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

Masatake Kobayashi^{1,2}, Masataka Watanabe¹, Stefano Coiro³, Matthieu Bercker⁴, Yuki Paku¹, Yoichi Iwasaki¹, Taishiro Chikamori¹, Akira Yamashina¹, Kevin Duarte², João Pedro Ferreira^{2,4}, Patrick Rossignol^{2,4}, Faiez Zannad^{2,4}, Nicolas Girerd^{2,4}

1. Department of Cardiology, Tokyo Medical University, Tokyo, Japan.

2. Université de Lorraine, INSERM, Centre d'Investigations Cliniques 1433, CHRU de Nancy, Inserm

U1116, Nancy, France and INI-CRCT (Cardiovascular and Renal Clinical Trialists) F-CRIN network, Nancy, France.

3. Division of Cardiology, University of Perugia, School of Medicine, Via S. Andrea delle fratte, Perugia, Italy.

4. Department de Cardiologie, CHU de Nancy, Institut Lorrain du coeur et des vaisseaux, Nancy, France.

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Corresponding Author: Nicolas GIRERD

Centre d'Investigation Clinique Pierre Drouin -INSERM - CHRU de Nancy, Institut lorrain du coeur et des, vaisseaux Louis Mathieu, Nancy, France

Address : 4, rue du Morvan. 54500 Vandoeuvre-Les-Nancy

E-mail: n.girerd@chru-nancy.fr Phone: +33383157496 Fax: +33383157324

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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 hospitalization⁵. Discharge congestion variables such as brain natriuretic peptide (BNP)^{6,7}, physical assessments⁸ and lung congestion assessed by lung ultrasound (LUS)⁹⁻¹¹ have been shown to be strongly associated with post-discharge morbidity and mortality¹². 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 hospital stay in patients admitted for myocardial infarction²⁰ and is associated with outcome in patients with chronic HF²¹. 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.

Methods

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 congestion¹² 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 of 3mg/dl or greater and infectious diseases (including C-reactive protein of 10mg/dl or greater). The study was conducted with the approval of the Ethics Guidelines Committee of the Tokyo Medical University.

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 hours 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).

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 method²¹. 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 [Figure 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:

CSI drop = CSI admission – CSI prior to discharge

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.

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 less than 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).

Results

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 $39\pm 17\%$. 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.

*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 [Supplement 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 [Supplement 1], although the association was weak, with ankle edema being associated with a 0.16 higher prior to discharge CSI ($\beta=0.16$, $p=0.04$).

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, $P=0.013$) [Figure 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].

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.

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].

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 [Supplement 2]. 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 (0.1-7.6), p=0.046], whereas high discharge BNP did not improve the risk classification on the aforementioned clinical covariates [Supplement 2]. 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].

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.

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 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 prevalence reported among trials²⁸⁻³⁰, 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 donors³¹, 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 HF²¹. 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.

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 $\geq$ 45 and B-lines $\geq$ 30, respectively) were able to predict short-term adverse prognosis although both timings had good prognostic ability. In contrast, Kochio 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.

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 hours 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.

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).

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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

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References

1. Gheorghiade M, Filippatos G, De Luca L and Burnett J. Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. *Am J Med.* 2006;119:S3-S10.
2. Girerd N, Seronde MF, Coiro S, Chouihed T, Bilbault P, Braun F, Kenizou D, Maillier B, Nazeyrollas P, Roul G, Fillieux L, Abraham WT, Januzzi J, Sebbag L, Zannad F, Mebazaa A and Rossignol P. Integrative Assessment of Congestion in Heart Failure Throughout the Patient Journey. *J Am Coll Cardiol.* 2017.
3. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F and Tavazzi L. EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail.* 2010;12:1076-84.
4. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB and Fonarow GC. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA.* 2006;296:2217-26.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M and Document R. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2016;18:891-975.
6. Bettencourt P, Azevedo A, Pimenta J, Frioies F, Ferreira S and Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation.* 2004;110:2168-74.
7. Pimenta J, Paulo C, Mascarenhas J, Gomes A, Azevedo A, Rocha-Goncalves F and Bettencourt

P. BNP at discharge in acute heart failure patients: is it all about volemia? A study using impedance cardiography to assess fluid and hemodynamic status. *Int J Cardiol.* 2010;145:209-214.

8. Rubio-Gracia J, Demissei BG, Ter Maaten JM, Cleland JG, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison BA, Givertz MM, Bloomfield DM, Dittrich H, Damman K, Perez-Calvo JJ and Voors AA. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. *Int J Cardiol.* 2018;258:185-191.

