International Journal of Cardiology 289 (2019) 91–98

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Mid-term prognostic impact of residual pulmonary congestion assessed by radiographic scoring in patients admitted for worsening heart failure

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ARTICLE INFO

Article history:
Received 29 May 2018
Received in revised form 3 December 2018
Accepted 25 January 2019
Available online 8 February 2019

ABSTRACT

Aims: Pulmonary congestion is associated with poor prognosis following hospitalization for worsening heart failure (HF), although its quantification and optimal timing during HF hospitalization remains challenging. The aim of this study was to assess the prognostic value of radiographic pulmonary congestion at admission and discharge in patients with worsening HF.

Methods and results: Clinical, echocardiographic, laboratory and chest X-ray data of 292 acute decompensated HF patients were retrospectively studied (follow-up 1 year). Lung congestion was blindly scored on chest X-ray performed at admission and discharge using a systematic 6-zone approach. Primary clinical outcome was a composite outcome of re-hospitalization for worsening HF or all cause death.

Patients were stratified according to the median of congestion score index (CSI) at both admission (median CSI (A) = 1.33) and discharge (median CSI(D) = 0.33). BNP levels, LVEF and eGFR did not differ between CSI categories. In multivariable Cox regression analysis, discharge CSI (HR for 1-point increase = 1.83 [1.02 to 3.27] p = 0.04) and discharge BNP were significantly associated with the composite outcome whereas NYHA class, physical signs, admission CSI and echocardiographic data were not. Furthermore, discharge CSI significantly increased reclassification on top of clinical covariates (continuous NRI = 19.6% [4.0 to 30.0] p = 0.03 and IDI = 2.2% [0.0 to 7.6] p = 0.046) while discharge BNP did not significantly improve risk reclassification.

Conclusions: Residual pulmonary congestion assessed by radiographic scoring predicts poor prognosis beyond physical assessment, echocardiographic parameters and BNP. These findings further support the capital prognostic value of radiographic pulmonary congestion in patients hospitalized for worsening HF.

1. Introduction

Signs and symptoms of congestion are the most important contributors of heart failure (HF) hospitalization and readmission [1,2] to a significantly greater degree than low cardiac output [3,4]. Thus, decongestive therapy has been a major goal of acute heart failure management during hospitalization [5]. Discharge congestion variables such as brain natriuretic peptide (BNP) [6,7], physical assessments [8] and lung congestion assessed by lung ultrasound (LUS) [9–11] have been shown to be strongly associated with post-discharge morbidity and mortality [12]. Nevertheless, no standardized evaluation of congestion and subsequent tailored therapeutic management are currently recommended by the latest clinical guidelines [5,13]. In addition, there is evidence that clinical signs and symptoms of congestion on admission are associated with adverse outcome following a hospitalization for worsening HF [14,15]. Consequently, it remains unclear whether the interplay between residual congestion and higher values of admission congestion predicts outcome or whether the change in congestion during hospital stay or achieved discharge decongestion per-se are the best predictors of outcome.

Chest X-ray is a fast, simple and classic method to assess pulmonary congestion, with good specificity and moderate sensitivity in diagnosing HF [16,17]. Representative signs of pulmonary congestion, such as cephalization, peribronchial cuffing and Kerley lines, are widely known in clinical practice [18,19]. Assessment of lung congestion by a composite radiological score is useful to predict the development of overt HF during

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https://doi.org/10.1016/j.ijcard.2019.01.091
0167-5273/

hospital stay in patients admitted for myocardial infarction [20] and is associated with outcome in patients with chronic HF [21]. However, there is lack of data regarding prognostic values of radiographic congestion in the setting of patients hospitalized for worsening HF. In the present study, we sought to evaluate the prognostic value of lung congestion assessed by chest X-ray scoring at admission and discharge (including changes from admission to discharge) in patients with worsening HF.

2. Methods

2.1. Study participants

This retrospective analysis included a total of 292 patients admitted for acute decompensated HF (ADHF) at the Tokyo Medical University from August 2009 to September 2015. ADHF was defined according to clinical and radiographic evidence of congestion [12] by treating cardiologists. Exclusion criteria were: acute coronary syndrome, infective endocarditis, acute pericarditis and myocarditis, cardiac device implantation, percutaneous coronary intervention during hospital stay and planned cardiac surgery. Other non-cardiac exclusion criteria were: pneumonitis, lung cancer/metastases, pneumothorax, post lung surgery, severe chronic obstructive pulmonary disease, severe obesity, transcutaneous pacing on admission, maintenance for hemodialysis, admission creatinine ≥ 3 mg/dl or greater and infectious diseases (including C-reactive protein ≥ 10 mg/dl or greater). The study was conducted with the approval of the Ethics Guidelines Committee of the Tokyo Medical University.

