (0.12–3.50)	0.50 (0.06–2.35)	0.005
Hb (g/L)	128 (114–142)	130 (115–142)	130 (113–145)	126 (114–139)	127 (110–143)	0.428
UA (μmol/L)	337 (274–414)	334 (272–395)	347 (266–443)	335 (269–401)	349 (282–458)	0.148
Cr (μmol/L)	80 (68–105)	79 (68–99)	84 (66–109)	75 (67–99)	94 (69–133)†	0.001
eGFR (mL/min/m²)	74 (55–95)	80 (61–98)	74 (49–97)	73 (61–94)	65 (41–92)†	<0.001
Echocardiography (median (IQR))						
EF (%)	45 (42–47)	45 (42–47)	44 (40–45)	45 (41–47)	45 (42–46)	0.181
LAs (mm)	36 (34–40)	36 (33–40)	36 (34–38)	36 (34–39)	37 (35–40)	0.150
LVd (mm)	50 (47–55)	50 (46–53)	51 (47–54)	50 (47–55)	51 (48–55)	0.042
IVSd (mm)	10 (9–10)	10 (9–10)	10 (9–10)	10 (9–11)	10 (9–10)	0.309
LVPWd (mm)	9 (9-10)	9 (9-10)	9 (9-10)	10 (9–10)	9 (9-10)	0.112
RAs (mm)	35 (33–38)	35 (33–38)	35 (32–38)	25 (33–38)	36 (34–38)	0.638
RVd (mm)	19 (18–20)	20 (18–28)	18 (17–20)	19 (17–20)	19 (18–22)†	<0.001
E/e′	13.5 (10.0–18.4)	12.4 (9.8–15.9)	12.5 (9.7–19.3)	14.1 (10.3–19.0)	15.4 (11.1–20.1)	0.002
PASP (mm Hg)	30.3 (21.5–39.6)	29.9 (22.3–36.1)	31.3 (24.1–37.5)	28.8 (12.8–40.7)	32.4 (24.0–42.8)	0.255
Outcome (n (%))						
All-cause death at 90 days	16 (2.8)	3 (1.2)	1 (2.4)	5 (3.4)	7 (5.2)	0.144
CV death at 90 days	15 (2.6)	3 (1.2)	1 (2.4)	4 (2.7)	7 (5.2)	0.139
CV event at 90 days	127 (22.1)	50 (20.0)	6 (14.3)	27 (18.4)	44 (32.6)‡	0.008
All-cause death at 1 year	45 (7.8)	12 (4.8)	5 (11.9)	12 (8.2)	16 (11.9)	0.066
CV death at 1 year	44 (7.7)	12 (4.8)	5 (11.9)	11 (7.5)	16 (11.9)	0.062

Continued

Table 1 Continued

	Total	Group 1 LUS-BL 0	Group 2 LUS-BL 1–2	Group 3 LUS-BL 3–9	Group 4 LUS-BL≥10	P value
CV event at 1 year	261 (45.5)	112 (44.8)	19 (45.2)	62 (42.2)	68 (50.4)	0.573

Categorical variables were compared using the Pearson χ^2 tests or Fisher's exact test. Differences on continuous data with normal distribution across groups were compared using one-way analysis of variance followed by either Tukey's or Games-Howell multiple comparison post hoc tests as appropriate. Variables with skewed distribution were compared using the Kruskal-Wallis test and the Dunn post hoc method, if applicable.
*P<0.05 versus group 1.
†P<0.05 versus group 2.
‡P<0.05 versus group 3.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; E/e′, ratio of early transmitral flow velocity to early mitral annular velocity; EF, ejection fraction; Hb, haemoglobin; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; IVSd, end-diastolic interventricular septal wall thickness; LAs, end-systolic left atrial anteroposterior diameter; LUS-BL, lung ultrasound-derived B-lines; LVd, end-diastolic left ventricle dimension; LVPWd, end-diastolic left ventricular posterior wall thickness; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RAs, right atrial diameter; RVd, right ventricular diameter; TnT, troponin T; UA, uric acid.

estimated glomerular filtration rate (eGFR) were gradually increased. CV event at 90 days after discharge was significantly increased with increased number of LUS-BL (group 1 vs 2 vs 3 vs 4: 20.0% vs 14.3% vs 18.4% vs 32.6%, p=0.008), while CV event rate at 1 year was similar among groups (44.8% vs 45.2% vs 42.2% vs 50.4%, p=0.573).

