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ORIGINAL RESEARCH ARTICLE

Prediction of readmissions and mortality in patients with heart failure: lessons from the IMPEDANCE-HF extended trial

Michael Kleiner Shochat[1]*, Marat Fudim[2], Avraham Shotan[1], David S. Blondheim[1], Mark Kazatsker[1], Iris Dahan[1], Aya Asif[1], Yoseph Rozenman[3], Ilia Kleiner[4], Jean Marc Weinstein[4], Gurusher Panjrath[5], Paul A. Sobotka[6] and Simcha R. Meisel[1]

[1]*Heart Institute, Hillel Yaffe Medical Center, PO Box 169, Hadera 38100, Israel, Rappaport School of Medicine, Technion, Haifa, Israel;* [2]*Department of Cardiology, Duke University Medical Center, Durham, NC, USA;* [3]*Cardiovascular Institute, Sackler Faculty of Medicine, Wolfson Medical Center, Holon, Tel-Aviv University, Tel-Aviv, Israel;* [4]*Cardiology Department, University Medical Center, Beer-Sheva, Israel;* [5]*Department of Medicine (Cardiology), George Washington University School of Medicine and Health Sciences, Washington, DC, USA;* [6]*Department of Cardiology, The Ohio State University, Columbus, OH, USA*

Abstract

Aims Readmissions for heart failure (HF) are a major burden. We aimed to assess whether the extent of improvement in pulmonary fluid content (ΔPC) during HF hospitalization evaluated by lung impedance (LI), or indirectly by other clinical and laboratory parameters, predicts readmissions.

Methods and results The present study is based on pre-defined secondary analysis of the IMPEDANCE-HF extended trial comprising 266 HF patients at New York Heart Association Class II–IV and left ventricular ejection fraction ≤ 35% randomized to LI-guided or conventional therapy during long-term follow-up. Lung impedance-guided patients were followed for 58 ± 36 months and the control patients for 46 ± 34 months ($P < 0.01$) accounting for 253 and 478 HF hospitalizations, respectively ($P < 0.01$). Lung impedance, N-terminal pro-brain natriuretic peptide, weight, radiological score, New York Heart Association class, lung rales, leg oedema, or jugular venous pressure were measured at admission and discharge on each hospitalization in both groups with the difference defined as ΔPC. Average LI-assessed ΔPC was 12.1% vs. 9.2%, and time to HF readmission was 659 vs. 306 days in the LI-guided and control groups, respectively ($P < 0.01$). Lung impedance-based ΔPC predicted 30 and 90 day HF readmission better than ΔPC assessed by the other variables ($P < 0.01$). The readmission rate for HF was lower if ΔPC > median compared with ΔPC ≤ median for all parameters evaluated in both study groups with the most pronounced difference predicted by LI ($P < 0.01$). Net reclassification improvement analysis showed that adding LI to the traditional clinical and laboratory parameters improved the predictive power significantly.

Conclusions The extent of ΔPC improvement, primarily the LI based, during HF-hospitalization, and study group allocation strongly predicted readmission and event-free survival time.

Keywords Heart failure; Monitoring heart failure; Lung impedance; Residual pulmonary congestion; Heart failure readmission

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**Correspondence to: Michael Kleiner Shochat, BSc, MD, PhD, FACC, Heart Institute, Hillel Yaffe Medical Center, PO Box 169, Hadera 38100, Israel. Tel: + 97239027474; Fax: + 97239015212. Email: shochat1@gmail.com*

Introduction

Readmissions due to worsening heart failure (HF) during the months following hospitalization for HF are frequent[1–4] and are influenced by residual congestion.[5] Haemodynamic monitoring was found to reduce re-hospitalizations due to recurrent HF but is invasive and expensive.[6] The ultrasound method for assessment of pulmonary congestion also seems encouraging in light of recently published data and supports the contention that residual pulmonary congestion on discharge is among the primary causes for readmissions after discharge.[5] However, this method is operator dependent and somewhat semi-quantitative. While the change in the level of blood N-terminal pro-brain natriuretic peptide (NT-proBNP) during hospitalization for HF was found to be a useful predictor of readmissions,[7] using of NT-proBNP to guide

therapy is controversial.[8,9] Finally, a promising method to monitor and assess lung fluid content is the lung impedance (LI) technique.[10–14] The recently published randomized IMPEDANCE-HF trial demonstrated the efficacy of LI-guided monitoring in the treatment of HF patients[15] and has shown that LI-guided therapy decreased hospitalizations for HF as well as HF-associated and all-cause mortality. The trial has also confirmed that a significant proportion of HF patients were discharged with residual excess pulmonary fluid.

Based on data from the IMPEDANCE-HF trial, which was extended for an additional year, we sought to evaluate the relationship between changes in pulmonary fluid content during HF hospitalization and post-discharge outcomes. We aimed to compare the accuracy of the LI-based method with other methods used to assess improvement of patients during HF hospitalization in order to predict time to next HF hospitalization and mortality.

Methods

The following analysis of the IMPEDANCE-HF extended trial was based on the data collected during the index hospitalization for HF and the clinical data from the post-hospital follow-up course. The IMPEDANCE-HF extended trial was a randomized controlled single-blinded trial of chronic systolic HF patients. Patients were eligible for participation if they were older than 18 years, had a left ventricular ejection fraction $\leq$ 35% with New York Heart Association (NYHA) functional Class II–IV, and have been hospitalized for HF within 12 months of recruitment[15] (ClinicalTrials.gov NCT01315223). The study required optimal medical therapy for HF according to current guidelines.[16] Patients had to be followed for at least 12 months. Exclusion criteria included implantation of a cardiac resynchronization device within the preceding 3 months and the presence of advanced chronic kidney disease (estimated glomerular filtration rate $<$ 25 mL/min per 1.73 m^2). All patients provided written informed consent. Half of the patients (n = 133) were assigned to the active LI-guided treatment arm where clinicians were unblinded to LI values and could base therapy on LI level during these monthly outpatient clinic visits. The medical protocol of treating LI-guided patients according to LI changes was described.[15] The other half of patient population was assigned to the control arm where LI values were recorded but not conveyed to the clinical treatment team. Hence, LI was measured in all patients at each monthly outpatient clinic visit. In the case of hospitalization, LI was recorded in all patients at admission and discharge, but this information was not conveyed to the treating physician. After discharge, patients were scheduled for an additional visit within 7–10 days. Following this visit, treatment of patients was resumed according to assignment group.