2.2. Measurements

Medical charts of all patients in the present cohort were carefully reviewed and coded within an electronic database. The following information was collected: age, gender, comorbidities, medications (at discharge), laboratory findings, blood pressure, heart rate, physical signs and symptoms (at admission and discharge). In addition, as part of routine care management, all patients underwent standard echocardiography (within 72 h of admission) and chest X-ray (at admission and a few days before discharge when the treating physician perceived patients as regaining a compensated status (2.0 [1.0–4.0] days).

2.3. Radiographic congestion scoring

The severity of lung congestion was quantified by a single physician-cardiologist blinded to the clinical data and to the timing of the assessment, namely admission or prior to discharge. Lung congestion was quantified by chest X-ray (antero-posterior view at admission and postero-anterior view prior to discharge) using a previously validated method [21]. To enhance the reproducibility of this scoring with regard to the degree of confluent edema, a part of the divided lung field which visually occupied a density similar to cardiac silhouette was regarded as an intense area whereas the field with weaker density was considered to be a mild area. The grades of congestion in each of the six areas were defined as follows: 0 = normal; 1 = cephalization, perihilar haze, peribronchial cuffing, or Kerley lines (A, B, C); 2 = interstitial pulmonary edema and localized or confluent mild edema; and 3 = confluent intense edema (Fig. 1). These values were summed into a congestion score ranging from 0 to 18. Segments covered with pleural effusion, atelectasis or cardiac silhouette were not scored, and the congestion score index (CSI) was calculated as the congestion score divided by number of available lung segments. In terms of reproducibility of CSI, two experienced clinical physicians (M.K. and M.B.) blinded to each other, to the clinical parameters and to the timing of the chest X-ray, performed a separate complete analysis of 20 randomly selected subjects. CSI demonstrated good test-retest reproducibility (intra-observer agreement was 0.96 (0.91–0.98) and inter-observer agreement was 0.83 (0.62–0.93).

In addition, CSI drop was defined as the change from admission to discharge in CSI:

$$\text{CSI drop} = \text{CSI admission} - \text{CSI prior to discharge}$$

2.4. Outcomes

All patients were followed 1 year from discharge. Follow-up data were extracted from medical records in a blinded manner. The primary outcome of this analysis was a composite outcome of re-hospitalization for worsening HF or all-cause mortality whichever occurred first.

2.5. Statistical analysis

Continuous variables are reported as mean ± standard deviation or median (25th–75th percentiles), as appropriate. Patients with ADHF were divided into four groups according to median CSI at admission [CSI(A)] (1.33) and median CSI prior to discharge [CSI(D)] (0.33), namely 'LowCSI(A)/LowCSI(D)', 'HighCSI(A)/LowCSI(D)', 'LowCSI(A)/HighCSI(D)' and 'HighCSI(A)/HighCSI(D)'. Reduced left ventricular ejection fraction (LVEF) was defined as ejection fraction of <40%. Continuous variables and categorical variables were compared using the Kruskal-Wallis test and χ^2 test respectively.

Interobserver and intraobserver agreements of CSI were assessed with the intraclass correlation coefficient (ICC).

A linear regression model was used to examine the correlations of lung congestion, at both admission and discharge; significant univariable predictors and other variables a priori considered as being relevant (reduced LVEF, estimated glomerular filtration rate (eGFR), total protein, BNP and diuretic therapy at discharge) were entered into multivariable analysis.

Kaplan-Meier analysis was used to estimate survival probabilities. Cox proportional-hazards models were used to obtain unadjusted and covariate adjusted hazard ratios, which were chosen from all variables with $p < 0.05$ by univariable analysis. The increase in discriminative value to predict a 1-year composite outcome following the additional of discharge variables (CSI and BNP) in survival model on a baseline set of covariates including age, a previous history of HF hospitalization, reduced LVEF, hemoglobin and eGFR at discharge were evaluated using continuous NRI and IDI [22].

Descriptive analyses, associations with CSI and Cox hazard models were performed using SPSS package version 24.0 (SPSS Inc., Chicago, IL, USA). R statistical software (3.1.3) was used for ICC, continuous NRI and IDI (ICC and survIDINRI packages).

3. Results

3.1. Patient characteristics

The admission and discharge data of the 292 included ADHF patients are reported in Table 1. The majority of patients were male with a mean age of 71 ± 14 years and LVEF of 39 ± 17%. Approximately 40% of patients had a history of HF hospitalization, and were in New York Heart Association (NYHA) class IV at admission. Median BNP at admission and discharge was 560 pg/ml (327–1089) and 274 pg/ml (134–499), respectively. Mean CSI dropped significantly between admission and discharge (respectively 1.49 ± 0.51 and 0.44 ± 0.40, $p < 0.001$).

Among patients with higher admission CSI (172/292, 59%), two-thirds still had a higher prior to discharge CSI (124/172, 72%). Compared with other groups, patients with HighCSI(A)/HighCSI(D) were more frequently in NYHA class IV and had more congestive HF symptoms (orthopnea and rales) at admission and ankle edema at discharge but similar laboratory findings as well as echocardiographic parameters. Patients with higher admission CSI had a higher dosage of furosemide at discharge regardless of prior to discharge CSI.