As shown in table 2, age, NYHA class III/IV, hypertension, diabetes, atrial fibrillation and renal dysfunction,

Table 2 Unadjusted clinical and echocardiographic risk factors associated with CV event at 90 days and 1 year in patients with ischaemic HFmrEF

	CV event at 90 days		CV event at 1 year	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.03 (1.02 to 1.05)	<0.001	1.02 (1.01 to 1.03)	<0.001
Male versus female		n.s.		n.s.
NYHA functional class				
IV/III versus II	2.02 (1.37 to 3.96)	<0.001	1.70 (1.29 to 2.15)	<0.001
Hypertension	2.51 (1.61 to 3.91)	<0.001	1.65 (1.26 to 2.16)	<0.001
Diabetes	1.44 (1.01 to 2.05)	0.044		n.s.
Atrial fibrillation	1.70 (1.03 to 2.79)	0.038	1.68 (1.17 to 2.42)	0.005
Stroke		n.s.	1.52 (1.07 to 2.16)	0.018
COPD		n.s.	1.65 (1.12 to 2.43)	0.011
Renal insufficiency	1.95 (1.31 to 2.89)	<0.001	1.62 (1.20 to 2.17)	0.001
Echocardiography				
EF (%)		n.s.		n.s.
LAs (mm)	1.07 (1.04 to 1.11)	<0.001	1.04 (1.02 to 1.07)	0.001
LVd (mm)	1.04 (1.01 to 1.07)	0.011	1.03 (1.00 to 1.05)	0.017
RAs (mm)	1.04 (1.01 to 1.07)	0.021		n.s.
RVd (mm)	1.05 (1.02 to 1.08)	<0.001	1.04 (1.02 to 1.06)	<0.001
E/e′	1.04 (1.02 to 1.06)	<0.001	1.03 (1.01 to 1.05)	<0.001
PASP (mm Hg)	1.01 (1.00 to 1.02)	0.038		n.s.

COPD, chronic obstructive pulmonary disease; CV, cardiovascular; E/e′, ratio of early transmitral flow velocity to early mitral annular velocity; EF, ejection fraction; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; LAs, end-systolic left atrial anteroposterior diameter; LVd, end-diastolic left ventricle dimension; n.s, no significant differences; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RAs, right atrial diameter; RVd, right ventricular diameter.

Table 3 Prognostic performance of LUS-BL for outcome at 90 days and 1 year in patients with ischaemic HFmrEF

	CV event	Event rate (%)	Unadjusted HR (95% CI)	P value	Clinical covariates adjusted HR (95% CI)	P value
Number of LUS-BL (1 unit increase)						
90-day CV mortality*	15/574	2.6	1.08 (1.02 to 1.13)	0.008	1.05 (0.99 to 1.12)	0.081
90-day CV event*	127/574	22.1	1.04 (1.02 to 1.06)	<0.001	1.03 (1.00 to 1.05)	0.024
1-year CV mortality†	44/574	7.7	1.05 (1.01 to 1.08)	0.005	1.03 (0.99 to 1.07)	0.108
1-year CV event†	261/574	45.5	1.02 (1.00 to 1.03)	0.036	1.01 (0.99 to 1.02)	0.421

*Adjusted for age, sex, NYHA functional class, hypertension, diabetes, atrial fibrillation and renal dysfunction.
†Adjusted for age, sex, NYHA functional class, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, stroke and renal dysfunction.
CV, cardiovascular; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; LUS-BL, lung ultrasound-derived B-lines; NYHA, New York Heart Association.

echocardiographic parameters including LAs, LVd, RAs, right ventricular diameter (RVd), ratio of early transmitral flow velocity to early mitral annular velocity (E/e′) and PASP were identified as unadjusted determinants associated with increased risk of CV event at 90 days. Age, NYHA class III/IV, hypertension, atrial fibrillation, stroke, COPD, renal dysfunction and echocardiographic parameters including LAs, LVd, RVd and E/e′ were identified as unadjusted determinants associated with increased risk of CV event at 1 year.

