Impact of Residual B-lines at Discharge on Outcome of Heart Failure Patients（IMP-OUTCOME)

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Research Article

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Abstract

Background Discharged heart failure (HF) patients might still have lung congestion (PC) expressed by residual lung ultrasound B-lines (LU-BL). Detection efficacy for PC is suboptimal with widely used imaging modalities, like x-ray or echocardiography, while lung ultrasound (LU) can sufficiently detect PC by visualizing LU-BL. In this trial, we sought to evaluate the impact of residual LU-BL at discharge and other clinical indexes on rehospitalization due to HF and all-cause mortality (composite primary outcome) up to 1 year post discharge in HF patients. The impact of intensive HF therapy post discharge on outcome up to 1 year after discharge will also be investigated for discharged HF patients with evidence of PC.

Aim: IMP-OUTCOME is a prospective, single-center, observational cohort study, which is designed to investigate whether residual LU-BL at discharge is one of the independent determinants of poor outcome in discharged HF patients and if intensive HF therapy (adding SGLT2 inhibitor and more frequent follow up including LU-BL assessment) post discharge could improve the outcome of discharged HF patients with residual LU-BL up to 1 year after discharge.

Methods and results: After receiving the standardized treatment of HF according to current guidelines, 233 discharged HF patients will be grouped into < 3 LU-BL and ≥ 3 LU-BL groups according to LU measurement within 48 hours before discharge. Patients in the ≥ 3 LU-BL group will be further divided into the conventional HF therapy group and the intensive HF therapy group at 1:1 ratio. Intensive HF therapy group will be treated with an SGLT2 inhibitor, if not contraindicated, beyond other HF medications and monitored by HF nurses and cardiologists at 1-month interval by clinical visit. Patient-relates basic clinical data including sex, age, blood chemistry, imaging examination, drug utilization, and so on will be obtained and analyzed. Following discharge from the hospital, patients in the LU-BL<3 group and conventional HF therapy group will be followed up at 1 month, 3 months, 6 months, post discharge by clinical visit or telephone call, by clinical visit at 12 months post discharge. LU-BL will be assessed monthly post discharge in the intensive HF therapy group, and at 12 months post discharge for patients in the conventional HF therapy group and LU-BL<3 group. Echocardiography examination will be performed for all patients at 12 months post discharge. The primary endpoint is the composite of re-hospitalization for worsening HF and all-cause death during follow-up. Secondary endpoints include the change in the Duke Activity Status Index (DASI), NT-pro BNP value and 6-min walk distance at each follow up, EF and number of LU-BL at 12 months post discharge.

Conclusion: This trial will explore the potential impact of residual B-lines on the outcome of discharged HF patients and the impact of intensive HF management on the outcome of discharged HF patients with residual LU-BL up to 1 year after discharge.

Trial Registration ClinicalTrials.gov; NCT05035459. Registration date, 2021/09/02, “prospectively registered”.

Introduction

The morbidities of heart failure (HF) are increasing with the aging population worldwide. Heart failure 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 that reported in the 2003 epidemiological survey in China.

Pulmonary congestion (PC) is one of the major characteristics of HF[3]. 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[4, 5]. Lung ultrasound (LU) acts as a semi-quantitative, effective, ready-made method to estimate PC[6, 7]. Previous study demonstrated that the increased number of LU-detected B lines (LU-BL) was associated with a lower 6-min walk distance and higher echocardiography-derived E / e ' value[8]. It was also shown that presence of PC was associated with worse 6-month outcomes in chronic heart failure patients[9, 10]. Various clinical studies have indicated the efficacy of targeting PC on reducing acute decompensation and improving walking capacity in chronic heart failure patients[2, 11, 12].

Treatment options for chronic heart failure is increasing steadily for decades and the outcome of HF patients is improved steadily with the advance of HF medication[13]. Recently, SGLT2 inhibitor has shown satisfactory effects on improving the outcome of various forms of chronic heart failure including HFpEF and HFrEF[14]. Nevertheless, the impact of SGLT2 on discharged HF patients with residual LU-BL is not explored yet.

