The Degree of the PredischARGE Pulmonary Congestion in Patients Hospitalized for Worsening Heart Failure Predicts Readmission and Mortality

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Keywords

Heart failure · Lung impedance · NT-proBNP level · Readmission · Residual pulmonary congestion

Abstract

Background: Prediction of readmission and death after hospitalization for heart failure (HF) is an unmet need. **Aim:** We evaluated the ability of clinical parameters, NT-proBNP level and noninvasive lung impedance (LI), to predict time to re-admission (TTR) and time to death (TTD). **Methods and Results:** The present study is a post hoc analysis of the IMPED-ANCE-HF extended trial comprising 290 patients with LVEF $\leq 45\%$ and New York Heart Association functional class II–IV, randomized 1:1 to LI-guided or conventional therapy. Of all patients, 206 were admitted 766 times for HF during a follow-up of 57 ± 39 months. The normal LI (NLI), representing the “dry” lung status, was calculated for each patient at study entry. The current degree of pulmonary congestion (PC) compared with its dry status was represented by $\Delta\text{LIR} =$

$([\text{measured LI/NLI}] - 1) \times 100\%$. Twenty-six parameters recorded during HF admission were used to predict TTR and TTD. To determine the parameter which mainly impacted TTR and TTD, variables were standardized, and effect size (ES) was calculated. Multivariate analysis by the Andersen-Gill model demonstrated that $\Delta\text{LIR}_{\text{admission}}$ (ES = 0.72), $\Delta\text{LIR}_{\text{discharge}}$ (ES = –3.14), group assignment (ES = 0.2), maximal troponin during HF admission (ES = 0.19), LVEF related to admission (ES = –0.22) and arterial hypertension (ES = 0.12) are independent predictors of TTR ($p < 0.01$, $\chi^2 = 1,206$). Analysis of ES showed that residual PC assessed by $\Delta\text{LIR}_{\text{discharge}}$ was the most prominent predictor of TTR. One percent improvement in predischARGE PC, assessed by $\Delta\text{LIR}_{\text{discharge}}$, was associated with a likelihood of TTR increase by 14% (hazard ratio [HR] 1.14, 95% confidence interval [CI] 1.13–1.15, $p < 0.01$) and TTD increase by 8% (HR 1.08, 95% CI 1.07–1.09, $p < 0.01$). **Conclusion:** The degree of predischARGE PC assessed by ΔLIR is the most dominant predictor of TTR and TTD.

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Introduction

Decompensated heart failure (HF) is a leading cause of rehospitalization among HF patients [1, 2]. PredischARGE pulmonary congestion (PC) seems to play a significant role in the evolution of this adverse outcome [3]. Hemodynamic monitoring, blood NT-proBNP (N-terminal probrain natriuretic peptide) levels, lung ultrasound (LUS), and lung impedance (LI) techniques have been previously proposed as alternative methods to assess PC [4–18].

In the IMPEDANCE-HF trial, 256 HF patients were either assessed clinically or by LI guidance in an outpatient setting. Assessment of the lung fluid status by the impedance device was found to be effective. Preemptive LI-guided treatment resulted in fewer HF readmissions and lower HF-associated and all-cause mortality [17]. The IMPEDANCE-HF trial was extended in order to answer the question of whether PC, assessed by LI, could improve risk stratification of readmission for HF in comparison with traditional methods. It also demonstrated that the difference between admission and discharge LI values (Δ PC), which represents the degree of improvement in PC during admission, was found to be a better predictor of clinical outcome than NT-proBNP [18]. However, some difficulties were observed with the use of Δ PC. In about 10% of patients, considerable improvement in Δ PC did not necessarily reflect effective decongestion at discharge. In addition, measuring LI during the first hours following HF admission in order to calculate Δ PC at discharge is difficult, especially if the patient is delayed in the emergency room. Therefore, we decided to evaluate Δ LIR_{discharge} that requires 1 measurement at discharge in comparison with Δ PC and other parameters measured during admission in order to select the best predictor of clinical outcome.