Analysis of data from the IMPEDANCE-HF trial showed that the probability of HF readmissions in the LI-guided and the control groups as assessed by LI and NT-proBNP was lower in the former, but the difference was not significant. The rate of HF hospitalizations in the groups and the number of patients at the termination of IMPEDANCE-HF trial were used to calculate sample size and period of trial extension in order to reach statistical significance. Therefore, the local institutional review board and data and safety monitoring board committees allowed to proceed with the identical treatment protocol as applied in the IMPEDANCE-HF trial for one additional year (IMPEDANCE-HF extended trial).

Inpatient study protocol

Patients hospitalized for HF underwent LI measurement within the first 16 h from admission and on discharge. Their vital signs, weight, jugular venous pressure (JVP), leg oedema (0–4 points according to the level of lower limb swelling), extent of lung rales (0—no rales, 1—basilar rales, 2—up to third of the lower lung field, 3—up to half of the lower lung field, and 4—rales beyond half of the lung field), and oximetry were recorded, and NYHA class was assessed. Chest radiographs (CXRs) were performed at hospital admission and discharge and interpreted by a radiologist and cardiologist. The 10-point radiological score (RS) was applied to assess the CXR[13] when RS = 0 signifies no congestion; RS of 1–4 represents evolving interstitial congestion; and RS in the range of 5–10 is compatible with mild, moderate, or severe alveolar oedema. Jugular venous pressure was graded according to a modified Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial scale,[17] that is, maximal level of venous pulsation above sternal angle $<$3 cm was defined as JVP = 0, a level of 3–5 cm as JVP = 1, 5–8 cm as JVP = 2, 8–11 cm as JVP = 3, and level of venous head $>$11 cm as JVP = 4. N-terminal pro-brain natriuretic peptide measurement was not an obligatory part of the protocol at the beginning of the study but was included in the protocol later during the study. N-terminal pro-brain natriuretic peptide was measured within 16 h after admission for HF and at discharge. Chest radiographs and NT-proBNP samples were used to substantiate the cause of admission, the degree of pulmonary congestion, and extent of improvement during hospitalization. Medical therapy administered during hospitalization was documented. Lung impedance was the focus of the present study; therefore, the degree of improvement in pulmonary fluid content (ΔPC) during hospitalization was defined as the difference between measured LI at admission and at discharge. Similarly, the difference between admission and discharge values of ΔNT-proBNP, weight (ΔW), ΔRS, ΔNYHA, lung rales (ΔLR), leg oedema (ΔLE), and ΔJVP were used as comparators to assess clinical improvement of patients during HF hospitalization. In despite of the fact that changes in 'clinical' parameters do not reflect directly changes in lung fluid content, the same abbreviation

(ΔPC) was used for ΔLI and for other parameters for the sake of simplicity. The ΔPC assessed by different parameters at the current HF hospitalization was utilized to calculate the predicted time only to the next HF hospitalization.

Lung impedance measurements and presentation

A non-invasive impedance device was used in this study to assess the lung fluid content. Unlike the existing impedance devices, the present device has the ability to differentiate a true signal from the lungs (positive signal) from the noise signal of surrounding chest wall, which is at least an order of magnitude larger. The sensitivity of this device to measure small accumulation of lung fluid has allowed the initiation of preemptive LI-guided treatment long before the appearance of the initial clinical signs of lung oedema and attendant deterioration.[10–14] A method to determine individual normal or 'dry' baseline LI for each HF patient has been previously reported.[14] Baseline LI for each patient was calculated upon entry to the study and was used to calculate a new parameter, the ΔLIR = [(current LI/BLI) − 1] × 100%. When pulmonary fluid content above the dry baseline is present, the electrical resistance of the lung tissue falls, and LI values are lower than BLI. In this case, the ΔLIR values are negative, and these were computed for each patient at admission for HF and at discharge.

Hospitalized patients were usually admitted and treated in the internal medicine departments of the two hospitals participating in the IMPEDANCE-HF extended trial. The decisions regarding admission and discharge, as well as the choice of treatment during hospitalization, were at the discretion of the hospital staff with no interaction or influence by the study team. The hospitalization was considered to be related to HF if the following criteria were fulfilled: (i) the main diagnosis at discharge in the medical record was HF exacerbation; (ii) the presence of clinical signs indicating worsening HF in comparison with pre-hospitalization visit such as increased dyspnoea or in the level of lung rales, the degree of JVP or leg oedema, the NYHA class (increasing by at least one NYHA class), or weight (≥1.5 kg); and (iii) increased pulmonary congestion as measured by CXR or NT-proBNP in comparison with previous findings. In the case that the cause for admission was not sufficiently clear, the decision was made by two independent cardiologists. The devices used in the study were manufactured and supplied by CardioSet Company (Tel Aviv, Israel).

Statistical analysis

The pre-defined purposes of the present analyses were (i) to find out if the degree of ΔPC during index HF hospitalization, as assessed by the different parameters, could predict time to the next HF hospitalization, as well as to HF-associated and all-cause mortality and (ii) to compare the predictive accuracy of the different parameters to identify defined outcomes.

Analyses were conducted according to intention to treat. Continuous variables were expressed as mean and standard deviation, if normally distributed according to the Kolmogorov–Smirnov and visual inspection tests, or median and interquartile range, if not conforming to a normal distribution. Comparisons between normally distributed continuous variables of two groups were performed by the two-sample *t*-test and between abnormally distributed independent continuous variables by the Mann–Whitney *U* test. Spearman method was used for calculation of correlations. Comparing of cumulative HF-related hospitalizations during the entire follow-up between groups was achieved by the Andersen–Gill model and additionally checked by using the Prentice, Williams, and Peterson model. Analysis of survival was performed by the Kaplan–Meier method (log-rank test). Analysis of time from discharge after HF-related hospitalization to the next HF hospitalization was carried out by the Andersen–Gill model. Multivariate regression analyses were used for the exploration of the predictive accuracy of different methods of pulmonary congestion assessment on the time of readmissions. Stepwise adjustment was applied to predict the time interval to the next HF readmission with standardized β coefficient, which compares the strength of the effect of each individual independent variable with the dependent variable. The continuous and categorical net reclassification improvement analysis was used to test the informational gain obtained by adding LI to predict future HF readmissions. We have applied two models to evaluate informational gain of LI. In the first model, LI was added to the parameters proved by multivariate analyses to be independent predictors of HF readmissions. In the second model, LI was added to all parameters tested in this study. The SPSS 21.0 statistical package, StatSoft Inc. (version 12.5), and R statistics version 3.2.3 were used for analysis.