The previous clinical studies regarding LU-BL guided HF therapy was performed prior to the SGLT2 era, present study is initiated to confirm the prognostic value of residual PC in discharged HF patients and to test the hypothesis that adding SGLT2 inhibitor on top of standard HF medications and frequent monitoring including LU-BL assessment at 1-month interval by HF nurses and cardiologists for discharged HF patients with residual LU-BL at discharge could improve their outcome up to 1 year after discharge.

Methods

Study Design: The main purpose of the IMP-OUTCOME trial (Clinical Trials.gov Identifier:NCT 05035459) is to investigate the impact of residual LU-BL at discharge on the outcome of HF patients and test the hypothesis that adding SGLT2 inhibitor and more frequent follow up including LU-BL assessment would improve the outcome of HF patients with residual LU-BL at discharge. HF Patients will be divided into < 3 LU-BL group and ≥ 3 LU-BL group according to LU assessment results within 48 hours before discharge. An 8-point method will be used[15]. Patients in the < 3 LU-BL group will receive standard HF medication and be followed up at 1, 3, and 6 months post discharge by HF nurses or cardiologists through telephone call or clinical visit, at 12 months post discharge by clinical visit. The group with ≥ 3 B-lines will be further

divided into the conventional HF therapy group and the intensive HF therapy group at a 1:1 ratio. The intensive HF therapy group will be treated with an SGLT2 inhibitor beyond other standard HF medications, if not contraindicated. Patients in the intensive HF therapy group will be followed up at 1-month interval up to 12 months post discharge by HF nurses or cardiologists through the clinical visit. Patients in control HF therapy group will receive standard HF medication and followed up at 1, 3 months, 6 months, after discharge by HF-nurses or cardiologists through telephone call or clinical visit, and at 12 months post discharge by clinical visit. LU-BL will be assessed monthly post discharge in the intensive HF therapy group, and at 12 months post discharge for patients in the conventional HF therapy group and for patients with LU-BL < 3 at discharge. Echocardiography examination will be performed for all patients at 12 months post discharge (Fig. 1, Table 1).

LU-BL = lung ultrasound detected B-lines

Table 1
Study protocol and follow up timeline

	Conventional HF therapy group				Intensive HF therapy group	
	Month 1	Month 3	Month 6	Month 12	Month 1 to 11	Month 12
Body Weight	x	x	x	x	x	x
Medication	x	x	x	x	x	x
DASI	x	x	x	x	x	x
NT-proBNP	x	x	x	x	x	x
6MWD	x	x	x	x	x	x
LU-BL				x	x	x
Echocardiography				x		x

DASI: the Duke Activity Status Index; NT-pro-BNP: N terminales pro brain natriuretic peptide; 6MWD: 6-minute working distance; LU-BL: Lung ultrasound detected B-lines

Participant Selection

Eligibility requirements included age of at least 18 years. Hospitalized heart failure patients with objective heart failure evidence during or before hospitalization. New York Heart Association (NYHA) class II, III, or IV. Patients with NT-pro-BNP levels of at least 600pg/mL (or ≥ 400 pg/meal if they had been hospitalized for heart failure 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. Exclusion criteria included patients with a life expectancy of less than 1-year due to malignancy. Lung ultrasonography (LU) examination will be performed by qualified researchers with a national lung ultrasound certificate on commercially available ultrasound machines (Versana Premier, GE) within 48 hours before discharge and

during follow up as indicated. LU examinations were be performed on the patient in the supine position. The ultrasound scanning of the anterior and lateral chest will be obtained and evaluated with the 8-point method offline[10]. Patients will be divided into LU-BL < 3 and ≥ 3 groups. 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 telephone or clinical visit for patients with LU-BL < 3 at discharge and for patients in conventional HF therapy group during months 1, 3 and 6 post discharge and by clinical visit at month 12 post discharge. Patients will be followed up monthly by clinical visits for patients in the intensive HF therapy group.

