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STUDY DESIGN

Impact of B-lines-guided intensive heart failure management on outcome of discharged heart failure patients with residual B-lines

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Abstract

Aims Pulmonary congestion (PC) expressed by residual lung ultrasound B-lines (LUS-BL) could exist in some discharged heart failure (HF) patients, which is a known determinant of poor outcomes. Detection efficacy for PC is suboptimal with widely used imaging modalities, like X-ray or echocardiography, while lung ultrasound (LUS) can sufficiently detect PC by visualizing LUS-BL. In this trial, we sought to evaluate the impact LUS-BL-guided intensive HF management post-discharge on outcome of HF patients discharged with residual LUS-BL up to 1 year after discharge. IMP-OUTCOME is a prospective, single-centre, single-blinded, randomized cohort study, which is designed to investigate if LUS-BL-guided intensive HF management post-discharge in patients with residual LUS-BL could improve the clinical outcome up to 1 year after discharge or not.

Methods and results After receiving the standardized treatment of HF according to current guidelines, 318 patients with ≥3 LUS-BL assessed by LUS within 48 h before discharge will be randomly divided into the conventional HF management group and the LUS-BL-guided intensive HF management group at 1:1 ratio. Patient-related basic clinical data including sex, age, blood chemistry, imaging examination, and drug utilization will be obtained and analysed. LUS-BL will be assessed at 2 month interval post-discharge in both groups, but LUS-BL results will be enveloped in the conventional HF management group, and diuretics will be adjusted based on symptom and physical examination results with or without knowing the LUS-BL results. Echocardiography examination will be performed for all patients at 12 month post-discharge. The primary endpoint is consisted of the composite of readmission for worsening HF and all-cause death during follow up as indicated. The secondary endpoints consisted of the change in the New York Heart Association classification, Duke Activity Status Index, N terminal pro brain natriuretic peptide value, malignant arrhythmia event and 6 min walk distance at each designed follow up, echocardiography-derived left ventricular ejection fraction, and number of LUS-BL at 12 month post-discharge. Safety profile will be recorded and managed accordingly for all patients.

Conclusions This trial will explore the impact of LUS-BL-guided intensive HF management on the outcome of discharged HF patients with residual LUS-BL up to 1 year after discharge in the era of sodium-glucose cotransporter-2 inhibitors and angiotensin receptor blocker-neprilysin inhibitor.

Trial Registration: ClinicalTrials.gov: NCT05035459

Keywords Heart failure; Lung ultrasound B-line; Pulmonary congestion; Follow up; Outcome

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Introduction

The morbidities of heart failure (HF) are increasing with the ageing population worldwide. HF occurs in up to 10% of patients over the age of 70 in developed countries.[1] Similarly, the prevalence of HF among urban residents in China was reported to be 10% in the 2018 epidemiological survey of China,[2] the incidence increased about 10 folds compared with that reported in the 2003 epidemiological survey in China.

Pulmonary congestion (PC) is one of the major characteristics of HF.[3,4] The importance of PC in the disease course of HF has been confirmed by numerous clinical trials, and the presence of PC is shown to be associated with a significantly increased risk of mortality and rehospitalization in HF patients.[5–7] Lung ultrasound (LUS) acts as a semi-quantitative, effective, ready-made method to estimate PC.[8] Previous study demonstrated that the increased number of LUS-detected B-lines (LUS-BL) was associated with a lower 6 min walk distance and higher echocardiography-derived E/e' value.[9] It was also shown that presence of PC was associated with worse 6 month outcomes in chronic HF patients.[10,11] Various clinical studies have indicated the efficacy of targeting PC on reducing acute decompensation and improving walking capacity in chronic HF patients.[3,12–14] The predicting role of residual PC at discharge is increasingly explored in recent studies. Platz *et al*. showed that in 132 patients with LUS data at discharge, the risk of HF hospitalization or all-cause death was greater in patients with a higher number of B-lines at discharge.[15] Coiro *et al*. analysed the LUS data from 60 consecutive HF patients and found that residual PC at discharge, as assessed by a B-line count ≥ 30, is a strong predictor of outcome. The 3 month event-free survival for the primary endpoint (all-cause death or HF hospitalization) was 27 ± 10% in patients with $\geq$30 B-lines and 88 ± 5% in those with $<$30 B-lines ($P < 0.0001$).[16]

Treatment options for chronic HF is increasing for decades, and the outcome of HF patients is improved steadily with the advance of HF management options.[17] Recently, the angiotensin receptor blocker-neprilysin inhibitor (ARNI)[18] and sodium-glucose cotransporter-2 (SGLT2) inhibitors[19] have shown satisfactory effects on improving the outcome of various forms of chronic HF including HF with preserved ejection fraction and HF with reduced ejection fraction.