The aim of the present post hoc analysis of the IMPEDANCE-HF extended trial was to demonstrate that the assessment of predischARGE PC by the impedance technique may reliably predict the time to readmission (TTR) and time to death (TTD), and that Δ LIR_{discharge} is indeed a better predictor of TTR and TTD than the other parameters measured in the study. If so, Δ LIR_{discharge} could guide the therapy of HF patients during admission and help to determine timing of discharge in order to reduce readmission.

Methods

The IMPEDANCE-HF extended trial was a randomized, controlled, 2-center, single-blinded trial. Patients were eligible for participation if they were older than 18 years, with a left ventricular ejection fraction (LVEF) $\leq 45\%$ at New York Heart Association

(NYHA) functional class II–IV, and hospitalized for HF within the 12 months prior to recruitment (ClinicalTrials.gov NCT01315223). Exclusion criteria included implantation of a cardiac resynchronization device within 3 months of planned recruitment and estimated glomerular filtration rate < 30 mL/min/1.73 m². Study patients were randomized 1:1 to LI-guided or conventional therapy. Patients were followed monthly in the outpatient clinics of participating hospitals. LI values were available to the treating physicians in the LI-guided patient group but not in the control group where therapeutic decisions were based on clinical assessment only. All patients provided written informed consent.

In the event of hospitalization due to HF, vital signs, jugular vein distention and the extent of leg edema (both assessed using a 5-point scale), and level of lung rales (basilar, lower 1/3 or 1/2 lung field, or higher) were documented on admission and at discharge. In addition, oximetry, chest X-ray (CXR), NYHA class, creatinine, hemoglobin, sodium and potassium levels, the highest troponin value during admission, body mass index, as well as LI and NT-proBNP (assessed within 16 h from admission and at discharge) were also recorded.

Criteria for HF Hospitalization

The cause of hospitalization was considered to be HF related if all of the following criteria were fulfilled: (1) the primary discharge diagnosis in the medical record was acute HF; (2) clinical signs indicating worsening HF such as increased dyspnea, peripheral edema, or jugular vein distention; weight gain (≥ 1.5 kg), or a change in NYHA class were present; and (3) increased PC assessed by CXR or an increase in the admission serum NT-proBNP versus the previous level. The event of all-cause death at home was accounted for in the TTD analysis. If the cause for admission or death was unclear, adjudication of the diagnosis (by chart review) was carried out by 2 independent cardiologists.

LI Measurements

The noninvasive impedance device (CardioSet Company, Tel Aviv, Israel) was used in this study to assess the lung fluid content. The normal “dry” LI (NLI) corresponding to normal lung fluid content for each patient was determined by a previously reported method [16], whose accuracy was validated by comparison with CXR ($r = 0.92$, $p < 0.01$ between NYHA-related LI and CXR) [16]. Calculated NLI was used to compute the Δ LIR = $([\text{measured LI}/\text{NLI}] - 1) \times 100\%$. Δ LIR represents the degree of instantaneous lung congestion compared to the normal lung fluid state. When pulmonary fluid content exceeds the normal level, the electrical resistance of the lung tissue decreases, and LI values decrease to lower levels than NLI, presenting Δ LIR as negative.

Statistical Analysis

Continuous variables are presented as means $\pm$ SD if normally distributed according to the Kolmogorov-Smirnov and visual inspection tests or as medians and interquartile ranges if not. Categorical variables were analyzed by χ^2 (Fisher) tests. Twenty-six variables recorded in the study were used for TTR and TTD analysis. Multivariate forward stepwise analysis utilized the Andersen-Gill modification of Cox regression analysis adopted for recurrent events with entrance criterion in the forward selection model when $p = 0.05$ and $p = 0.15$ for removal. Variables (x_i^*) were standardized using mean (m) and standard deviation (sd) for reaching comparability of effect size (ES) of the different parameters as follows:

Fig. 1. Study flowchart.