Endpoints

The primary outcome consisted of readmission for worsening heart failure and all-cause death during follow-up. The secondary endpoint includes the patient's Duke Activity Status Index, NT-pro BNP and 6-minute walk distance values at each follow up, EF and number of LU-BL values during the follow up at month 12 post discharge.

Sample Size And Statistical Analysis

Event rates of the IMP-OUTCOME study is assumed based on the data of previous studies[15]. The study showed that the incidence of the composite outcome of worsening heart failure or all-cause death was 19.8% in the 3 B-lines group versus 45.8% in the ≥ 3 groups (hazard ratio, 4.08; 95% confidence interval (CI), 1.96 to 8.54; P < 0.001). Thus, we estimated that the difference in primary endpoint could be achieved by enrolling 186 patients (60 patients in 3 LU-BL groups and 126 patients in ≥ 3 LU-BL group). The power of the study is set at 90% with a 2-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 233 patients (75 patients in the3 LU-BL groups, 158 patients in the ≥ 3 LU-BL group). The level of significance to be used in the trial will be 0.05.

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 enrollment. Funding is provided by the Department of Cardiology, the Xiangtan Central Hospital. An independent data monitoring committee (DMC), 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 DMC may make recommendations to the steering committee and study sponsor based on monitoring activities. The study has not started enrollment, and we plan to complete the enrollment of all subjects

between October 2021 and December 2022, and the follow-up will then be ended on December 2023, and primary results would be available by early 2024.

Discussion

This study is designed to evaluate and confirm the prognostic role of LU-BL in discharged HF patients. Moreover, to observe if adding new comer of HF medication SGLT2 inhibitor to discharged HF patients with residual LU-BL in combination with frequent LU-BL guided HF medication adjustment and medical follow up, could improve the outcome of these patients or not.

Effects of noninvasive LU monitoring on HF patients, especially in acute HF patients, have been documented by various clinical studies[16], research on its role in chronic HF patients is also emerging now[12]. SGLT2, as a new class of HF medication, is gaining more and more attention in the field of HF management, while there is no report on its effects on discharged HF patients with residual LU-BL. Our trial will clarify its effect with the simultaneous help of frequent LU-BL monitoring guided HF medication adjustment during follow up. This trial is a prospective single-center observational cohort study. The study design was based on the LUS-HF trial[9]. It was shown that LU-BL was present at discharge in 40% of HF patients. The LUS-HF trial demonstrated a significantly higher rate (46%) for the primary outcome of in HF patients with residual PC compared to 15% MACE rate in HF patients without PC during the 6-month follow-up period. LUS-HF trial was demonstrated significant impact of LU-guided diuretic therapy. We expect even a better result of LU-guided HF therapy in the presence of SGLT-2 inhibitor in our patients.

Present study sets the hard endpoints: HF rehospitalization and all-cause death as primary endpoints. It is to note, we take DASI, NT-pro-BNP, 6MWD and EF as well as LU-BL changes, as secondary endpoints, these data might be helpful to explain the expected beneficial effects of intensive HF therapy protocol post discharge in our patients.

In conclusion, this study aims to identify the contribution of residual LU-BL on HF readmission and mortality in discharge HF patients, highlight the effects of SGLT2 inhibitor added HF therapy in discharged HF patients with LU-BL with help of frequent LU-guided HF medication, our results might supply evidence if intensive HF therapy based on our study protocol on the outcome of discharged HF patients with residual LU-BL at discharge.

Declarations

Funding No funding was received for this work.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics Approval The IMP-OUTCOME study was approved by the local Institutional Review Board or Ethics Committee.

Data Availability Statement Data sharing is not applicable to this article now as patient enrollment is not started yet.