In the LUS-HF study, 123 patients admitted for HF were randomized to either a standard follow up (n = 62, control group) or a LUS-guided follow up (n = 61, LUS group), and results showed that tailored LUS-guided diuretic treatment of PC in this proof-of-concept study reduced the number of decompensations and improved walking capacity in patients with HF.[3] The IMPEDANCE-HF trial included 256 patients from 2 medical centres with chronic HF and left ventricular ejection fraction $\leq$ 35% in New York Heart Association (NYHA) classes II–IV; patients were randomized to a control group treated by clinical assessment and a monitored group whose therapy was also assisted by lung impedance, and followed for at least 12 months, and results showed that lung impedance-guided therapy reduced hospitalizations for acute HF as well as the incidence of HF, cardiovascular, and all-cause mortality.[20] The previous clinical studies assessing the impact of LUS-BL-guided HF therapy on various outcomes were performed prior to the ARNI/SGLT2 era; a present study is initiated to test the hypothesis that LUS-BL-guided intensive HF management could significantly improve the outcome of discharged HF patients with residual LUS-BL up to 1 year after discharge in the ARNI/SGLT2 era.

Methods

Study design

The main purpose of the IMP-OUTCOME trial (Clinical Trials.gov Identifier: NCT 05035459) is to test the hypothesis that LUS-BL-guided intensive HF management would improve the outcome of HF patients with residual LUS-BL at discharge. HF patients with $\geq$3 LUS-BL assessed by LUS within 48 h before discharge will be enrolled. Lung ultrasonography (LUS) examination will be performed by two to three qualified researchers with a national LUS certificate on commercially available ultrasound machines (Phillips CX50 equipped with S5–1 probe) within 48 h before discharge and during follow up as indicated. The results will be recorded and analysed real time at bedside. The 8-point method will be used to assess LUS-BL with the patient examined in supine position,[21] and if $\geq$3 B-lines are symmetrically detectable at $\geq$2 points, the patient will be defined as $\geq$3 LUS-BL patient. The area with the highest number of B-lines was taken as the number of B-lines for that patient. Enrolled patients will then be randomly divided into the conventional HF management group and the LUS-BL-guided intensive HF management group at 1:1 ratio. The randomization will be made according to the method of computer-generated randomization numbers. The patient and the sonographer are blinded to the allocation status. After randomization, HF nurses and cardiologists are not blinded to the allocation status. The standard treatment option for the two groups will be guided by 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF.[1] All patients will be followed up at 2 month interval up to 12 month post-discharge by HF nurses or cardiologists through the clinical visit. There is no pre-specified treatment protocol, and the therapeutic changes will be left up to the cardiologists in charge. For patients assigned in the LUS-BL-guided intensive HF management group, the managing cardiologist will be encouraged to pay special attention to adjust the type or dosage of diuretics (furosemide, torasemide, tolvaptan, and combination with thiazide) based on

symptoms, physical examination results, and LUS-BL status during follow-up. In patients assigned to the conventional HF management group, medication adjustment will be based on symptoms and physical examination results. For resistant lung congestion patients, rehospitalization will be considered in both groups. LUS-BL will be assessed at 2 month interval post-discharge in both groups, and results will be transferred to HF nurses, who will present the LUS-BL results to managing cardiologist or envelope the results till study end according to the randomization assignment. Echocardiography examination will be performed for all patients at 12 month post-discharge (*Figure 1* & *Table 1*).

Participant selection

Eligibility requirements included (i) age of at least 18 years; (ii) hospitalized HF patients with objective HF evidence during or before hospitalization; (iii) NYHA class II, III, or IV; and (4) patients with NT-pro-BNP level of at least 600 pg/mL, or ≥400 pg/mL if they had been hospitalized for HF within the previous 12 months, atrial fibrillation or atrial flutter patients with NT-pro-BNP levels of at least 900 pg/mL, regardless of their history of HF hospitalization.[22,23] Exclusion criteria included patients with a life expectancy of less than 1 year due to malignancy. Patients with interstitial lung disease/pulmonary fibrosis, acute respiratory distress syndrome, and pneumonia and patients on dialysis will also be excluded because they might also impact the number of B-lines. The 8-point method will be used to assess LUS-BL with the patient examined in supine position. Patients with ≥3 LUS-BL would be eligible for enrolment (*Figure 2*). After obtaining informed consent, inclusion and exclusion criteria will be evaluated and baseline information (including clinical, laboratory, and imaging results) will be collected from qualified participants. Follow up will be made by clinical visit for all patients at 2 month interval.