Univariable and multivariable Cox regression analysis showed that increased number of LUS-BL was significantly and independently associated with increased CV event rate at 90 days after adjusted for clinical covariates (per 1 B-line increase, adjusted HR 1.03, 95% CI 1.00 to 1.05, p=0.024). However, an increased number of LUS-BL was not significantly associated with an increased risk of CV mortality or CV event at 1 year, after adjusted for clinical covariates (both p>0.05, table 3). Kaplan-Meier curves also showed that LUS-BL>11 was associated with increased CV event rate at 90 days (Log rank p<0.001; figure 3).

We then built different multivariable Cox regression models to identify potential risk factors independently associated with increased risk of CV event at 90 days (table 4). In model A, which includes unadjusted clinical risk factors and LUS-BL, the analysis revealed that hypertension (HR 1.97, 95% CI 1.25 to 3.01, p=0.004), older age (HR 1.02, 95% CI 1.00 to 1.04, p=0.014) and an increased number of LUS-BL (HR 1.03, 95% CI 1.00 to 1.05, p=0.024) remained significant predictors of CV event risk at 90 days, irrespective of sex, NYHA class, diabetes, atrial fibrillation and renal dysfunction. In model B, which includes unadjusted echocardiographic risk factors and LUS-BL, the analysis indicated that higher RVd (HR 1.06, 95% CI 1.02 to 1.09, p<0.001), an increased number of LUS-BL (HR 1.03, 95% CI 1.01 to 1.05, p=0.006) and a higher E/e′ ratio (HR 1.03, 95% CI 1.01 to 1.05, p=0.009) remained significant predictors of CV event at 90 days, irrespective of EF, LAs, RAs, PASP and LVd. In model C, the most significant and independent risk factors strongly associated with 90-day CV event in this cohort were identified as RVd, hypertension, LUS-BL, age and E/e′ ratio. Classification tree using CHAID algorithm demonstrated that age>52 years, RVd>23 mm, E/e′ >24 and LUS-BL>11 were identified as potential cut-off points for predicting CV event at 90 days, respectively (online supplemental figure 2). In model D, it was observed that higher RVd (>23 mm, HR 2.01, 95% CI 1.37 to 2.94, p<0.001), hypertension (HR 2.06, 95% CI 1.31 to 3.25, p=0.002), older age (>82 years vs ≤52 years, HR 5.57, 95% CI 1.66 to 18.73, p=0.006; 53–82 vs ≤52 years, HR 3.56, 95% CI 1.12 to 11.27, p=0.031), a higher E/e′ ratio (>24, HR 1.79, 95% CI 1.11 to 2.86, p=0.016) and an increased number of LUS-BL (>11, HR 1.51, 95% CI 1.01 to 2.26, p=0.045) were identified as independent risk