3.2. Predictors of chest radiographic scoring at admission and prior to discharge

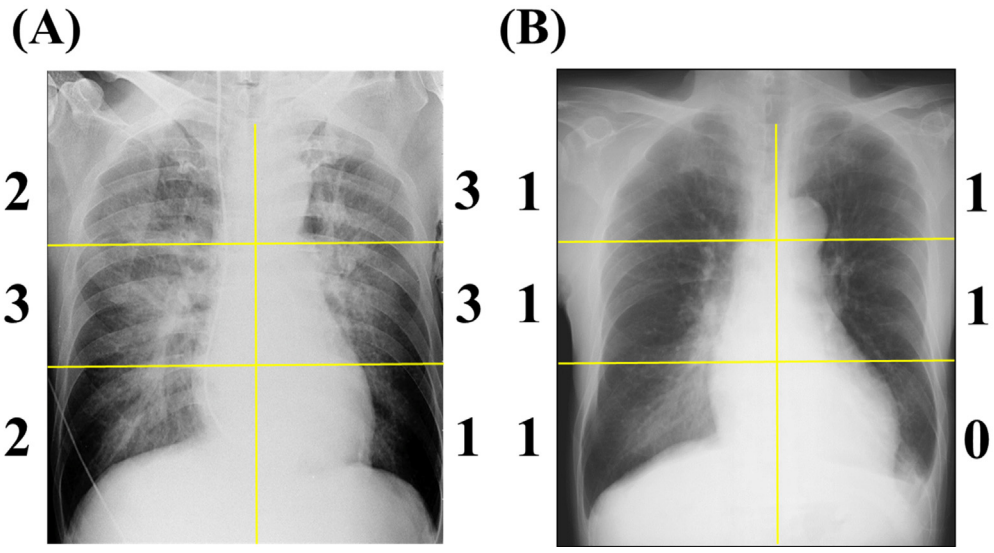
In multivariable analysis, SBP, NYHA class IV and rales were independently associated with higher admission CSI whereas BNP was not (Supplementary table 1).

When considering prior to discharge CSI as outcome, the only independent predictor of higher prior to discharge CSI was ankle edema at discharge. When considering variables measured at both admission and discharge, ankle edema at discharge remained the only independent predictor of higher prior to discharge CSI (Supplementary table 1), although the association was weak, with ankle edema being associated with a 0.16 higher prior to discharge CSI ($\beta = 0.16$, $p = 0.04$).

3.3. Association between admission and prior to discharge radiological pulmonary congestion and post-discharge outcome

During the first year after discharge, a total of 71 patients experienced one of the components of the composite events (67 HF re-hospitalizations and 7 all-cause deaths). The unadjusted Kaplan-Meier curves showed that the risk of composite outcome was higher in patients with HighCSI (A)/HighCSI(D) (log rank = 10.8, $p = 0.013$) (Fig. 2).

In univariable Cox analysis, unit increase in prior to discharge CSI was significantly associated with a 1.9-fold higher risk of the composite endpoints [HR (95% CI) = 1.85 (1.05–3.28), $p = 0.03$] whereas admission CSI was not significantly associated with outcome. In multivariable analysis using variable selection procedures, prior to discharge CSI was retained as a significant predictor for the composite endpoint [HR for a 1-unit increase in CSI (95% CI) = 1.83 (1.02–3.27), $p = 0.04$], along with discharge BNP [HR for a 100 pg/ml increase in BNP (95% CI) = 1.09 (1.04–1.14), $p < 0.001$] and furosemide dose (Table 2).



	1	2		3
Superior	Cephalization	Interstitial pulmonary edema	Alveolar pulmonary edema	
Middle	Peribronchial cuffing Perivascular cuffing Kerley A line		Localized edema	Confluent mild edema*	Confluent intense edema*
Inferior	Kerley B line Kerley C line			
No congestive sign; Vanishing tumor / Costophrenic angle				

Fig. 1. Radiographic congestion scoring. The scoring is performed in six lung fields. Examples A and B provide examples of grades 0 to 3. *With regard to confluent edema, when the density in a part of divided lung field was visually similar to that of cardiac silhouette, the field was regarded as intense edema.

HighCSI(A)/HighCSI(D) was significantly associated with a higher risk for the composite outcomes after adjustment for discharge BNP and furosemide dose [HR (95% CI) = 2.34 (1.09–5.01), p = 0.03] compared with LowCSI(A)/LowCSI(D). Importantly, there was no significant interaction between admission and prior to discharge CSI either used as continuous variables (p = 0.49) or dichotomous variables (p = 0.65), thus suggesting that the predictive value of prior to discharge CSI was not dependent on admission CSI.

3.4. Association between changes in radiological pulmonary congestion during hospital stay and post-discharge outcome

The drop in CSI adjusted for admission CSI was significantly associated with better outcome in crude analysis [HR for a 1-unit drop (95% CI) = 0.55 (0.31–0.97), p = 0.04]. When adjusting for furosemide dose, discharge BNP and admission CSI [HR (95% CI) = 1.94 (0.96–3.92), p = 0.07], the drop in CSI remained significantly associated with better outcome [HR for a 1-unit drop (95% CI) = 0.55 (0.31–0.99), p = 0.048].