Endpoints

The primary endpoints consisted of composite of readmission for worsening HF and all-cause death. Rehospitalization for worsening HF is defined as stay in the hospital for more than 24 h for signs and/or symptoms of worsening HF as the main cause of hospitalization.

The secondary endpoint includes the patient's NYHA classification, Duke Activity Status Index, NT-pro-BNP, arrhythmia

Table 1 Visits and interventions protocol

Visits Interventions	V0	V1	V2	V3	V4	V5	V6
Informed consent	x						
Personal history	x						
Inclusion/exclusion criteria	x						
Medication	x	x	x	x	x	x	x
Outcomes		x	x	x	x	x	x
NYHA classification	x	x	x	x	x	x	x
NT-pro-BNP	x	x	x	x	x	x	x
DASI	x	x	x	x	x	x	x
Blood test	x						x
LUS	x	x	x	x	x	x	x
6MWD	x	x	x	x	x	x	x
ECG	x	x	x	x	x	x	x
Echocardiography	x						x
Safety sheets	x	x	x	x	x	x	x

6MWD, 6 min walk test; DASI, Duke Activity Status Index; LUS, lung ultrasound; NT-proBNP, N terminal pro-brain natriuretic peptide value.

Figure 1 Flow chart of study design. ECG, electrocardiogram; HF, heart failure; LUS-BL, lung ultrasound detected B-lines; NT-proBNP, N terminal pro-brain natriuretic peptide value; NYHA, New York Heart Association.