$x_i^* = (x_i - m)/sd$. Because of nonlinearity, NT-proBNP variables were logarithmically transformed. Adjusted hazard ratio (HR) and 95% confidence intervals (CI) for postdischarge outcomes in study patients were calculated by LI and NT-proBNP level quartiles. Receiver-operating characteristic (ROC) curves were used to assess the discriminative capability of LI and NT-proBNP to predict clinical outcome. A value of $p < 0.05$ was considered significant. The SPSS 21.0 statistical package, StatSoft Inc. (version 12) and the MedCalc statistical software (version 14.8.1) were used for statistical analysis.

Results

Two hundred and ninety HF patients participating in the IMPEDANCE-HF extended trial were randomized 1:1 to the LI-guided and control groups. The follow-up period of study patients was 57.2 ± 39 months. Of the 290 patients participating in the study, 84 were not hospitalized for HF, and 206 patients were admitted 766 times due to HF exacerbation (Fig. 1). During the follow-up, 155 patients died; 85 patients (55%) died due to HF. For 634 HF hospitalizations, 153 all-cause deaths, and 85 HF-associated deaths, details were available for multivariate analysis required for the formulation of the model to predict TTR and TTD (Fig. 1). Table 1 presents demographic, clinical, and laboratory data of the study population. The impedance, clinical, and lab-

oratory parameters related to HF admissions are shown in Table 2.

Seventy-eight patients in the LI-guided group completed the study follow-up (70.9 ± 41 months) while 67 in this group died during follow-up (49.9 ± 33 months), with an overall follow-up period in the LI-guided group of 61.2 ± 40 months. In the control group, the mean follow-up of 56 patients that remained alive at study completion lasted 70.5 ± 38 months while it was 42.3 ± 38.1 months in those who died during the follow-up, with an overall follow-up of 53.2 ± 40.5 months ($p < 0.01$ vs. LI group).

Univariate analysis of the association between the 26 variables recorded during HF admissions found 8 variables to be significantly related to TTR (online suppl. Table 1; see www.karger.com/doi/10.1159/000510073 for all online suppl. material).

Multivariate analysis revealed that only 6 variables independently predict TTR (Table 3). After standardization of all variables, $\Delta LIR_{\text{discharge}}$ was found as the dominant predictor of TTR with an ES coefficient equal to 3.14, whereas ES of the other independent predictors varied between 0.12 and 0.72 (online suppl. Table 2). For $\Delta LIR_{\text{discharge}}$ alone, χ^2 was 1,062 ($p < 0.01$), while the 6-variable model yielded a χ^2 of 1,206 ($p < 0.01$). A 1% decrease in $\Delta LIR_{\text{discharge}}$ was also associated with a 14% probability increase in TTR (HR 0.86, $p < 0.01$). The degree of PC on admission ($\Delta LIR_{\text{admission}}$) was the second

Table 1. Patient characteristics

Variables	Study entry (<i>n</i> = 290)	First admission for HF (<i>n</i> = 206)
Age, years	68.2±9.9	69.8±10.7
Male, %	86	84
Left ventricular ejection fraction (IQR), %	30 (25–35)	30 (14–35)
NYHA class, %		
II	46	30
III	32	65
IV	22	5
Ischemic etiology, %	75	80
S/P coronary artery bypass graft, %	19	25
Atrial fibrillation/flutter, %	26	34
Diabetes mellitus, %	52	61
Hypertension, %	75	76
Hyperlipidemia, %	79	80
Chronic lung disease/bronchial asthma, %	5	4
Chronic renal failure, %	35	36
Smoking, %	39	40
Implantable cardioverter defibrillator, <i>n</i> (%)	83 (29)	62 (30)
CRT-D, <i>n</i> (%)	107 (40)	84 (41)
Medication		
ACEI or ARB, %	96	96
β-Blockers, %	92	92
Mineralocorticoid receptor antagonist, %	74	73
Nitrates, %	42	43
Statin, %	91	90
Aspirin, %	80	80
Digoxin, %	35	36
Diuretics %	97	100
Furosemide equivalent dose, mg/day	103	117
Body mass index, kg/m ²	29.2±4.1	29.3±5.1
Systolic blood pressure, mm Hg	128±18	125±17
JVD ¹	0.8±0.7	1.6±1.2
Dyspnea on admission, %	93	95
Estimated glomerular filtration rate, mL/min/1.73 m ²	61.2±18.9	58.5±17.8