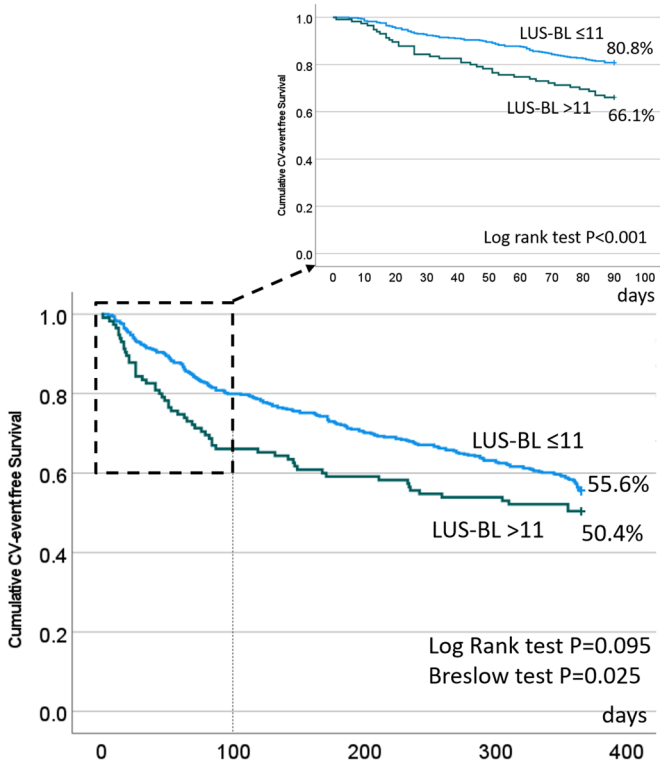

Figure 3 Kaplan-Meier curves for cardiovascular (CV) event at 90 day stratified by the numbers of lung ultrasound detected B-lines (LUS-BL).

Table 4 Independent risk factors for CV event at 90 days in patients with ischaemic HFmrEF

	Multivariable HR (95% CI)	Wald	P value
Model A (clinical risk factors and LUS-BL)			
Hypertension versus no hypertension	**1.97 (1.25 to 3.01)**	**8.50**	**0.004**
Age	**1.02 (1.00 to 1.04)**	**6.07**	**0.014**
LUS-BL	**1.03 (1.00 to 1.05)**	**5.12**	**0.024**
Renal insufficiency	1.46 (0.97 to 2.21)	3.33	0.068
NYHA class IV/III versus II	1.46 (0.97 to 2.21)	3.32	0.068
Atrial fibrillation	1.40 (0.84 to 2.32)	1.67	0.196
Diabetes	1.26 (0.88 to 1.81)	1.57	0.210
Male versus female	1.01 (0.70 to 1.47)	0.01	0.939
Model B (echocardiographic risk factors and LUS-BL)			
RVd (mm)	**1.06 (1.02 to 1.09)**	**13.43**	**<0.001**
LUS-BL	**1.03 (1.01 to 1.05)**	**7.59**	**0.006**
E/e′	**1.03 (1.01 to 1.05)**	**6.91**	**0.009**
LAs (mm)	1.04 (1.00 to 1.09)	3.16	0.076
LVEF (%)	0.97 (0.91 to 1.03)	0.91	0.340
PASP (mm Hg)	1.00 (0.99 to 1.02)	0.59	0.444
RAs (mm)	0.99 (0.95 to 1.03)	0.27	0.604
LVd (mm)	1.00 (0.97 to 1.04)	0.01	0.907
Model C (clinical and echocardiographic risk factors and LUS-BL, continuous variables)			
RVd (mm)	1.05 (1.02 to 1.08)	13.24	<0.001
Hypertension	1.96 (1.24 to 3.09)	8.35	0.004
LUS-BL	1.03 (1.01 to 1.05)	7.47	0.006
Age	1.02 (1.01 to 1.04)	6.75	0.009
E/e′	1.02 (1.00 to 1.05)	4.93	0.026
Model D (clinical and echocardiographic risk factors and LUS-BL, categorical variables)			
RVd>23 vs ≤23 mm	2.01 (1.37 to 2.94)	12.77	<0.001
Hypertension versus no hypertension	2.06 (1.31 to 3.25)	9.84	0.002
Age			
≤52 years	Reference		
53–82 years	3.56 (1.12 to 11.27)	4.65	0.031
>82 years	5.57 (1.66 to 18.73)	7.70	0.006
E/e′>24 vs ≤24	1.79 (1.11 to 2.86)	5.82	0.016
LUS-BL>11 vs ≤11	1.51 (1.01 to 2.26)	4.04	0.045

CV, cardiovascular; E/e′, ratio of early transmitral flow velocity to early mitral annular velocity; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; LAs, end-systolic left atrial anteroposterior diameter; LUS-BL, lung ultrasound-derived B-lines; LVd, end-diastolic left ventricle dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RAs, right atrial diameter; RVd, right ventricular diameter.