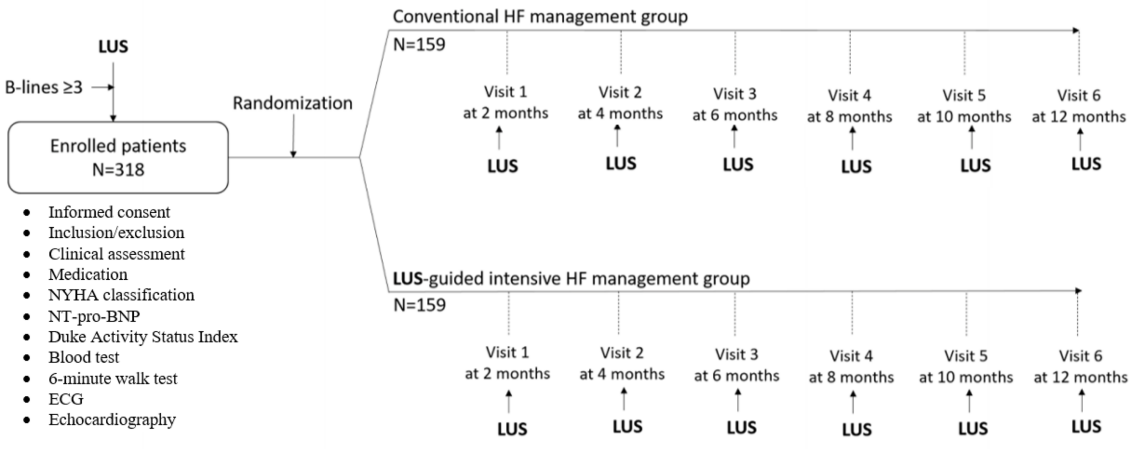

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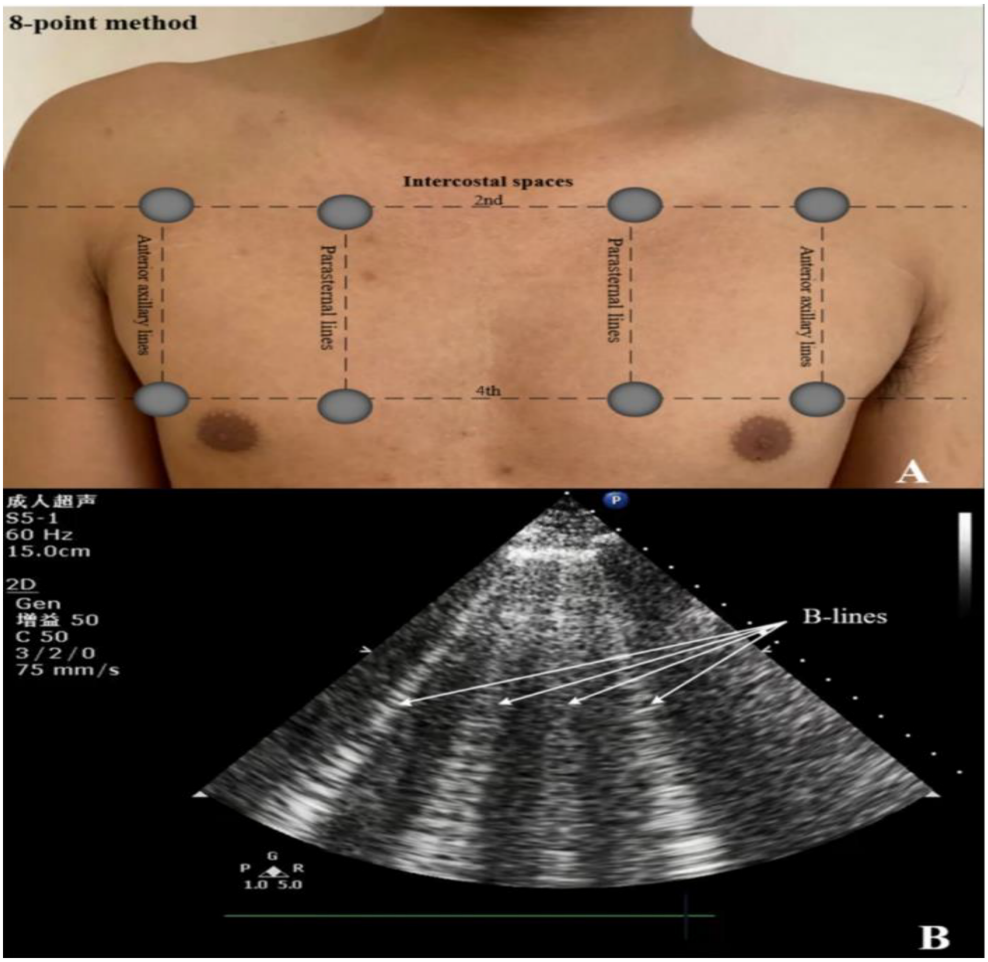
Figure 2 Lung ultrasound detected B-line. (A) Eight-point methods. (B) Four B-lines were detected in a 78-year-old male patient admitted to our department due to decompensated heart failure.



and 6 min walk distance values at each follow up, and number of LUS-BL values during the follow up and EF at 12 month post-discharge. Arrhythmias documented by ECG during follow up including sick sinus syndrome, rapid atrial fibrillation, paroxysmal supraventricular tachycardia, and sustained ventricular tachycardia will be registered, managed, and analysed. The laboratory and imaging endpoints listed as secondary endpoints will be assessed at the site. The patient himself will be blinded to the allocation status of the patient. Ultrasound results will be assessed real time and informed to HF nurses and who will transfer or envelope the results according to group assignment. Managing clinicians will be informed timely after LUS examination to ensure timely medication adjustment in the LUS-BL guided intensive HF management group. Left ventricular ejection fraction change is not a study endpoint, but LVEF as well echocardiographic parameters reflecting diastolic function (LAVi, SPAP, and E/E') at baseline and at the study end will be evaluated and compared between the two groups and between events group and events-free groups.

Safety outcomes are detailed in Supporting Information *Data S1*, which are mainly adopted from the LUS-HF study,[3] include (I) hypotension, defined as a blood pressure $<$ 90/60 mmHg; (II) hyperkalaemia, defined as a potassium level of $>$5.5 mmol/L; (III) hypokalaemia, defined as a potassium level of $<$3.5 mmol/L; (IV) worsening of renal function leading to an increase in creatinine of $\geq$50% from discharge during follow up; (V) ketoacidosis, defined as pH $<$ 7.3 or bicarbonate $<$ 15 mmol/L; (VI) allergy, which manifests as skin itching, chest tightness, and shortness of breath; (VII) oedema, which manifests as oedema of both lower extremities and is severe enough to present as angioedema; (VIII) severe liver dysfunction, which manifests as jaundice, ascites, and haemorrhage; (IX) hypoglycaemia, random blood glucose $<$ 2.8 mmol/L; diabetic patients random blood glucose $\leq$ 3.9 mmol/L; (X) others: bronchospasm,

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bradycardia, conduction block, sepsis, pyelonephritis, hypoglycaemia, perineal necrotizing and mucositis, and genital fungal infection. Above safety outcomes will be recorded and managed accordingly during the follow-up period.