3.5. Improvement in reclassification associated with prior to discharge CSI

The increase in discriminative value to predict 1-year composite outcomes following the addition of prior to discharge CSI and BNP in survival models on top of age, previous HF hospitalization, reduced LVEF, hemoglobin and eGFR at discharge, were evaluated using continuous NRI and IDI (Supplementary figure 1). The addition of high prior to discharge CSI (≥0.33) significantly improved reclassification [NRI (95% CI) = 19.6 (4.0–30.0), p = 0.03 and IDI (95% CI) = 2.2 (0–7.6), p = 0.046], whereas high discharge BNP did not improve the risk classification on the aforementioned clinical covariates (Supplementary figure 1). Furthermore, after including high BNP in the baseline model, high prior to discharge CSI still significantly improved reclassification [NRI (95% CI) = 19.6 (4.1–30.9), p = 0.02 and IDI (95% CI) = 2.2 (0.1–7.0), p = 0.04].

4. Discussion

The principal findings of the present study are that residual pulmonary congestion (rather than admission pulmonary congestion) as assessed by chest X-ray scoring is a prognostic factor over and above BNP and other clinical markers of congestion, and that the drop in pulmonary congestion is a key predictor of outcome in patients admitted for ADHF. In addition, prior to discharge CSI was associated with a significant reclassification on clinical risk stratification variables (whereas discharge BNP was not in this cohort), thus suggesting a relevant improvement in risk assessment at discharge following ADHF.

4.1. Radiographic congestion scoring

As demonstrated by our team [9,23] and others [10,11], residual pulmonary congestion, assessed by LUS at discharge, is a key prognostic

Table 1
Patient characteristics according to the levels of pulmonary radiologic congestion at admission and discharge.