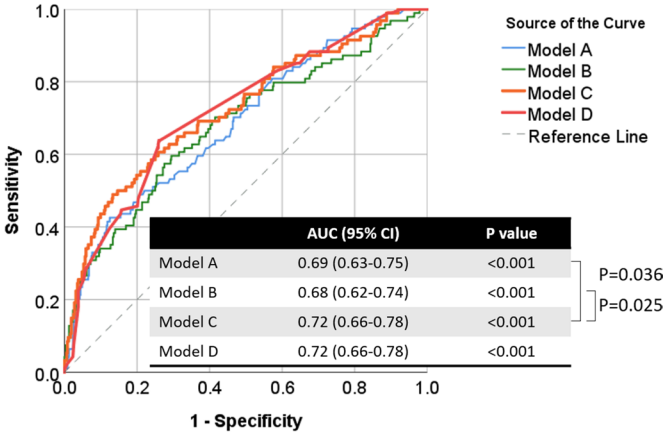

Figure 4 Comparison of the discriminative ability of the multivariable Cox models using the areas under the curve (AUC) of receiver operating characteristics base on Harrell's C-Statistic analysis.

factors for predicting an increased risk of CV event at 90 days in the ischaemic HFmrEF patient cohort.

As depicted in figure 4, the Harrell's C-Statistic analysis, which is based on the Cox regression models (models A–D), demonstrates a significant improvement in the predictive ability of model C. This model includes clinical and echocardiographic risk factors in addition to LUS-BL. When compared with model A (comprising clinical risk factors and LUS-BL, AUC 0.69), model C (AUC 0.72) exhibits a noteworthy increase in predictive ability (p=0.036). Similarly, in comparison to model B (comprising echocardiographic risk factors and LUS-BL, AUC 0.68), model C (AUC 0.72) also demonstrates a significant improvement in predictive ability (p=0.025).

DISCUSSION

This study investigated the prognostic impact of LUS-BL on 90 days and 1-year CV outcome of ischaemic HFmrEF patients. Results show that LUS-BL>11 at admission are independently associated with increased CV event at 90 days after discharge in HFmrEF patients with ischaemic heart disease, irrespective of other clinical covariates. The most significant and independent risk factors strongly associated with increased 90-day CV event risk in this cohort were identified as RVd, hypertension, LUS-BL, age and E/e′ ratio. The Harrell's C-Statistic analysis, based on the Cox regression models, demonstrated a significant improvement in the predictive ability of the model that incorporated both clinical and echocardiographic risk factors along with LUS-BL (AUC=0.72) compared with the model comprising only clinical risk factors and LUS-BL (AUC=0.69, p=0.036), or to the model with echocardiographic risk factors and LUS-BL (AUC=0.68, p=0.025). To our knowledge, this is the first clinical study with a relative larger patient cohort exploring the prognostic impact of LUS-BL on 90 days and 1-year CV outcome of ischaemic HFmrEF patients.

LUS assessed number of LUS-BL is a simple and clinical reliable method for the estimation of pulmonary congestion, a common universal pathophysiological feature of HF patients. The prognostic value of LUS-BL on outcome of HF patients has been extensively investigated, with the exception of HFmrEF patients. Cogliati *et al* reported that the LUS-BL at discharge was a prognostic marker for 100 day readmission and death of patients with HF.[12] Platz *et al* studied the short-term and long-term impact of LUS-BL obtained at admission and at discharge, results showed the association between number of LUS-BL and short-term and long-term outcomes persisted after adjusting for important clinical variables, including N-terminal pro-B-type natriuretic peptide.[7] It was reported that LUS-BL was related to poor outcome in HFpEF and HFrEF patients.[13 14] In line with results obtained from a small patient cohort, which showed LUS-BL was related to readmission during 2-year follow-up among 71 HFmrEF patients,[10] we found that LUS-BL at admission was independently related to poor CV outcome at 90 days after discharge among ischaemic HFmrEF patients, especially in patients with concomitant hypertension. The results hint that more guideline-directed medical therapies, as shown by up-titration of guideline-directed medical therapies for acute HF (STRONG-HF) trial, which demonstrated that intensive treatment strategy of rapid up-titration of guideline-directed medication and close follow-up after an acute HF admission was readily accepted by patients because it reduced symptoms, improved quality of life and reduced the risk of 180-day all-cause death or HF readmission compared with usual care,[15] might be also helpful to improve the CV outcome of ischaemic HFmrEF patients with LUS-BL>11, especially those with concomitant hypertension. The ongoing IMP-OUTCOME (Impact of B-lines-guided Intensive Heart Failure Management on Outcome of Discharged Heart Failure Patients with Residual B-lines) trial might provide some clinical evidence on this issue.[16]