IQR, interquartile range; *n*, number of events; HF, heart failure; NYHA, New York Heart Association; CRT-D, cardiac resynchronization therapy-defibrillator; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; S/P, status post. ¹ Jugular vein distention (JVD), 5-point scale: JVD = 0, means there is no JVD >2 cm above the sternal notch; 4, maximal distention.

most significant predictor of TTR (Table 3; online suppl. Table 2) with ES coefficient = 0.72. $\Delta PC = (\Delta LIR_{\text{admission}} - \text{discharge})$, which reflects the improvement in PC during admission, was not found to independently predict TTR.

Univariate analysis of the association between the evaluated parameters and TTD demonstrated that 5 parameters significantly impacted on TTD (online suppl. Table 3). Adjusted multivariate analysis of the variables evaluated as predictors of TTD demonstrated that 8 variables are independent predictors of TTD (Table 3). The

most powerful predictor was $\Delta LIR_{\text{discharge}}$ ($p < 0.01$) according to standardized variable analysis (online suppl. Table 4). A 1% decrease in residual congestion at discharge corresponded to a likely increase in TTD by 8% (HR 1.08, 95% CI 1.07–1.09, $p < 0.01$).

Discharge ΔLIR and NT-proBNP as Predictors of Outcome

The values of $\Delta LIR_{\text{discharge}}$ and log NT-proBNP_{discharge} were stratified by quartiles (Table 2). TTR stratified by $\Delta LIR_{\text{discharge}}$ and log NT-proBNP_{discharge} quartiles dem-

Table 2. Parameters of patients ($n = 206$) hospitalized for heart failure (HF)

Age at HF discharge, years	72.3±11.2
Left ventricular ejection fraction related to HF admission	26.7±6.3%
$\Delta\text{LIR}_{\text{admission}}/\Delta\text{LIR}_{\text{discharge}}$	-46.5±8.6/-32.9±13.4%
$\Delta\text{LIR}_{\text{discharge}}$	
Quartile 1	0 to -21.7%
Quartile 2	-21.8 to -32.2%
Quartile 3	-32.3 to -41.1%
Quartile 4	-41.2 to -73.0%
Median NT-proBNP (IQR), pg/mL	
On admission	11,467 (8,930–14,700)
At discharge	6,800 (4,784–9,200)
NT-proBNP _{discharge}	
Quartile 1	<4,789
Quartile 2	4,790–6,800
Quartile 3	6,801–9,200
Quartile 4	>9,200
Median NYHA (IQR)	
On admission	4.0 (3.0–4.0)
At discharge	3.0 (2.0–3.0)
Median jugular vein distention (IQR)	
On admission	3.0 (2.0–3.0)
At discharge	2.0 (1.0–3.0)
Length of hospital stay, days	5.2±3.9
Creatinine _{admission/discharge} , mg/dL	1.6±0.6/1.7±0.7
Hemoglobin _{discharge} , g/dL	12.1±1.6
Sodium _{discharge} , mmol/L	138.0±4.0
Potassium _{discharge} , mmol/L	4.4±0.6
Troponin (highest value during HF admission), ng/mL	69±66
Post-HF discharge 30-day/1-year rate of HF readmission, %	33/79
Distribution according quartiles 1–4 of ΔLIR , %	
30-day HF readmission	0:3:29:68
1-year HF readmission	4:30:32:34
30-day HF death	0:0:0:100
1-year HF death	3:23:26:48
30-day all-cause death	0:0:0:100
1-year all-cause death	6:28:27:39
Distribution according quartiles 1–4 of NT-proBNP, %	
30-day HF readmission	3:8:23:66
1-year HF readmission	16:19:27:38
30-day HF death	0:8:19:73
1-year HF death	8:17:29:46
30-day all-cause death	3:18:18:61
1-year all-cause death	14:23:27:36
Post-HF discharge 30-day/1-year rate of HF death, %	4:10
Furosemide dose/day of hospital stay, mg	122±28