Results

Baseline demographic, clinical, and laboratory data of the 266 patients randomized to the LI-guided and control groups (n = 133 each) in the IMPEDANCE-HF extended trial are presented in *Table 1*. *Figure 1* shows a flow chart of patients enrolled in the trial and details the rate and cause of hospitalizations. Lung impedance-guided patients were followed for 58 ± 36 months and the control patients for 46 ± 34 months ($P < 0.01$) accounting for 253 and 478 HF hospitalizations, respectively ($P < 0.01$). The rate of HF readmissions was similar in the IMPEDANCE-HF extended trial (39 vs. 94/per 100 patients × year, *Figure 1*) to the primary IMPEDANCE-HF trial (41 vs. 94 per 100 patients × year

Table 1 Baseline patient characteristics

Variable	All patients (n = 266)	LI-guided group (n = 133)	Control group (n = 133)
Age	67.6 ± 9.9	67.5 ± 11.7	67.7 ± 10.5
Male (%)	85	82	87
Ejection fraction, median (IQR)	30 (25–30)	30 (25–30)	30 (25–30)
NYHA functional capacity			
II (%)	47	48	46
III (%)	30	29	31
IV (%)	23	23	23
Ischaemic aetiology (%)	71	66	75
S/P coronary artery bypass graft (%)	22	17	26
Atrial fibrillation/flutter (%)	26	27	25
Diabetes mellitus (%)	52	52	53
Hypertension (%)	74	75	74
Hyperlipidaemia (%)	74	75	73
Chronic renal failure (%)	33	34	33
Smoking (%)	40	41	39
ICD, *n* (%)	83 (31)	42 (32)	41 (31)
CRT-D, *n* (%)	107 (40)	53 (40)	54 (41)
Baseline medications (at randomization)			
ACE-I or ARB (%)	96	96	96
Beta-blockers (%)	91	92	90
MRA (%)	61	65	58
Nitrates (%)	47	48	46
Statin (%)	84	86	83
Aspirin (%)	77	78	76
Digoxin (%)	36	39	33
Diuretics	95	96	95
Furosemide equivalent dose (mg/day)	97	99	95
Physical examination			
BMI (kg/m^2)	29.2 ± 4.1	29.6 ± 4.5	28.7 ± 5.2
Systolic blood pressure (mmHg)	128 ± 18	129 ± 21	127 ± 21
Heart rate (b.p.m.), median (IQR)	70 (64–79)	70 (65–81)	70 (62–79)
JVP (grade: 0–4), median	0.8	0.8	0.8
Dyspnoea at admission (%)	92	92	93
Peripheral oedema (grade: 0–4), median	0.8	0.7	0.8
Laboratory results			
Estimate of GFR (mL/min/1.73 m^2)	62.4 ± 18.9	62.7 ± 22.7	60.2.4 ± 20.6
Urea, median (IQR)	43 (29–66)	38 (26–57)	46 (30–67)
Sodium (mg/L), median (IQR)	140 (138–142)	140 (138–142)	139 (137–141)
Potassium (mg/L), median (IQR)	4 (4–5)	4 (4–5)	4 (4–5)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRT-D, cardiac resynchronization therapy defibrillator; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; JVP, jugular vein pressure; LI, lung impedance; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

in the LI-guided and control groups, respectively). Upper respiratory tract infections, myocardial ischaemia, arrhythmias, uncontrolled hypertension, and non-adherence to medical therapy or diet were identified as the precipitating factors for deterioration of HF in two-thirds of patients in both groups.

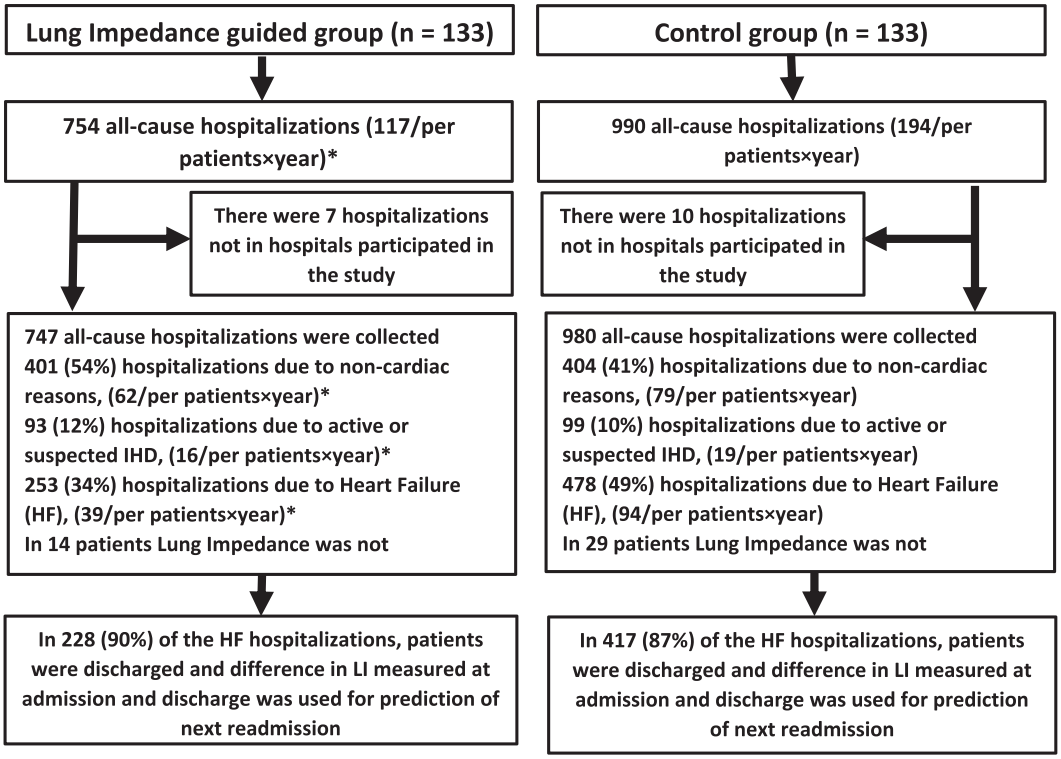
A significant difference between the cumulative risk ratio for HF readmissions of study groups during the entire follow-up period was observed (*Figure 2A*). During the study period, there were 23 and 57 HF-related deaths ($P < 0.01$) and 56 and 76 all-cause deaths ($P < 0.01$) in the LI-guided and the control groups, respectively. The rate of HF-related mortality was 3.6 per 100 patients × year in the LI-guided group and 11.1 per 100 patients × year in the control group ($P < 0.01$), while all-cause mortality was 8.7 and 14.9 per 100 patients × year ($P < 0.01$) in these groups, respectively (*Figure 2B* and *C*).