	Overall ADHF patients (N = 292)	Low CSI (A) Low CSI (D) (N = 57)	Low CSI (A) High CSI (D) (N = 63)	High CSI (A) Low CSI (D) (N = 48)	High CSI (A) High CSI (D) (N = 124)	p-Value
Age, years	71.1 ± 13.6	69.1 ± 13.5	71.5 ± 13.5	70.3 ± 12.6	72.1 ± 14.2	0.37
Male, n (%)	188 (64.4%)	38 (66.7%)	44 (69.8%)	31 (64.6%)	75 (60.5%)	0.62
Body weight, kg	61.0 ± 15.9	60.2 ± 12.9	63.4 ± 13.5	58.1 ± 18.7	61.2 ± 17.1	0.12
Clinic characteristics, n (%)						
Previous HF hospitalization	123 (42.1%)	21 (36.8%)	25 (39.7%)	19 (39.6%)	58 (46.8%)	0.57
Coronary artery disease	62 (21.2%)	6 (10.5%)	11 (17.5%)	10 (20.8%)	35 (28.2%)	**0.045**
Atrial fibrillation	143 (49.0%)	24 (42.1%)	38 (60.3%)	29 (60.4%)	52 (41.9%)	**0.03**
Hypertension	210 (71.9%)	36 (63.2%)	42 (66.7%)	32 (66.7%)	100 (80.6%)	**0.04**
Diabetes mellitus	100 (34.2%)	14 (24.6%)	22 (34.9%)	14 (29.2%)	50 (40.3%)	0.17
Physical examinations at admission						
NYHA IV, n (%)	118 (40.4%)	10 (17.5%)	21 (33.3%)	27 (56.2%)	60 (48.4%)	<**0.001**
Orthopnea, n (%)	105 (36.1%)	10 (17.5%)	13 (20.6%)	26 (54.2%)	56 (45.2%)	<**0.001**
Rales, n (%)	154 (52.7%)	20 (35.1%)	29 (46.0%)	31 (64.6%)	74 (59.7%)	**0.004**
III sound, n (%)	151 (51.7%)	24 (42.1%)	30 (47.6%)	31 (64.6%)	66 (53.2%)	0.12
Ankle edema, n (%)	190 (65.1%)	37 (64.9%)	41 (65.1%)	30 (62.5%)	82 (66.1%)	0.98
Systolic blood pressure, mm Hg	141.9 ± 32.4	129.5 ± 23.3	130.0 ± 34.2	144.6 ± 36.1	152.6 ± 29.8	<**0.001**
Heart rate, bpm	96.3 ± 27.2	92.9 ± 26.2	92.9 ± 27.3	99.6 ± 23.3	98.3 ± 28.9	0.30
Laboratory findings at admission						
WBC, $10^3/\mu l$	7.2 ± 2.9	6.6 ± 2.2	7.2 ± 3.9	7.7 ± 3.4	7.3 ± 2.4	0.15
Lymphocyte, %	22.2 ± 10.7	23. ± 9.8	21.0 ± 8.6	25.0 ± 12.4	20.9 ± 11.2	0.07
Hemoglobin, g/dl	12.6 ± 2.5	13.0 ± 2.4	12.8 ± 2.6	13.0 ± 2.3	12.2 ± 2.5	
C-reactive peptide, mg/dl	1.0 ± 1.1	0.8 ± 1.0	1.0 ± 1.0	1.2 ± 1.2	1.1 ± 1.2	**0.01**
Total-bilirubin, mg/dl	1.2 ± 0.8	1.1 ± 0.6	1.4 ± 1.1	1.1 ± 0.6	1.1 ± 0.7	0.47
Serum sodium, mEq/l	141.2 ± 3.7	141.4 ± 3.5	140.9 ± 3.2	141.0 ± 4.6	141.3 ± 3.7	0.61
Blood urea nitrogen, mg/dl	23.6 ± 12.4	22.5 ± 9.9	24.2 ± 13.6	22.0 ± 10.2	24.4 ± 13.5	0.72
eGFR, ml/min/1.73 m^2	55.1 ± 23.0	56.2 ± 18.5	57.0 ± 25.0	56.3 ± 20.1	53.3 ± 24.9	0.36
BNP, pg/ml	560 (327–1089)	593 (332–997)	574 (254–1160)	524 (320–1100)	555 (365–1112)	0.80
Physical examinations at discharge						
Rales, n (%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0.72