ΔLIR , lung impedance ratio; NT-proBNP, N-terminal probrain natriuretic peptide.

onstrated a strong association between the degree of PC at discharge and TTR (Fig. 2; $p < 0.01$).

The probability of HF readmission and of all-cause mortality within 30 days/1 year was compared between patients who achieved optimal decongestion (Q_1) and those discharged with mild, moderate, and moderate-to-

severe residual congestion (Q_{2-4}). This analysis indicated that residual PC assessed by $\Delta\text{LIR}_{\text{discharge}}$ and log NT-proBNP_{discharge} is a strong predictor of TTR and TTD (Fig. 3a–d).

ROC analysis assessing the accuracy of $\Delta\text{LIR}_{\text{discharge}}$ to predict rehospitalizations yielded an AUC of 0.93 for 30-

Fig. 2. Time to heart failure readmission: assessment of the pulmonary congestion at discharge by lung impedance (Δ LIR) compared with log NT-proBNP allows better discrimination of the times to readmission.

Table 3. Multivariate stepwise models predicting unplanned heart failure (HF) hospitalizations and all-cause death

Impact of independent variables in multivariate stepwise models	HR	95% CI	χ^2
Likelihood of TTR prolongation ($n = 634$)			
LI-guided vs. control group	1.22	1.06–1.42	7.15
Δ LIR _{admission} (decrease of 1%)	1.06	1.05–1.08	104
Δ LIR _{discharge} (decrease of 1%)	1.14	1.13–1.15	1,062
Maximal troponin (decrease of 100 ng/ml)	6.81	2.90–16.3	19.3
Left ventricular ejection fraction (increase of 1%)	1.02	1.01–1.03	8.7
Arterial hypertension (absent)	1.23	1.03–1.48	5.0
Likelihood of TTD prolongation ($n = 153$)			
Age (decrease of 1 year)	1.03	1.01–1.05	12.5
Δ LIR _{discharge} (decrease of 1%)	1.08	1.07–1.09	134
log NT-proBNP _{admission} – discharge (increase of 1 unit)	1.72	1.08–2.86	4.70
JVD _{admission} – JVD _{discharge} (increase of 1 point)	1.39	1.08–1.79	6.10
Creatinine _{admission} (decrease of 0.1 mg/dL)	1.38	1.10–1.72	7.90
Maximal troponin (decrease of 100 ng/mL)	11.5	1.39–94.9	5.12
Na _{discharge} (increase of 1 mmol/L)	1.04	1.01–1.08	5.59
Left ventricular ejection fraction (increase of 1%)	1.03	1.01–1.06	4.86

TTR, time to readmission; TTD, time to death; χ^2 , chi square test; n , the number of events; CI, confidence interval. Other abbreviations as in Tables 1 and 2. All hazard ratios (HR) are statistically significant, $p < 0.03$.

day readmissions due to HF and 0.97 for 1-year readmissions. Levels of log NT-proBNP_{discharge} for prediction of HF readmission yielded AUC values of 0.68 and 0.62 for the 30-day and 1-year readmission, respectively (Fig. 4a, b). The AUC for 30-day all-cause mortality was 0.90 by the Δ LIR_{discharge} and 0.80 for log NT-proBNP_{discharge}, and

the AUC for the 1-year all-cause mortality was 0.89 and 0.73 for Δ LIR_{discharge} and log NT-proBNP_{discharge}, respectively (Fig. 4c, d). PC assessed by Δ LIR_{discharge} was found to be a better predictor of TTR and TTD than NT-proBNP_{discharge} at all time points ($p < 0.05$).