Fifty-two patients (39%) of the LI-guided group were not hospitalized for HF at all during follow-up, whereas the other 81 patients were hospitalized 253 times (one HF admission every 18.8 months). Of the latter, 228 HF-associated hospitalizations (90%) were available for analysis of predictive accuracy of future readmissions (*Figure 1*). In the control group, 37 patients (28%) were not hospitalized for HF during follow-up (P = 0.05), while 96 patients were hospitalized 478 times for HF (one HF admission every 9.2 months). Of these, 417 HF hospitalizations (87%) were available for analysis (*Figure 1*).

Readmissions for heart failure and ΔPC

Table 2 and Supporting Information, *Table S1* show the time from discharge to readmission for HF in study patients as a

Figure 1 Flow chart for the IMPEDANCE-HF extended trial. *$P < 0.01$ between lung impedance (LI)-guided and control groups. IHD, ischaemic heart disease.



function of the extent of ΔPC improvement of the different assessed variables presented by quartiles or medians. The data demonstrate that patients of both study groups were equally congested on admission regardless of the variable assessed. A finding, which was consistent for all variables of ΔPC assessment, was that larger improvements in ΔPC led to longer delays to next readmission. *Table 3* and Supporting Information, *Table S2* show the readmission rate at different intervals of time after HF hospitalization according to quartiles or medians of ΔPC improvement. Decongestion during

Figure 2 (A) Cumulative incidence of hospitalizations due to heart failure (HF, by Anderson–Gil Model). (B) The Kaplan–Meier curve of HF-associated mortality. (C) The Kaplan–Meier curve of all-cause mortality. Hazard ratio (HR) of hospitalizations due to heart failure evaluated by Prentice, Williams, and Peterson model was 2.5 [95% confidence interval (CI): 1.2–1.8, $P < 0.0001$]. LI, lung impedance; RR, relative risk.

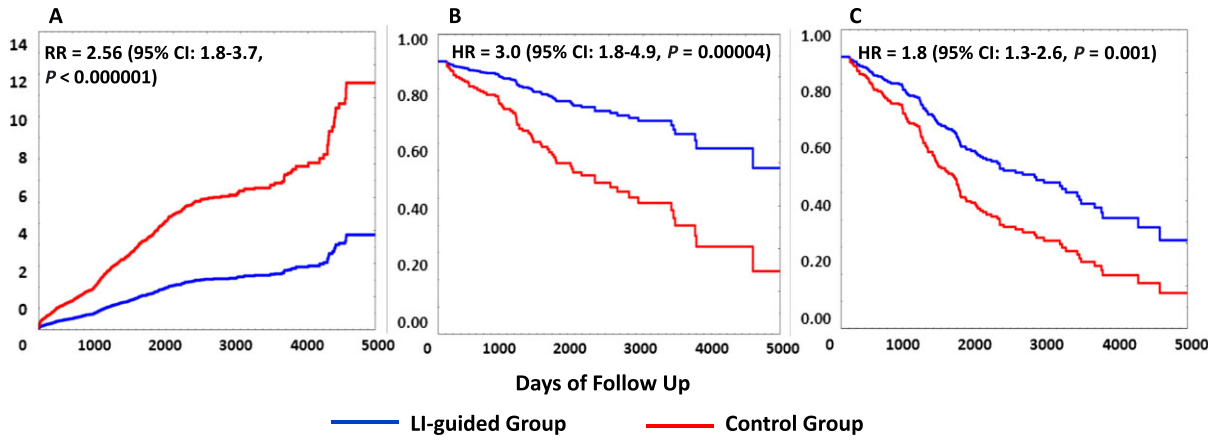


Table 2 Parameters for assessment of the pulmonary fluid content (ΔPC) improvement during HF hospitalizations and time from discharge to readmission

	LI-guided group			Control group				
		1	2		3	4		
Variable	*n*	Mean ± SD	Days to readmission	*n*	Mean ± SD	Days to readmission	*P* 1, 3	*P* 2, 4
Differences of patient's lung impedance (ΔLIR in %) between HF admission and discharge								
ΔLIR at admission	228	−44.4 ± 7.4		417	−45.1 ± 8.8		0.31	
ΔLIR at discharge	228	−32.5 ± 11.1		417	−36.0 ± 11.6		<0.01	
ΔLIR	228	12.1 ± 8.1	658 ± 903	417	9.2 ± 6.2	305 ± 581	<0.01	<0.01
Q_1: ΔLIR ≤ 4.7%	47	3.0 ± 1.2	16 ± 30	116	2.7 ± 1.4	13 ± 25	0.23	0.48
Q_2: 4.7 < ΔLIR ≤ 9.8%	55	7.7 ± 1.6	65 ± 54	107	7.0 ± 1.6	68 ± 110	<0.01	0.85
Q_3: 9.8 < ΔLIR ≤ 13.7%	48	12.8 ± 1.4	338 ± 198	114	12.2 ± 1.4	198 ± 268	0.05	<0.01
Q_4: ΔLIR > 13.7%	78	22.2 ± 5.3	992 ± 756	80	19.9 ± 3.9	541 ± 478	<0.01	<0.01
Differences of patient's NT-proBNP [ΔNT-proBNP$_{adm–dis}$ (pg/mL)] between HF admission and discharge								
NT-proBNP at admission	178	15 159 ± 100 372		320	16 497 ± 8987		0.13	
Time from admission to NT-proBNP test (h)		2.8 ± 1.9			2.7 ± 1.4		0.27	
NT-proBNP at discharge	178	7945 ± 6605		320	10 411 ± 8461		<0.01	
ΔNT-proBNP	178	7511 ± 7677	398 ± 711	320	6117 ± 5352	246 ± 506	<0.01	<0.05
ΔNT-proBNP ≤ median	90	1906 ± 1282	356 ± 742	186	2020 ± 1351	96 ± 220	0.5	<0.01
ΔNT-proBNP > median	88	13 811 ± 6419	448 ± 636	134	9739 ± 4920	380 ± 637	<0.01	0.45
ΔNT-proBNP ≤ 50%	98	2537 ± 2896	304 ± 755	153	3826 ± 3540	57 ± 104	<0.01	<0.01
ΔNT-proBNP > 50%	80	12 233 ± 7379	503 ± 648	167	9372 ± 5649	506 ± 693	<0.01	0.97

HF, heart failure; LI, lung impedance; ΔLIR, lung impedance ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q_1–Q_4, quartiles 1–4: $0 \le Q_1 \le$ 25th percentile, $25 < Q_2 \le$ 50th percentile, $50 < Q_3 \le$ 75th percentile, and $Q_4 >$ 75th percentile; SD, standard deviation.