Ankle edema, n (%)	33 (11.3%)	5 (8.8%)	13 (20.6%)	2 (4.2%)	13 (10.5%)	**0.04**
Systolic blood pressure, mm Hg	112.9 ± 18.5	109.6 ± 18.6	110.5 ± 18.6	117.3 ± 20.7	113.9 ± 17.2	0.11
Heart rate, bpm	68.3 ± 12.2	66.2 ± 12.6	70.5 ± 12.9	66.8 ± 10.0	68.8 ± 12.3	0.15
Laboratory findings at discharge						
Hemoglobin, g/dl	12.9 ± 2.5	13.4 ± 2.4	13.1 ± 2.5	13.1 ± 2.3	12.4 ± 2.5	0.08
Serum sodium, mEq/l	139.8 ± 3.1	140.3 ± 2.6	140.2 ± 3.1	140.0 ± 2.8	139.3 ± 3.5	0.14
Blood urea nitrogen, mg/dl	24.9 ± 14.4	22.6 ± 10.7	23.1 ± 14.1	23.8 ± 13.7	27.3 ± 16.1	0.07
eGFR, ml/min/1.73 m^2	53.2 ± 21.8	53.6 ± 18.6	56.8 ± 21.2	52.7 ± 18.3	51.4 ± 24.5	0.26
BNP, pg/ml	274 (134–499)	239 (158–437)	280 (90–601)	284 (146–453)	288 (140–470)	0.83
Echocardiography at admission (within 72 h)						
LVDD, mm	56.0 ± 9.5	57.6 ± 8.1	54.1 ± 10.1	57.1 ± 10.1	55.8 ± 9.5	0.15
LVEF, %	39.4 ± 17.4	36.2 ± 17.4	43.7 ± 18.7	37.4 ± 16.0	39.5 ± 17.0	0.12
LVEF < 40%, n	163 (55.8%)	41 (71.9%)	28 (44.4%)	26 (54.2%)	68 (54.8%)	**0.03**
MR (≥moderate), n (%)	162 (56.4%)	33 (58.9%)	33 (52.4%)	23 (48.9%)	73 (60.3%)	0.50
PASP, mm Hg	40.9 ± 17.8	41.2 ± 15.6	42.9 ± 17.4	35.5 ± 16.7	41.9 ± 19.1	0.19
IVC diameter, mm	18.3 ± 5.2	19.0 ± 4.9	18.2 ± 5.4	17.4 ± 5.2	18.5 ± 5.1	0.52
Congestion score index						
CSI admission	1.5 ± 0.5	1.0 ± 0.2	1.1 ± 0.1	1.9 ± 0.5	1.8 ± 0.4	<**0.001**
CSI prior to discharge	0.4 ± 0.4	0.0 ± 0.1	0.7 ± 0.3	0.1 ± 0.1	0.7 ± 0.3	<**0.001**
CSI drop	1.0 ± 0.6	1.0 ± 0.2	0.4 ± 0.3	1.8 ± 0.5	1.1 ± 0.5	<**0.001**
Pleural effusion, n (%)						
PE admission	168 (57.5%)	31 (54.4%)	37 (58.7%)	30 (62.5%)	70 (56.5%)	0.78
PE admission (bilateral)	109 (37.3%)	17 (29.8%)	26 (41.3%)	17 (35.4%)	49 (39.5%)	0.55
PE discharge	51 (17.5%)	7 (12.3%)	12 (19.0%)	7 (14.6%)	25 (20.2%)	0.56
PE discharge (bilateral)	21 (7.2%)	1 (1.8%)	4 (6.3%)	3 (6.3%)	13 (10.5%)	0.20
Medications at discharge						
ACE-I/ARB, n (%)	228 (78.1%)	48 (84.2%)	41 (65.1%)	40 (83.3%)	99 (79.8%)	**0.04**
Beta-blockers, n (%)	245 (83.9%)	51 (89.5%)	50 (79.4%)	43 (89.6%)	101 (81.5%)	0.26
Aldosterone antagonist, n (%)	228 (78.1%)	48 (84.2%)	49 (77.8%)	37 (77.1%)	94 (75.8%)	0.65
Diuretics, n (%)	234 (80.1%)	42 (73.7%)	46 (73.0%)	39 (81.2%)	107 (86.3%)	0.09
Furosemide, mg/day	20.0 (0.0–20.0)	10.0 (0.0–20.0)	20.0 (0.0–20.0)	20.0 (2.5–20.0)	20.0 (10.0–40.0)	**0.04**
Digitalis, n (%)	47 (16.1%)	8 (14.0%)	13 (20.6%)	9 (18.8%)	17 (13.7%)	0.59