In this study, the relative low CV event rate at 90 days after discharge was identified in HFmrEF patients without hypertension (12.1%) or patients with hypertension and LUS-BL≤11 (22.7%) compared with HFmrEF patients with both LUS-BL>11 and hypertension (42.7%). This finding is in line with the previous report indicating suboptimal blood pressure levels were a significant risk factor for an adverse outcome in HFmrEF.[17] Taken this fact in mind, ischaemic HFmrEF patients complicating hypertension should receive special care to achieve both HF control and blood pressure control to improve the outcome of these patients. Again, future clinical trial is needed to answer this clinical question.

Limitations

This study is retrospective in nature, and it is important to acknowledge that certain biases, such as selection bias and recall bias, are inherent and unavoidable. Another limitation of the study is the use of automated algorithms to identify covariates of interest, which may introduce potential bias. Given the retrospective design, inter-rater and intrarater agreement assessments were not conducted. The impact of LUS-BL on non-ischaemic HFmrEF patients needs to be explored in other patient cohort. Additionally, it is worth noting that comparing the findings from HFmrEF patients with those from HFrEF and HFpEF patients is of significant importance. Our team has recently completed data collection and follow-up for the HFpEF cohort and will commence the analysis shortly. We have also established the HFrEF cohort, and the follow-up is currently in progress. We are committed to providing comparative study results as soon as possible.

Lay summary

LUS-BL can predict the prognosis of patients with HF. In our research, LUS-BL>11 suggests that patients with HFmrEF and ischaemic cardiomyopathy have a worse prognosis, especially in patients with hypertension. LUS-BL can be used as a useful marker to guide the treatment of HF patients, especially in the case of other complications.

Clinical perspectives

LUS-BL detection is a helpful biomarker for the risk stratification of ischaemic HFmrEF patients, LUS-BL>11 is independently related worse CV outcome of of ischaemic HFmrEF patients during the 'vulnerable phase',[18] our results provide clinical evidence of detecting LUS-BL, as a supplementary biomarker to guide the management of ischaemic HFmrEF patients during the 'vulnerable phase', future studies are needed to observe if intensive HF management for patients with LUS-BL>11 could improve their CV outcome or not. Moreover, studies are needed to know if optimal blood pressure control could improve the CV outcome of ischaemic hypertensive HFmrEF patients with LUS-BL>11 at admission.

CONCLUSIONS

In HFmrEF patients with ischaemic heart disease, admission LUS-BL>11 is independently associated with an increased risk of CV event at 90 days following discharge.

Author affiliations
[1]Department of Cardiology, Xiangtan Central Hospital, Xiangtan, Hunan, China
[2]University of South China, Hengyang, Hunan, China
[3]Xiangtan Central Hospital, Xiangtan, Hunan, China
[4]Department of Cardiology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China

Twitter Zhican Liu @Heart failure

Contributors JPZ guided the writing idea and structural framework of this manuscript. HZ and YYZ were responsible for writing this manuscript and collecting relevant references. HZ, YYZ and YLZ were responsible for the production of image. FQC, NL, XP, MXW, HBH, LLZ, ML, SX, YLC, SHC, ZCL, LQY, JF and others collected patient data and follow-up. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. JPZ and YLZ are responsible for the overall content as the guarantors.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the Human Research Committee of the Xiangtan Central Hospital. Written informed consents were obtained from all patients or their guardians on admission with agreement for the anonymous use of their clinical data for medical research purpose. Participants gave informed consent to participate in the study before taking part.

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ORCID iDs
Yunlong Zhu http://orcid.org/0000-0002-4994-995X
Zhican Liu http://orcid.org/0000-0002-5532-1632
Jianping Zeng http://orcid.org/0000-0002-4485-6164

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