Fig. 3. Event-free 30-day and 1-year heart failure (HF) readmission and all-cause mortality stratified by lung impedance ratio (ΔLIR) and NT-proBNP quartiles (Q1–Q4). **a** Risk of HF readmission stratified by ΔLIR . Hazard ratio (HR) and 95% confidence interval (CI). Q2/Q1: 7.1 (5.7–8.8), $p < 0.01$; Q3/Q1: 28.1 (22.5–35.2), $p < 0.01$; Q4/Q1: 66.4 (50.3–87.5), $p < 0.01$. **b** Risk of HF readmission stratified by NT-proBNP. Q2/Q1: 1.3 (0.9–1.7), $p = 0.15$; Q3/Q1:

2.5 (1.7–3.5), $p < 0.01$; Q4/Q1: 22 (12–40), $p < 0.01$. **c** Risk of all-cause death stratified by ΔLIR . Q2/Q1: 3.1 (2.1–4.7), $p < 0.01$; Q3/Q1: 8.5 (5.4–13.4), $p < 0.01$; Q4/Q1: 37.7 (23.2–61.1), $p < 0.01$. **d** Risk of all-cause death stratified by NT-proBNP. Q2/Q1: 1.5 (0.9–2.4), $p = 0.12$; Q3/Q1: 2.1 (1.2–3.5), $p < 0.01$; Q4/Q1: 15.6 (7.5–32), $p < 0.01$.

Discussion

Using multivariate stepwise analysis of data from the IMPEDANCE-HF extended trial, $\Delta\text{LIR}_{\text{discharge}}$ was shown to be the most prominent independent predictor of TTR and TTD while ΔPC did not predict outcome.

Prediction of readmission due to worsening HF was attempted using LUS and NT-proBNP levels [4–8, 10–12]. LUS was found to be effective in predicting short- and long-term outcome in HF patients and showed good prognostic accuracy related to HF readmissions within 180 days [7]. However, LUS is operator dependent and

expensive. NT-proBNP is the most widely used parameter for outcome stratification in HF, with the contention that the discharge NT-proBNP had the best performance in predicting 1-year mortality or HF readmissions [11]. Therefore, in the present study, it was particularly important to compare the predictive accuracy of NT-proBNP levels with the LI method. Multivariate analysis demonstrated that if discharge ΔLIR was used for risk stratification, then the NT-proBNP level was no longer an independent predictor.

This result is especially important since the noninvasive LI technique has certain potential advantages. First,

Fig. 4. a–d Receiver-operating curve analysis assessing the accuracy of the lung impedance ratio ($\Delta\text{LIR}_{\text{discharge}}$) and log NT-proBNP to predict 30-day and 1-year rehospitalizations. Prediction by $\Delta\text{LIR}_{\text{discharge}}$ is more accurate than by log NT-proBNP_{discharge}. The asterisks indicate statistically significant differences between AUC for $\Delta\text{LIR}_{\text{discharge}}$ and NT-proBNP_{discharge}.

ΔLIR directly reflects the degree of PC, which is the primary cause of HF deterioration. Second, NT-proBNP is affected by concomitant disease and physiologic stressors [19], while ΔLIR has no such interaction. Third, ΔLIR is cheap and noninvasive requiring <1 min to perform with an intra- and inter-variability of <2%.