Values are mean ± SD for all continuous variables, except BNP and furosemide (interquartile range); values for categorical variables are expressed as number of cases (%). Bold values statisically significance at P-value < 0.05.
ADHF, acute decompensated heart failure; CSI, congestion score index; HF, heart failure; NYHA, New York Heart Association; WBC, white blood cells; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; IVC, inferior vena cava; PE, pleural effusion; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

marker in patients hospitalized for worsening HF [9,10,24]. Specifically, we previously demonstrated that pulmonary congestion assessed by LUS was more strongly associated with outcome than echocardiographic, clinical and laboratory (namely BNP) measurements of congestion. While there is increasing evidence for the value of LUS, the utilization of this novel tool is dependent on portable ultrasound device availability and operator expertise [25,26].

Chest X-ray is usually considered to be poorly sensitive for excluding pulmonary congestion despite being a useful tool in clinical practice [12,16,17,27]. There are large differences in pulmonary congestion

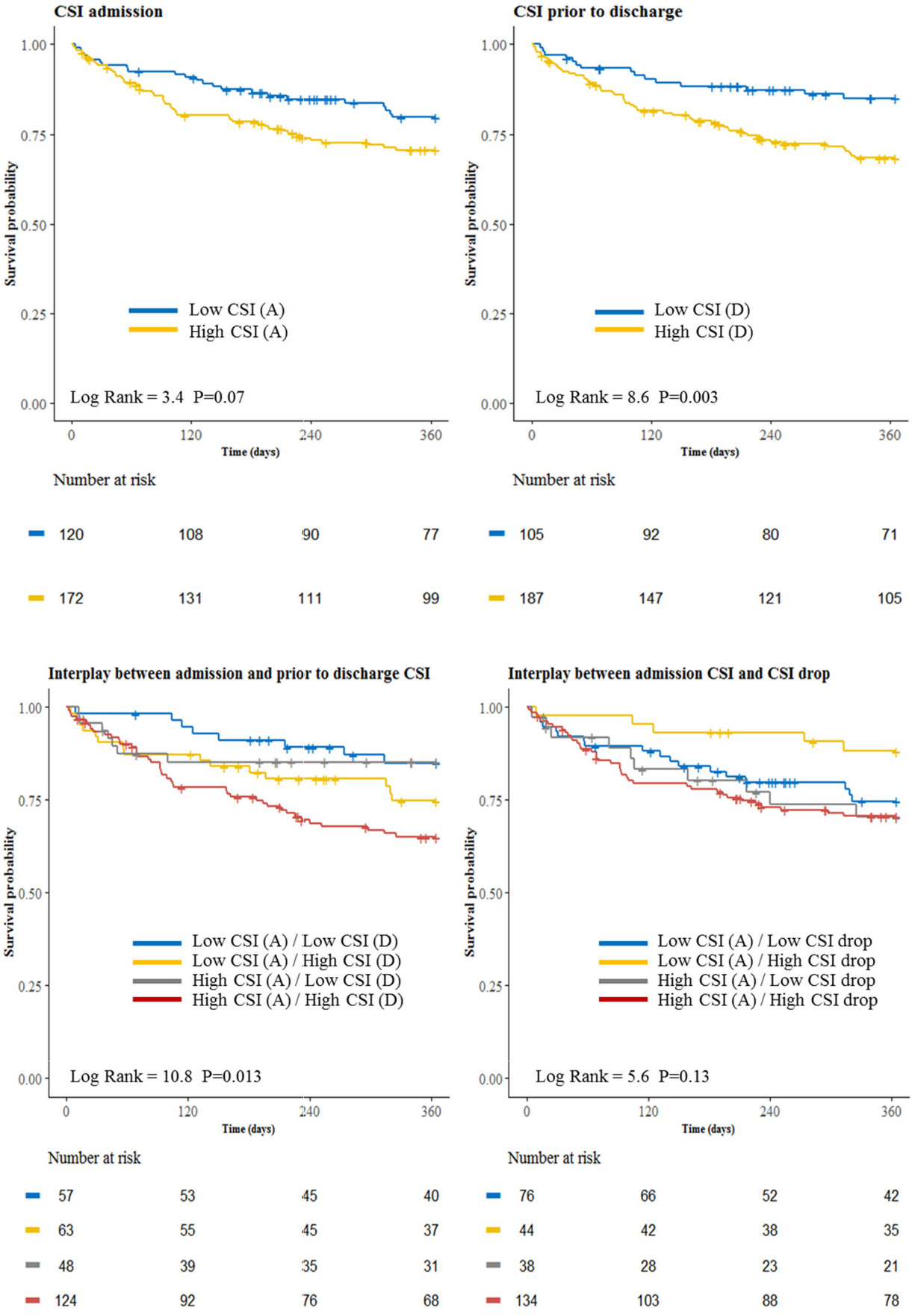


Fig. 2. Survival curves for the composite of all-cause death and heart failure re-hospitalization according to admission CSI, discharge CSI and the interplay among admission CSI, discharge CSI and CSI drop. Congestion score index was dichotomized using median values of 1.33 (admission), 0.33 (prior to discharge) and 1.0 (drop from admission and discharge), respectively. CSI; congestion score index.

Table 2
Univariable and multivariable Cox model analysis for the composite of heart failure re-hospitalization or all cause death.

	Univariable			Multivariable model with continuous CSI			Multivariable model with admission and discharge CSI interplay categories			Multivariable model with continuous drop CSI		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Continuous CSI variables												
CSI admission	1.16	0.75–1.79	0.51	/	/	/	/	/	/	1.94	0.96–3.92	0.07
CSI prior to discharge	1.85	1.05–3.28	**0.03**	1.83	1.02–3.27	**0.04**	/	/	/	/	/	/
CSI drop	0.85	0.57–1.26	0.42	/	/	/	/	/	/	0.55	0.31–0.99	**0.048**
Categorical CSI variables												
Low CSI (A)/Low CSI (D)	/	(Reference)	/	/	/	/	/	(Reference)	/	/	/	/
Low CSI (A)/High CSI (D)	1.85	0.78–4.35	0.16	/	/	/	1.59	0.67–3.80	0.30	/	/	/
High CSI (A)/Low CSI (D)	1.13	0.41–3.11	0.82	/	/	/	0.85	0.30–2.38	0.75	/	/	/
High CSI (A)/High CSI (D)	2.73	1.28–5.83	**0.01**	/	/	/	2.34	1.09–5.01	**0.03**	/	/	/
Adjustment variables												
Hypertension	1.41	0.81–2.46	0.23	/	/	/	/	/	/	/	/	/
SBP admission, mm Hg (per 10 mm Hg)	1.00	0.93–1.08	0.97	/	/	/	/	/	/	/	/	/
NYHA IV admission	1.20	0.75–1.91	0.46	/	/	/	/	/	/	/	/	/
Orthopnea admission	0.95	0.58–1.56	0.84	/	/	/	/	/	/	/	/	/
Rale admission	1.08	0.68–1.72	0.76	/	/	/	/	/	/	/	/	/
Ankle edema discharge	1.26	0.65–2.46	0.50	/	/	/	/	/	/	/	/	/
Sodium discharge, mEq/l	0.97	0.90–1.05	0.43	/	/	/	/	/	/	/	/	/
Baseline IVC, mm	1.00	0.96–1.05	0.91	/	/	/	/	/	/	/	/	/
Baseline PASP, mm Hg (per 10 mm Hg)	1.04	0.91–1.19	0.57	/	/	/	/	/	/	/	/	/
BNP admission, pg/ml (per 100 pg/ml)	1.01	0.99–1.04	0.30	/	/	/	/	/	/	/	/	/
BNP discharge, pg/ml (per 100 pg/ml)	1.10	1.05–1.15	<**0.001**	1.09	1.04–1.14	<**0.001**	1.10	1.05–1.15	<**0.001**	1.09	1.04–1.14	<**0.001**
Furosemide, mg/day (per 10 mg)	1.02	1.01–1.03	<**0.001**	1.18	1.08–1.29	<**0.001**	1.17	1.07–1.29	**0.001**	1.17	1.07–1.29	<**0.001**

CSI, congestion score index; HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; NYHA, New York Heart Association; IVC, inferior vena cava; PASP, pulmonary artery systolic pressure; BNP, brain natriuretic peptide. Bold values statisically significance at P-value < 0.05.