Author's Contribution Jianping Zeng, Yunlong Zhu, Na Li, and Zhiliu Peng designed this study, Yunlong Zhu and Na Li wrote the manuscript. All other authors were major contributors for patients' enrollment and management. All authors read and approved the final manuscript.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2016;37(27):2129–200. doi:10.1093/eurheartj/ehw128.
2. Wu C. Epidemiological survey of heart failure and its prevalence in China. The road to health. 2018;17:207.
3. Rivas-Lasarte M, Álvarez-García J, Fernández-Martínez J, Maestro A, López-López L, Solé-González E, et al. Lung ultrasound-guided treatment in ambulatory patients with heart failure: a randomized controlled clinical trial (LUS-HF study). Eur J Heart Fail. 2019;21(12):1605–13. doi:10.1002/ejhf.1604.
4. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12(5):423–33. doi:10.1093/eurjhf/hfq045.
5. Gargani L, Pugliese NR, Frassi F, Frumento P, Poggianti E, Mazzola M, et al. Prognostic value of lung ultrasound in patients hospitalized for heart disease irrespective of symptoms and ejection fraction. ESC heart failure. 2021;8(4):2660–9. doi:10.1002/ehf2.13206.
6. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol. 2014;63(12):1123–33. doi:10.1016/j.jacc.2013.11.053.
7. Bailón MM, Rodrigo JMC, Lorenzo-Villalba N, Cerqueiro JM, García JC, Manuel EC, et al. Effect of a Therapeutic Strategy Guided by Lung Ultrasound on 6-Month Outcomes in Patients with Heart Failure: Randomized, Multicenter Trial (EPICC Study). Cardiovasc Drugs Ther. 2019;33(4):453–9. doi:10.1007/s10557-019-06891-z.
8. Miglioranza MH, Gargani L, Sant'Anna RT, Rover MM, Martins VM, Mantovani A, et al. Lung ultrasound for the evaluation of pulmonary congestion in outpatients: a comparison with clinical

assessment, natriuretic peptides, and echocardiography. JACC Cardiovasc Imaging. 2013;6(11):1141–51. doi:10.1016/j.jcmg.2013.08.004.

9. Rivas-Lasarte M, Maestro A, Fernández-Martínez J, López-López L, Solé-González E, Vives-Borrás M, et al. Prevalence and prognostic impact of subclinical pulmonary congestion at discharge in patients with acute heart failure. ESC heart failure. 2020;7(5):2621–8. doi:10.1002/ehf2.12842.
10. Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. Eur J Heart Fail. 2017;19(9):1154–63. doi:10.1002/ejhf.839.
11. Araiza-Garaygordobil D, Gopar-Nieto R, Martinez-Amezcua P, Cabello-López A, Alanis-Estrada G, Luna-Herbert A, et al. A randomized controlled trial of lung ultrasound-guided therapy in heart failure (CLUSTER-HF study). Am Heart J. 2020;227:31–9. doi:10.1016/j.ahj.2020.06.003.
12. Marini C, Fragasso G, Italia L, Sisakian H, Tufaro V, Ingallina G, et al. Lung ultrasound-guided therapy reduces acute decompensation events in chronic heart failure. Heart. 2020;106(24):1934–9. doi:10.1136/heartjnl-2019-316429.
13. Normand C, Kaye DM, Povsic TJ, Dickstein K. Beyond pharmacological treatment: an insight into therapies that target specific aspects of heart failure pathophysiology. Lancet. 2019;393(10175):1045–55. doi:10.1016/s0140-6736(18)32216-5.
14. Seferović PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(5):853–72. doi:10.1002/ejhf.1170.
15. Platz E, Lewis EF, Uno H, Peck J, Pivetta E, Merz AA, et al. Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory heart failure patients. European heart journal. 2016;37(15):1244–51. doi:10.1093/eurheartj/ehv745.
16. Price S, Platz E, Cullen L, Tavazzi G, Christ M, Cowie MR, et al. Expert consensus document: Echocardiography and lung ultrasonography for the assessment and management of acute heart failure. Nat Rev Cardiol. 2017;14(7):427–40. doi:10.1038/nrcardio.2017.56.