9. Coiro S, Rossignol P, Ambrosio G, Carluccio E, Alunni G, Murrone A, Tritto I, Zannad F and Girerd N. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. *Eur J Heart Fail.* 2015;17:1172-81.

10. Gargani L, Pang PS, Frassi F, Miglioranza MH, Dini FL, Landi P and Picano E. Persistent pulmonary congestion before discharge predicts rehospitalization in heart failure: a lung ultrasound study. *Cardiovasc Ultrasound.* 2015;13:40.

11. Cogliati C, Casazza G, Ceriani E, Torzillo D, Furlotti S, Bossi I, Vago T, Costantino G and Montano N. Lung ultrasound and short-term prognosis in heart failure patients. *Int J Cardiol.* 2016;218:104-8.

12. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G, European Society of C and European Society of Intensive Care M. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail.* 2010;12:423-33.

13. Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL and American College of Cardiology Foundation/American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* 2013;128:e240-327.

14. Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuzat M, Givertz MM, Davison BA, Mansoor GA, Ponikowski P, Voors AA, Cotter G, Metra M, Massie BM and O'Connor CM. Predictors of postdischarge outcomes from information acquired shortly after admission for acute heart failure: a report from the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) Study. *Circ Heart Fail.* 2014;7:76-87.

15. Frassi F, Gargani L, Tesorio P, Raciti M, Mottola G and Picano E. Prognostic value of extravascular lung water assessed with ultrasound lung comets by chest sonography in patients with dyspnea and/or chest pain. *J Card Fail.* 2007;13:830-5.

16. Sartini S, Frizzi J, Borselli M, Sarcoli E, Granai C, Gialli V, Cevenini G, Guazzi G, Bruni F,

Gonnelli S and Pastorelli M. Which method is best for an early accurate diagnosis of acute heart failure? Comparison between lung ultrasound, chest X-ray and NT pro-BNP performance: a prospective study. *Intern Emerg Med*. 2016.

17. Mueller-Lenke N, Rudez J, Staub D, Laule-Kilian K, Klima T, Perruchoud AP and Mueller C. Use of chest radiography in the emergency diagnosis of acute congestive heart failure. *Heart*. 2006;92:695-6.

18. Milne EN, Pistolesi M, Miniati M and Giuntini C. The radiologic distinction of cardiogenic and noncardiogenic edema. *AJR Am J Roentgenol*. 1985;144:879-94.

19. Pistolesi M and Giuntini C. Assessment of extravascular lung water. *Radiol Clin North Am*. 1978;16:551-74.

20. Shochat M, Shotan A, Trachtengerts V, Blondheim DS, Kazatsker M, Gurovich V, Asif A, Shochat I, Rozenman Y and Meisel SR. A novel radiological score to assess lung fluid content during evolving acute heart failure in the course of acute myocardial infarction. *Acute Card Care*. 2011;13:81-6.

21. Melenovsky V, Andersen MJ, Andress K, Reddy YN and Borlaug BA. Lung congestion in chronic heart failure: haemodynamic, clinical, and prognostic implications. *Eur J Heart Fail*. 2015;17:1161-71.

22. Uno H, Tian L, Cai T, Kohane IS and Wei LJ. A unified inference procedure for a class of measures to assess improvement in risk prediction systems with survival data. *Stat Med*. 2013;32:2430-42.

23. Coiro S, Porot G, Rossignol P, Ambrosio G, Carluccio E, Tritto I, Huttin O, Lemoine S, Sadoul N, Donal E, Zannad F and Girerd N. Prognostic value of pulmonary congestion assessed by lung ultrasound imaging during heart failure hospitalisation: A two-centre cohort study. *Sci Rep*. 2016;6:39426.

24. Platz E, Lewis EF, Uno H, Peck J, Pivetta E, Merz AA, Hempel D, Wilson C, Frasure SE, Jhund PS, Cheng S and Solomon SD. Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory heart failure patients. *Eur Heart J*. 2016;37:1244-51.