Sample size and statistical analysis

Event rates of the IMP-OUTCOME study is assumed based on the data of previous studies.[24] In a national observational study, Tuppin *et al*. showed that the incidence of the 1 year survival rates was 71%, and HF readmission rates was 45%. Thus, we estimated that the difference in primary endpoint could be achieved by enrolling 254 patients with ≥3 LUS-BL. The power of the study is set at 90% with a two-sided type I error rate of 0.05. Assuming that 2% of patients would withdraw or be lost to follow up, the final sample size is determined to be 318 patients (159 in the conventional HF management group and 159 in the LUS-BL-guided intensive HF management group). The level of significance in the trial is set at 0.05. Statistical analysis will be performed using IBM SPSS Statistics 28.0.0 (SPSS Inc., Chicago, IL, USA) and EmpowerStats 2.2 (American X&Y Solutions Inc., USA). Data will be expressed as mean ± SD, median (interquartile range), or percentage when appropriate. For group comparisons, pair and unpaired Student's *t*-test, $\chi 2$ test, or Fisher's exact test and Wilcoxon matched-pairs sign rank test will be used as appropriate. The relative risk and 95% CI will be defined. The primary outcome would be estimated with the Kaplan–Meier method and compared by long-rank test. $P < 0.05$ will be considered statistically significant to reject the null hypothesis.

Study administration and management

The trial is registered as ClinicalTrails.gov identifier: NCT05035459. The local Institutional Review Board or Ethics Committee has approved the study, and all patients must provide written informed consent prior to enrolment. Funding is provided by the Department of Cardiology, the Xiangtan Central Hospital. An independent data monitoring committee, composed of three physicians from the fields of cardiology and interventional cardiology and one biostatistician, will review aggregate and individual patient data related to safety, data integrity, and overall conduct of the trial, on a periodic basis. The data monitoring committee may make recommendations to the steering committee and study sponsor based on monitoring activities. We will try to complete the enrolment of all patients before December 2022, and the follow up will then be ended on December 2023.

Discussion

This study is designed to evaluate the impact of LUS-BL-guided intensive HF management for patients with residual LUS-BL at discharge on their outcome up to 1 year post-discharge. Patients in the LUS-BL-guided intensive HF management will receive guideline recommended medication and diuretics will be adjusted by LUS-BL status in addition to symptoms and physical examination results at 2 month interval during the follow-up period. Patients in the conventional HF management group will be treated in the same way as patients in the LUS-BL-guided intensive HF group, without knowing the status of LUS-BL.

Effects of non-invasive LUS monitoring on HF patients, especially in acute HF patients, have been documented by various clinical studies,[25] research on its role in chronic HF patients is also emerging now.[13] Our trial will clarify frequent LUS-BL monitoring and LUS-BL-guided HF medication adjustment at 2 month interval during follow up could improve the outcome of discharged HF with residual LUS-BL or not during the HF medication era with ARNI/SGLT2 inhibitors. It is reasonable to speculate that the outcome of discharged HF patients with residual LUS-BL could be further improved by adding LUS assessment at 2 month interval and timely adjusting the medication in the era of new HF medications. This trial is a prospective single-centre single blind cohort study. The study design was based on the urgent requirement to improve the survival and reduce HF rehospitalization rate by clinical studies. The study by Tuppin *et al*.[24] reported the outcome of 69 958 patients hospitalized for the first time for HF and showed that the 1 year survival rate was 71% and 1 year HF readmission rate was 45% in this patient cohort. We expect to achieve similar satisfactory results for discharged HF patients with residual LUS-BL in our study setting as reported by Rivas-Lasarte *et al*.,[3] in the LUS-HF study with the availability of ARNI/SGLT-2 inhibitors on top of diuretic therapy in our patients.

The present study sets the hard endpoints including HF rehospitalization and all-cause death as the primary endpoints. NYHA classification, DASI, NT-pro-BNP, 6 min walk test, arrhythmia, and EF as well as LUS-BL changes are selected as the secondary endpoints; these data might be helpful to explain the expected beneficial effects of LUS-BL-guided intensive HF management protocol post-discharge in our patients.

In conclusion, this study aims to identify the impact of LUS-BL-guided intensive HF management (follow up at 2 month interval, medication adjustment according to LUS-BL status in addition to symptom, and physical examination results in the era of ARNI/SGLT-2 inhibitors) in discharged HF patients with residual LUS-BL on HF readmission and mortality. Our results might supply evidence if LUS-BL-guided intensive HF management could improve the outcome of discharged HF patients with residual LUS-BL at discharge or not in the era of ARNI/SGLT-2 inhibitors.

Conflict of interests

The authors declare that they have no competing interests.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information.
Data S2. Supporting Information.

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