HF admissions as evaluated by changes in all assessed variables was a significant predictor for readmissions in both groups ($P < 0.01$).

Discharge with minimal or small improvement in lung fluid content [($Q_1 + Q_2$) or ≤median] conferred a high risk for readmission in both groups, especially during the first 30 and 90 days after the index hospitalization (*Table 3* and Supporting Information, *Table S2*). In contrast, those who achieved moderate or large improvement in ΔPC [($Q_3 + Q_4$) or >median] on discharge, regardless of the method used to demonstrate this change, were readmitted less frequently ($P < 0.01$). Assignment to the LI-guided group resulted in a

Table 3 Frequencies of HF readmissions at different time intervals as a function of pulmonary fluid content (ΔPC) improvement between admission and discharge

Variable	Group	Readmissions (0–30 days)	Readmissions (31–90 days)	Readmissions (91–365 days)	Readmissions till the end of FU	*P* within group
		n of readmissions/*n* of discharges on corresponding quartiles/medians				
Rate of HF readmissions as a function of lung impedance improvement (ΔLIR)						
Q_1: ΔLIR ≤ 4.7%	LI-guided	42/47 (89%)	3/47 (7%)	2/47 (4%)	0/47 (0%)	<0.01
	Control	112/116 (97%)	3/116 (3%)	1/116 (1%)	0/116 (0%)	<0.01
Q_2: 4.7% < ΔLIR ≤ 9.8%	LI-guided	19/55 (35%)	25/55 (45%)	11/55 (20%)*	0/55 (0%)	<0.01
	Control	50/107 (47%)	48/107 (45%)	9/107 (8%)	0/107 (0%)	<0.01
Q_3: 9.8% < ΔLIR ≤ 13.7%	LI-guided	2/48 (4%)	1/48 (2%)	26/48 (54%)	7/48 (15%)	<0.01
	Control	7/114 (6%)	33/114 (29%)	62/114 (54%)	12/114 (11%)	<0.01
Q_4: ΔLIR > 13.7%	LI-guided	0/78 (0%)	1/78 (1%)	12/78 (15%)*	55/78 (71%)*	<0.01
	Control	3/80 (4%)	6/80 (7%)	29/80 (36%)	42/80 (53%)	<0.01
Rate of HF readmissions as a function of ΔNT-proBNP (pg/mL) improvement						
ΔNT-proBNP ≤ median	LI-guided	39/90 (43%)	21/90 (23%)	22/90 (24%)	8/90 (9%)	<0.01
Median = 4500	Control	83/186 (45%)	35/186 (19%)	25/186 (13%)	9/186 (5%)	<0.01
ΔNT-proBNP > median	LI-guided	13/88 (15%)	11/88 (13%)	21/88 (24%)	29/88 (33%)	<0.01
	Control	32/134 (24%)	31/134 (23%)	29/134 (22%)	42/134 (31%)	<0.01
ΔNT-proBNP improvement ≤ 50%	LI-guided	43/98 (44%)*	20/98 (20%)	12/98 (12%)	9/98 (9%)*	<0.01
	Control	99/153 (65%)	35/153 (23%)	14/153 (9%)	5/153 (3%)	<0.01
ΔNT-proBNP improvement > 50%	LI-guided	8/80 (10%)	12/80 (15%)	29/80 (36%)	31/80 (39%)	<0.01
	Control	7/167 (4%)	20/167 (12%)	61/167 (37%)	46/167 (28%)	<0.01

FU, follow-up; HF, heart failure; LI, lung impedance; ΔLIR, lung impedance ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q_1–Q_4, quartiles: $0 \le Q_1 \le$ 25th percentile, $25 < Q_2 \le$ 50th percentile, $50 < Q_3 \le$ 75th percentile, and $Q_4 >$ 75th percentile.
*$P \le 0.05$, between groups for the same parameter at the same quartile or median.

shift of the readmissions to a later time point. This result was found to be consistent for all methods of ΔPC assessment but appeared most pronounced for ΔPC evaluated by LI (*Table 3* and Supporting Information, *Table S2*). *Table 4* and Supporting Information, *Table S3* present the probability of HF hospitalizations as a function of the degree in ΔPC improvement within and between groups. The discriminative accuracy of ΔPC to predict HF readmission was higher when assessed by LI and was consistently better for patients of the LI-guided group ($P < 0.01$) regardless of the method used to assess ΔPC.

The accuracy of the different methods for ΔPC calculation to predict the time interval to the next HF readmission, based on data obtained at the current HF hospitalization, was also compared by multivariate regression analysis. Age, gender, left ventricular ejection fraction, and glomerular filtration rate at the beginning of the study were also included in multivariate analyses. All variables in the LI-guided group (n = 175) and control group (n = 317) demonstrated acceptable collinearity (variance inflation factors range between 1.3 and 3.7 for different combinations of variables). Stepwise adjustment demonstrated that in the LI-guided group, only ΔLI and ΔLE could independently predict the time interval to the next HF readmission with standardized β coefficient of 0.39 for LI and 0.26 for leg oedema ($P < 0.01$). In the control group, only ΔLI and ΔNT-proBNP could predict independently the time to next HF readmission with standardized β coefficients of 0.34 and 0.17, respectively ($P < 0.01$).

ΔPC and time to heart failure readmission and mortality

Figure 3A demonstrates the probable time from discharge to the next hospitalization as a function of the degree of improvement in lung fluid content [$\Delta PC = (\Delta LIR_{admission} - \Delta LIR_{discharge})$] in both groups. It is evident that practically all patients of both groups discharged with minimal or mild degree of improvement in lung fluid content (ΔPC ≤ median) were readmitted within 4–5 months (P = 0.3). On the other hand, patients of both groups discharged with moderate and high level of pulmonary decongestion (ΔPC > median) demonstrated a low rate of readmission, which was lower in the LI-guided group than in the control group ($P < 0.01$). Conversely, patients of both groups discharged with minimal and small (ΔPC ≤ median) improvement in lung fluid status had a higher probability for HF-associated and all-cause death within 3 months after discharge compared with patients who enjoyed moderate and large improvement (ΔPC > median) in lung fluid content (*Figure 3B* and *C*). Again, time from discharge to possible death due to HF was longer in the LI-guided group than in the control group ($P \leq 0.05$).