25. Gargani L, Sicari R, Raciti M, Serasini L, Passera M, Torino C, Letachowicz K, Ekart R, Fliser D, Covic A, Balafa O, Stavroulopoulos A, Massy ZA, Fiaccadori E, Caiazza A, Bachelet T, Slotki I, Shavit L, Martinez-Castelao A, Coudert-Krier MJ, Rossignol P, Kraemer TD, Hannedouche T, Panichi V, Wiecek A, Pontoriero G, Sarafidis P, Klinger M, Hojs R, Seiler-Mussler S, Lizzi F, Onofriescu M, Zarzoulas F, Tripepi R, Mallamaci F, Tripepi G, Picano E, London GM and Zoccali C. Efficacy of a remote web-based lung ultrasound training for nephrologists and cardiologists: a LUST trial sub-project. *Nephrol Dial Transplant*. 2016;31:1982-1988.

26. Scali M, Simioniuc A, Dini FL and Marzilli M. The potential value of integrated natriuretic peptide and echo-guided heart failure management. *Cardiovasc Ultrasound*. 2014;12:27.

27. Collins SP, Lindsell CJ, Storrow AB, Abraham WT, Adhere Scientific Advisory Committee I and Study G. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. *Ann Emerg Med*. 2006;47:13-8.

28. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, Bart BA, Bull DA, Stehlik J, LeWinter MM, Konstam MA, Huggins GS, Rouleau JL, O'Meara E, Tang WH, Starling RC, Butler J, Deswal A, Felker GM, O'Connor CM, Bonita RE, Margulies KB, Cappola TP, Ofili

EO, Mann DL, Davila-Roman VG, McNulty SE, Borlaug BA, Velazquez EJ, Lee KL, Shah MR, Hernandez AF, Braunwald E, Redfield MM and Network NHFCR. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA*. 2013;310:2533-43.

29. Felker GM, Lee KL, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E and O'Connor CM. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797-805.

30. CHF) PCftViVitMfA. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531-40.

31. Ware LB, Neyrinck A, O'Neal HR, Lee JW, Landeck M, Johnson E, Calfee CS, Matthay MA and California Transplant Donor N. Comparison of chest radiograph scoring to lung weight as a quantitative index of pulmonary edema in organ donors. *Clin Transplant*. 2012;26:665-71.

32. Ter Maaten JM, Voors AA, Damman K, van der Meer P, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Metra M, Navis G, Ng L, Ouwerkerk W, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Zwinderman AH and de Borst MH. Fibroblast growth factor 23 is related to profiles indicating volume overload, poor therapy optimization and prognosis in patients with new-onset and worsening heart failure. *Int J Cardiol*. 2018;253:84-90.

33. Gimpelewicz C, Metra M, Cleland JGF, Szecsy P, Chang Wun CC, Boer-Martins L, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Pang P, Ponikowski P, Severin T, Voors AA and Teerlink JR. Effects of serelaxin on the outcome of patients with or without substantial peripheral edema: A subgroup analysis from the RELAX-AHF trial. *Am Heart J*. 2017;190:113-122.

34. Logeart D, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, Bouvier E and Solal AC. PredischARGE B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol*. 2004;43:635-41.

35. Kociol RD, Horton JR, Fonarow GC, Reyes EM, Shaw LK, O'Connor CM, Felker GM and Hernandez AF. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) linked to Medicare claims. *Circ Heart Fail*. 2011;4:628-36.

36. Metra M, Cleland JG, Weatherley BD, Dittrich HC, Givertz MM, Massie BM, O'Connor CM, Ponikowski P, Teerlink JR, Voors AA and Cotter G. Dyspnoea in patients with acute heart failure: an analysis of its clinical course, determinants, and relationship to 60-day outcomes in the PROTECT pilot study. *Eur J Heart Fail*. 2010;12:499-507.

Figure 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.

	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					

Figure 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 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, yrs	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, mmHg	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 /μl	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/1.73m 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, mmHg	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/1.73m 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, mmHg	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 as median (interquartile range); values for categorical variables are expressed as number of cases (%).

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.

Table2; 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, n	1.41	0.81 - 2.46	0.23	/	/	/	/	/	/	/	/	/
SBP admission, mmHg (per 10mmHg)	1.00	0.93 - 1.08	0.97	/	/	/	/	/	/	/	/	/
NYHA IV admission, n	1.20	0.75 - 1.91	0.46	/	/	/	/	/	/	/	/	/
Orthopnea admission, n	0.95	0.58 - 1.56	0.84	/	/	/	/	/	/	/	/	/
Rale admission, n	1.08	0.68 - 1.72	0.76	/	/	/	/	/	/	/	/	/
Ankle edema discharge, n	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, mmHg (per 10mmHg)	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 100pg/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 10mg)	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.