The impedance technique has been introduced in the early 1980s and was used as a tool for measuring and monitoring PC for many years. The impedance technique is a simple method for monitoring PC, but its clinical efficacy was unproven for many years. A feasible explana-

tion is that the traditional impedance technique measured the impedance of the entire chest (transthoracic impedance), which is 10-fold larger than LI which is the signal of interest (Fig. 5). Thus, the signal from the surrounding chest wall tissue (the noise signal) masked the minor lung tissue signal and thus precluded precise assessment of the lung fluid content.

In the basic paper, noninvasive transthoracic impedance was used for risk stratification of HF decompensation [20]. This study found that the technique was effective for prediction of short-term HF deterioration but

Fig. 5. Evolution of the pulmonary edema during hospital admission.

could not predict long-term HF exacerbation. Hence, the technique enabled to differentiate between patients with high and low risk to develop HF decompensation, but it was insensitive to determine the status of the PC of the individual patient. An explanation of this finding is that the measured transthoracic impedance reflects the resistance of the entire chest which is about 10-fold larger than LI, which reflects the fluid content of the lung. The device used in the present study utilizes an algorithm that calculates the impedance of the lung parenchyma by measuring total chest wall resistance and subtracting chest wall resistance.

Via incorporating LI measurement, the algorithm of implantable pacemakers was an attempt to substitute intrathoracic fluid measurement for the relatively low sensitive transthoracic signal. However, intrathoracic impedance measurements by the implantable devices did not improve outcome or decrease HF hospitalizations and outpatient visits in HF patients [21]. Charles et al. [22] have described the reasons for the limited effectiveness of these devices. The device used in the IMPED-

ANCE-HF trial is capable of differentiating the LI signal from the noise signal and, therefore, allows more reliable assessment of lung fluid, leading to impedance-guided therapy. This may be a possible explanation of the high efficacy of the new impedance technique in the IMPED-ANCE-HF trial [17] for preventing HF readmissions and reliable assessment of predischage PC in the IMPED-ANCE-HF extended trial [18].

The practical implication of the present analysis is that measurement of ΔLIR at discharge following hospitalization for HF worsening could allocate patients into groups at low and high risk for 30-day readmission and death. The current analysis demonstrated an increased and unacceptable rate of HF readmissions and death in patients discharged with higher PC quartiles (Q_{3-4}). A feasible explanation of the large proportion of patients discharged with significant residual congestion is the absence of clinical tools to adequately assess the extent of lung fluid overload and the pressure of insurers to discharge HF patients early, or, alternatively, that patients with advanced HF may demonstrate only minimal response to medical

therapy. However, this does not indicate that more effective decongestion cannot be achieved in these patients. We found that about a third of HF patients discharged with inadequate decongestion (Q_4) achieved better decongestion during their next HF admission.

Limitations

The present study was a single-blinded, 2-center trial designed to assess the impact of LI guidance on the long-term management of patients with clinically significant HF treated in the hospital and followed-up in the outpatient clinic. Therefore, there was a potential bias in the decision of readmission in the LI-guided group. However, according to the protocol, the investigators were not involved throughout the trial in clinical decisions regarding in-hospital treatment or the timing of discharge, while patient group assignment was unknown to in-house treating physicians. Hence, crossover interaction was practically impossible and possible bias minimized. In addition, approximately 9% of all-cause hospitalizations of study patients occurred in hospitals not participating in the study, so their data were not available.

Conclusions

Of 26 variables evaluated, PC at discharge, assessed by Δ LIR, was the best predictor of TTR and TTD. Residual congestion measured by LI at discharge was associated with an increased readmission rate and death.

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Statement of Ethics

The study protocol was approved by the local IRB (HYMC-0002-13 and SOR 0284-13) and ClinicalTrials.gov NCT01315223. All patients provided written informed consent.

Conflict of Interest Statement

M.K.S. is a member of the board of directors of the CardioSet Startup Company, the manufacturer and supplier of the devices used in the trial.

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Author Contributions

M.K.S. and S.M. contributed to the conception, study design, analysis, interpretation of data, and final approval, while all other authors were involved in the interpretation of data and final approval.

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