In-hospital treatment, length of hospital stays, and readmissions

We have found no difference in the mean dosage of furosemide administered at the ED or during hospitalization per day per patient between the LI-guided and control groups. The length of hospital stay tended to be longer in the control group, but this did not reach statistical significance (5.3 vs. 5.7 days, respectively, P = 0.5).

Net reclassification improvement analyses

Net reclassification improvement analyses were performed to assess whether ΔPC measured by LI provided informational gain to predict HF admissions beyond the traditional methods of direct and indirect assessment of changes in pulmonary decongestion (*Table 5* and Supporting Information, *Table S4*). In the first model, values of ΔPC assessed by LI added significant predictive accuracy to that provided by changes in LE in the LI-guided group and to NT-proBNP dynamics in the control group. These were the only variables found by multivariate analyses to independently predict time to HF hospitalization. In the second model, LI-assessed ΔPC values were added to

Table 4 Probability of HF readmissions as a function of the degree in pulmonary fluid content improvement during index HF hospitalization assessed by various parameters

Variable	LI-guided group		Control group		Control (c)/LI-guided (g) groups HR and P values between groups
	HR	P inside group	HR	P inside group	
Risk of HF readmission assessed by changes in lung impedance (ΔLIR) between admission and discharge					
ΔLIR: ≤median vs. >median	21.4	<0.01	16.0	<0.01	ΔLIR: $\leq M_c/\leq M_g$, HR = 1.4, P = 0.05 ΔLIR: $>M_c/>M_g$, HR = 2.0, $P < 0.01$
Risk of HF readmission assessed by changes in NT-proBNP (ΔNT-proBNP) between admission and discharge					
ΔNT-proBNP: ≤median vs. >median	1.7	0.06	3.7	<0.01	ΔNT-proBNP: $\leq M_c/\leq M_g$, HR = 3.2, $P < 0.01$ ΔNT-proBNP: $>M_c/>M_g$, HR = 2.9, $P < 0.01$
ΔNT-proBNP: ≤50% vs. >50%	2.6	<0.01	8.2	<0.01	$\Delta NT\text{-proBNP}_{imp}$: $\leq 50\%_c/\leq 50\%_g$, HR = 2.4, $P < 0.01$ $\Delta NT\text{-proBNP}_{imp}$: $>50\%_c/>50\%_g$, HR = 1.1, P = 0.63

CI, confidence interval; HF, heart failure; HR, hazard ratio; LI, lung impedance; ΔLIR, lung impedance ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Figure 3 (A) Event-free survival after admission for worsening heart failure (HF) according to mean improvement of pulmonary fluid content (ΔPC), assessed by lung impedance (LI). The hazard ratio (HR) of the LI-guided patients with ΔPC ≤ median for admission due to recurrent HF was 22.1 [95% confidence interval (CI): 13.8–35.1, $P < 0.01$] compared with that of the LI-guided patients with ΔPC > median. The HR of the control group with ΔPC ≤ median to experience re-hospitalization for HF was 31.2 (95% CI: 20.0–48.8, $P < 0.01$) higher than that of the control group with ΔPC > median, and that of the control group with ΔPC > median was 2.0 (95% CI: 1.3–3.3, $P < 0.01$) higher than that of the LI-guided group ΔPC > median. (B) Survival from HF-associated death after admission for worsening HF according to mean ΔPC, assessed by LI. The HR of the LI-guided patients with ΔPC ≤ median of HF death was 27.7 (95% CI: 10.2–75.1, $P < 0.01$) compared with that of the LI-guided patients with ΔPC > median. The HR of the control group with ΔPC ≤ median for HF-associated death was 34.6-fold (95% CI: 13.7–87.4, $P < 0.01$) higher than that of the LI-guided group with ΔPC > median, and that of the control group with ΔPC > median was 2.7 (95% CI: 1.1–5.6, $P = 0.05$) higher than that of the LI-guided group ΔPC > median. (C) Survival from all-cause death of patients discharged following admission due to HF according to mean improvement in ΔPC as assessed by LI. The HR of all-cause mortality of the LI-guided group with ΔPC ≤ median compared with that of the LI-guided group with ΔPC > median was 14.1 (95% CI: 7.0–28.4, $P < 0.01$), whereas the HR of the control group with ΔPC ≤ median and that of the control group with ΔPC > median were 12.6 (95% CI: 6.6–24.2, $P < 0.01$) and 1.2 (95% CI: 0.7–2.1, $P = 0.13$) higher, respectively, than that of the LI-guided group ΔPC > median. In all analyses, the LI-guided group with the ΔPC > median was used as a reference group.