Figures

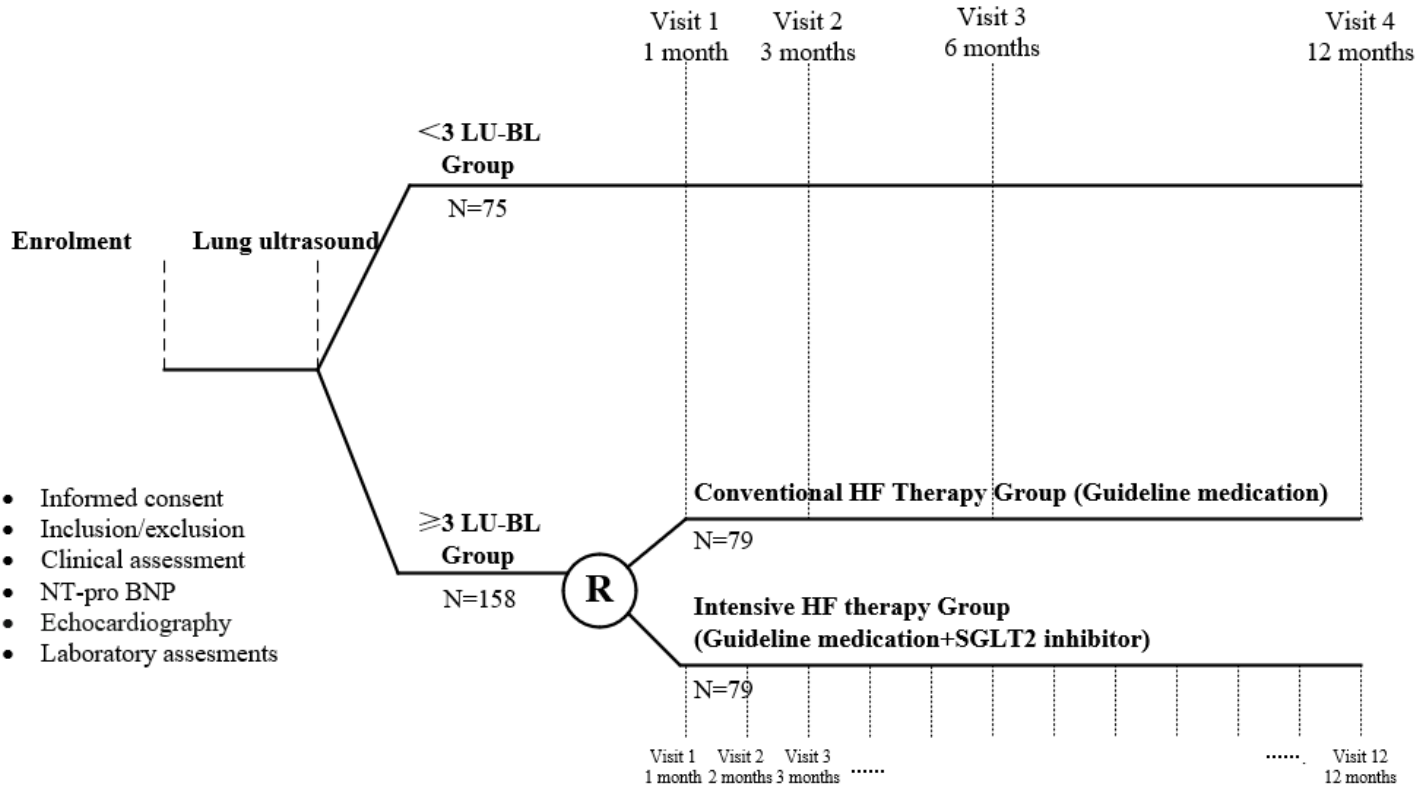

Figure 1

Flow chart of study design LU-BL=lung ultrasound detected B-lines