prevalence reported among trials [28–30], likely due to the inconsistent definition of X-ray-based pulmonary congestion and large inter-observer variability. A simple and standardized evaluation of congestion on chest X-ray (such as performed herein) could overcome this limitation and increase its diagnostic and prognostic value. Ware et al. reported that systematic radiographic congestion scoring was closely correlated with actual lung weights in 84 brain dead organ donors [31], which strongly supports the value of X-ray scoring in quantifying extravascular lung water. In addition, Melenovsky et al. reported that CSI was significantly associated with clinical outcome independently of pulmonary artery wedge pressure and natriuretic peptides in patients with chronic HF [21]. In this study, we demonstrated that radiographic pulmonary congestion using CSI was also a strong predictor of clinical outcome in patients with worsening HF, more so than other clinical and biological markers of congestion (including natriuretic peptides). Taken together, these data suggest a strong prognostic value of pulmonary congestion as assessed by a simple standardized chest X-ray scoring. In addition, higher prior to discharge CSI was found to improve reclassification on traditional clinical covariates (e.g. age, previous history of HF hospitalization, systolic function and renal function) whereas BNP did not increase discrimination. These findings further strengthen the prognostic value of congestion scoring using CSI in patients with worsening HF.

4.2. Congestion trajectories and clinical outcome

Most previous studies have focused on congestion assessment at either admission [14,32,33] or discharge [8,9,34] but only few have focused on the change from admission to discharge [35,36]. It is essential to determine the optimal period for predicting long-term outcomes, in order to guide the most clinically useful congestion assessment strategy. With regard to LUS, our group recently demonstrated that different cut-offs at admission and discharge (B-lines ≥ 45 and B-lines ≥ 30, respectively) were able to predict short-term adverse prognosis although both timings had good prognostic ability. In contrast, Kociol et al. who reported that discharge BNP was the most important predictor of post-discharge outcome at 1 year compared with BNP evaluated at other timings (including admission BNP and change from admission to discharge BNP) [35]. However, in addition to prognostic value at discharge, we identified that change in CSI from admission to discharge was strongly associated with better outcome when adjusting for baseline CSI (HR for 10% decrease), which is in keeping with the neutral prognosis of patients with HighCSI (A)/LowCSI(D); HR (95% CI) = 0.85 (0.30–2.38) p = 0.75). Importantly, it is likely that admission congestion variables are associated with worse mid-term outcome solely because a higher level of admission congestion increases the risk of residual congestion (due to the fact that a higher change in congestion status is needed to achieve decongestion). More importantly, our results provide evidence that pulmonary congestion using CSI could represent a valuable actionable target in clinical routine. Eventually, clinical trials should evaluate whether this standardized assessment of pulmonary congestion could help optimizing decongestive therapy and identifying the most appropriate timing of discharge.

4.3. Limitations

This retrospective single-center cohort study has several limitations. First, the moderate size of our study cohort limits the statistical power of our analysis. In addition, the proportion of NYHA IV was rather low at admission and our results may consequently not apply to the sickest population of ADHF patients. In addition, different approaches in performing the chest X-ray exam (i.e. antero-posterior view at admission and postero-anterior view at discharge) could have impacted the results: antero-posterior chest radiograms may detect the extent of congestion with a lower sensitivity.) Additionally, discharge chest X-rays were not necessarily performed at discharge but on the day when patients were considered to have reached a compensated status by the treating cardiologists, which might not be reproducible across physicians and countries. Patients with coronary artery disease or pneumonia were excluded in the present study in order to better assess the predictive value of congestion; this methodological point could limit the generalizability of our results. Certain important variables (e.g., jugular vein distention, abdominal-jugular reflux and intravenous diuretic administration) were not available and consequently could not be adjusted for. All patients with ADHF underwent echocardiography within 72 h of admission, which may partly explain the absence of strong association of echocardiographic parameters with admission CSI. In addition, we did

not have information regarding discharge echocardiography, which was not performed in most patients. As a result, we cannot assess the added value of CSI on top of discharge echocardiographic data in patients with ADHF.

5. Conclusions

In worsening HF patients, radiographic pulmonary congestion assessed by CSI was the best predictor of post-discharge outcome. This result should promote performing congestion assessment during the latter portion of the hospital stay for worsening HF, and possibly targeting decongestion based on clinical, laboratory and imaging parameters, such as echocardiographic (LUS) or radiological parameters (CSI).

Acknowledgments

We thank all patients who participated in this study.

Conflict of interests

F.Z. has received consulting fees from Actelion, Amgen, AstraZeneca, Bayer, Boehringer, Boston Science, CEVA, CVRx, Vifor-Fresenius, GE Healthcare, J&J, KBP BioSciences, Livanova, Novartis, NovoNordisk, Pfizer, Quantum Genomics, Relypsa, Resmed, Roche, Takeda and ZS pharma. P.R. has received fees from Honoraria, research grants and/or travel grants from AstraZeneca, Bayer, BG Medicine, BMS, CVRx, Daichii-Sankyo, Fresenius, Gambro, HAC-Pharma, Novartis, Relypsa, Roche, Sanofi, Servier, Stealth Peptides, CTMA and Vifor Fresenius Medical Care Renal Pharma. PR and FZ are CardioRenal cofounders. N.G. has received Board and consulting Fees (Honoraria) for Novartis and consulting fees (Honoraria) for Servier. MW has received consulting fees from Medtronic and Philips and YI has received consulting fees from Medtronic.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.091.

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