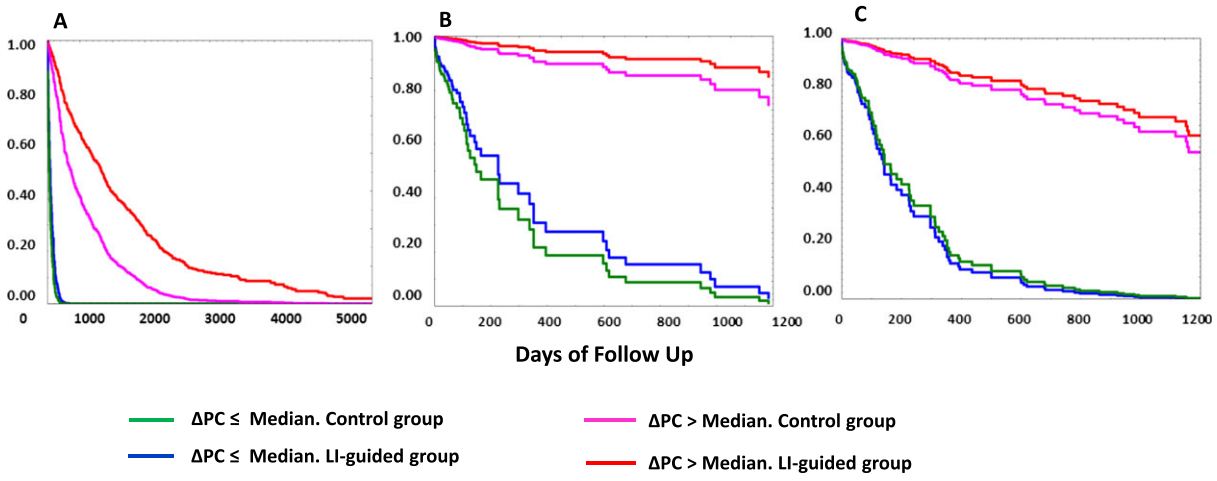


Table 5 Impact of LI on prediction of HF readmissions calculated by NRI and IDI

Name of index	30 day readmissions			90 day readmissions		
	Index	95% CI	*P*-value	Index	95% CI	*P*-value
LI-guided group: Model A. LI added to leg oedema (continues variables were used for analyses)						
NRI	1.52	1.34–1.69	<0.0001	0.38	0.05–0.71	0.026
NRI for events (1–3)	0.85	0.72–0.98	<0.0001	0.32	0.01–0.62	0.040
NRI for non-events (2–4)	0.67	0.56–0.78	<0.0001	0.06	−0.08 to 0.21	0.383
IDI	0.50	0.43–0.57	<0.0001	0.02	0.01–0.04	0.005
LI-guided group: Model A. LI added to leg oedema (variables were grouped in category for analyses)						
NRI	1.30	1.07–1.53	<0.0001	0.67	0.42–0.93	<0.0001
NRI for events (1–3)	0.56	0.35–0.76	<0.0001	0.74	0.52–0.95	<0.0001
NRI for non-events (2–4)	0.74	0.64–0.85	<0.0001	−0.06	−0.21 to 0.08	0.380
IDI	0.47	0.40–0.55	<0.0001	0.02	0.01–0.03	0.027
Control group: Model A. LI added to NT-proBNP (continues variables were used for analyses)						
NRI	1.09	0.90–1.27	<0.0001	0.48	0.32–0.65	<0.0001
NRI for events (1–3)	0.65	0.51–0.79	<0.0001	0.88	0.76–0.99	<0.0001
NRI for non-events (2–4)	0.44	0.31–0.56	<0.0001	−0.39	−0.51 to 0.28	<0.0001
IDI	0.22	0.17–0.26	<0.0001	0.01	0.0001–0.001	0.041
Control group: Model A. LI added to NT-proBNP (variables were grouped in category for analyses)						
NRI	1.15	0.96–1.34	<0.0001	0.41	0.15–0.67	0.0017
NRI for events (1–3)	0.33	0.16–0.50	0.0002	0.36	0.14–0.59	<0.0015
NRI for non-events (2–4)	0.88	0.74–0.90	<0.0001	0.05	−0.08 to 0.17	0.45
IDI	0.29	0.24–0.34	<0.0001	0.01	−0.01 to 0.01	0.13

The corrected *P* value for the seven different variables used in the analysis is 0.0071. Categorical variables used for calculation: changes in LI during HF admission (Q_1 vs. Q_4) and changes in NT-proBNP during HF admission (NT-proBNP ≤ 50% vs. >50%).
CI, confidence interval; IDI, integrated discrimination improvement; LI, lung impedance; LIR, lung impedance ratio; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-brain natriuretic peptide.

ΔPC values obtained by measuring changes during admission of NT-proBNP, weight, RS, NYHA, LR, LE, and JVP. Using LI in addition to traditional parameters for assessment of pulmonary decongestion improved informational gain of 30 and 90 day HF admissions in both groups by more than 100% ($P < 0.01$, *Table 5* and Supporting Information, *Table S4*).

Discussion

The present study was a pre-specified secondary analysis of the IMPEDANCE-HF extended trial. We found that in both study groups, the extent of the pulmonary fluid content decrease during hospitalization for worsening HF, as assessed by LI, demonstrated a higher predictive accuracy for next readmission than all other clinical variables.

The results of the present study show that about half of all patients hospitalized for HF are discharged with only minor or mild improvement in pulmonary fluid content (ΔPC ≤ median). In other words, they are discharged with considerable residual pulmonary fluid content as assessed by the variables used in this study. ΔPC assessed by LI showed that patients discharged with only a minimal (Q_1) or mild (Q_2) decrease in their pulmonary fluid content had a 94% and 43% probability of being readmitted within 30 days.

Study groups were well matched on entry to the study, but the follow-up period was 25% longer in the LI-guided group who achieved better lung fluid reduction during HF hospitalizations. The longer follow-up period in the LI-guided group could be explained by the better survival in this group. Mean ΔLIR measured at all visits during entire follow-up in both study groups showed that the LI-guided patients were consistently less congested by about 20% ($P < 0.01$). Decreased lung fluid content in the LI-guided group was likely the result of available information regarding lung fluid status of the patients, which was associated with 47% fewer hospitalizations than in control patients. The mean overall NYHA for all clinic visits during the entire follow-up was 2.0 for the LI-guided group compared with 2.3 for the control group ($P < 0.01$). This, again, attests to better decongestive therapy in the LI-guided patients and may explain their improved clinical outcome. More outpatient clinic visits per month were recorded in the LI-guided group than in the control group, but this difference was insignificant (4%, $P = 0.35$) and cannot account for the better clinical outcome in the former.

The degree of the pulmonary congestion at HF admission, as assessed by all parameters, was practically the same, but the extent of improvement in congestion (ΔPC) was more prominent in the LI-guided group. This finding is important especially in light of the fact that all parameters were registered at admission and discharge, but the study physicians and treating physicians were blinded to results. The main objective of the IMPEDANCE-HF extended trial was to prove that LI-guided treatment of HF patients in the outpatient clinic could reduce HF readmissions. Therefore, we wanted to exclude any effect of study team on in-hospital treatment. Therefore, at the stage of study protocol development, it was decided to keep in hospital treatment independent of accessed parameters. The larger improvement in lung fluid content in LI-guided group could be explained by fact that patients of LI-guided group were less sick during the whole period of follow-up. In the LI-guided group, there was a lower incidence of HF hospitalizations, which feasibly resulted in less myocardial micro-damage, less pulmonary congestion, and better NYHA class throughout the follow-up period. This, with some reservations, may lead to the conclusion that patients of LI-guided group were less sick during monitoring period. Additionally, it is important to emphasize that comparison of patients of the LI-guided and control groups discharged with the same level of decongestion (Q_1, Q_2, Q_3, or Q_4 of LI-guided vs. respective control subgroups) has shown that time to readmission was practically the same at the Q_1 and Q_2 levels of improvement but significantly better in the LI-guided for Q_3 and Q_4 subgroups. This demonstrates that small improvement in pulmonary decongestion does not allow LI-guiding monitoring to confer any beneficial effect on HF admissions. In contrast, discharge of patients with Q_3 and Q_4 level of decongestion permits enough time to adjust treatment according to LI level and thus effectively prevent readmissions.

The population presently studied was similar to that of other contemporary HF studies[6,18–20] with regard to readmission rate, length of stay, and in-hospital mortality. In-hospital mortality was 4% in the ADHERE registry, 4.7% in the PROTECT registry,[4] 3.8% in the common cohort, and 8.6% for patients readmitted for HF between 60th and 90th days after discharge in the OPTIMIZE-HF registry,[19] 14.3% in the ESCAPE trial,[17] and 16.1% in the present study. The IMPEDANCE-HF trial differs substantially from the other studies by the longer duration of mean follow-up, which was more than 4.5 years. As far as we know, there are no reports relating the extent of pulmonary decongestion during HF hospitalizations to readmission rate. Maggioni *et al*.[21] using clinical assessment only found that 25% of HF patients showed at discharge signs or symptoms of peripheral and/or pulmonary congestion. The lung impedance method is probably more sensitive than clinical assessment of pulmonary congestion[12,22]; hence, we can assume that the incidence of residual pulmonary fluid detected by the lung impedance method would be even higher. In the present study, we obtained a ΔLIR mean value of −30% at discharge in the ΔPC ≤ median subgroup, representing significant residual congestion, and mean ΔLIR = −20% in the ΔPC > median subgroup when ΔLIR = 0 corresponds to the normal baseline condition. Previously, we have shown that a ΔLIR value of −30% is compatible

with mild to moderate alveolar oedema, while a value of −20% corresponds to mild–moderate interstitial congestion.[13,14] This explains the absence of rales on lung auscultation at discharge in 52% of patients in the present study, at a time when lung impedance and the chest radiograph demonstrate interstitial congestion.[12,13] Only 10% of ΔPC > median subgroup patients were discharged with an acceptable level of, or with no pulmonary congestion at all, that is, ΔLIR > −18%, defined previously as the threshold level.[15]

Comparison of the different methods of in-hospital improvement

In this study, we evaluated changes in the functional NYHA class, LR, LE, and JVP as physical signs, weight, RS, and NT-proBNP as a biochemical marker, and LI as markers of lung decongestion. We found that all clinical parameters could contribute to the prediction of HF readmission, but the assessment was operator dependent with considerable inter-observer variability and with a relatively weak predictive power. Changes in patient weight during HF hospitalization indicated increased probability for HF readmission. The mean weight decrease during HF hospitalization was 2.7 kg in the LI-guided group and 2.5 kg in the control group ($P < 0.01$), respectively, nearly the same as observed in the ASCEND-HF trial.[20] The radiological score was found to be a very useful tool to predict HF hospitalization. To the best of our knowledge, there are no reports on the use of the CXR to assess the risk of HF readmission. However, the radiation burden and lack of agreement among physicians treating HF patients regarding the radiological score may impede the widespread use of this method. The usefulness of NT-proBNP measurements during index HF admission for risk stratification of readmissions was already investigated.[7] In our study, we found that insufficient decrease of NT-proBNP level at discharge compared with its admission value is a useful predictor of readmission. NT-proBNP decreased by more than 50% during hospitalization in more than 42% of patients. Noveanu *et al*.[23] measured an NT-proBNP decrease of more than 50% in 67% of patients during HF admissions but could not use this for prediction of readmissions. The predictive accuracy for HF readmissions assessed by NT-proBNP was weaker than that for LI (*Table 4* and Supporting Information, *Table S3*). Therefore, it is not surprising that multivariate regression analysis has shown that changes in NT-proBNP are not predictive in the LI-guided group and only borderline predictive in the control group. Net reclassification improvement analyses shown that using LI in addition to the classical clinical and laboratory parameters for predicting HF readmissions improved informational gain by more than 100%.

Impedance techniques

Traditional impedance techniques measure the conductivity of the whole chest, whereas the impedance of the lung is only a small component (near 10–15%) of this resistance,[8,15] and the remainder is that of the chest wall impedance. Therefore, traditional techniques are not sufficiently sensitive to measure small changes in lung conductivity at the pre-clinical stage of evolving pulmonary congestion. Packer *et al*.[24] have shown that the traditional impedance scheme has limited utility for identification of short-term risk of clinical deterioration. Pacemaker-based devices were also found to be too insensitive to allow detection of small shifts in pulmonary fluid content in evolving HF.[25] The physical basis of the limited effectiveness of such devices was described in the work of Charles *et al*.[26]

In the present study, we used the technique that eliminates noise impedance of the chest wall and calculates the net lung impedance.[11–16] The sensitivity of this approach is sufficiently high to allow detection of the pre-clinical stage of evolving pulmonary fluid accumulation and thus permits pre-emptive adjustment of treatment in LI-guided patients.

Practical implications

According to current clinical experience, patients are usually considered for discharge after initial therapy during the first 4–5 days of hospitalization following the amelioration of symptoms as a result of the decrease in pulmonary fluid content. In the present study, as in some others, the median length of stay was only 4–4.5 days.[18–20] Current data show that only half of all patients of both groups achieve ΔPC > median level of decongestion during their hospital stay. The impedance technique used in this study elicits patients with insufficient lung fluid decongestion, and the extension of in-hospital treatment until ΔPC > median level is achieved could allow better readmission rate.

Conclusions

The extent of reduction in pulmonary fluid content during HF hospitalization as measured by lung impedance strongly predicts readmission rate and event-free survival for HF hospitalization, as well as HF-related and all-cause mortality. The extent of clinical improvement as measured by other variables used in this study also predicts readmission rates but significantly less accurately than by lung impedance. The study shows that about half of HF patients have persistently increased pulmonary fluid content at discharge and suggests the intensification of treatment until moderate-level or high-level decongestion is achieved in order to decrease 30 day readmissions.

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Conflict of interest

M.K.S. is co-founder and member of the board of directors of the CardioSet Startup Company that manufactured and supplied the devices used in the trial.

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None.

Supporting information

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

Table S1. Parameters for assessment of the pulmonary fluid content (ΔPC) improvement during Heart Failure (HF) Hospitalizations and time from discharge to readmission.

Table S2. Frequencies of Heart Failure (HF) readmissions at different time intervals as a function of pulmonary fluid content (ΔPC) improvement between admission and discharge.

Table S3. Probability of Heart Failure (HF) readmissions as a function of the degree in pulmonary fluid content improvement during index HF hospitalization assessed by various parameters.

Table S4. Impact of Lung Impedance (LI) on prediction of Heart Failure (HF) readmissions calculated by net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

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