



Shoaib, A. et al. (2019) Characteristics and outcome of acute heart failure patients according to the severity of peripheral oedema. *International Journal of Cardiology*, 285, pp. 40-46. (doi: [10.1016/j.ijcard.2019.03.020](https://doi.org/10.1016/j.ijcard.2019.03.020))

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/182983/>

Deposited on: 1 April 2019

Enlighten – Research publications by members of the University of Glasgow  
<http://eprints.gla.ac.uk>

## Characteristics and Outcome of Acute Heart Failure Patients According to the Severity of Peripheral Oedema

Ahmad Shoaib<sup>a,c</sup>, Mamas A Mamas<sup>a</sup>, Qazi S Ahmad<sup>e</sup>, Theresa M McDonagh<sup>b</sup>, Suzanna MC Hardman<sup>c</sup>, Muhammad Rashid<sup>a</sup>, Robert Butler<sup>a</sup>, Simon Duckett<sup>a</sup>, Duwarakan Satchithananda<sup>a</sup>, James Nolan<sup>a</sup>, Henry J Dargie<sup>d</sup>, Andrew L Clark<sup>e</sup>, John GF Cleland<sup>e-f</sup>

- a) Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University and Royal Stoke Hospital, Stoke-on-Trent
- b) Faculty of Life Sciences and Medicine, King's College London, London, UK
- c) Clinical & Academic Department of Cardiovascular Medicine, Whittington Hospital, London, UK
- d) Department of Cardiology, University of Glasgow
- e) Department of Academic Cardiology, University of Hull, Kingston upon Hull, UK
- f) Robertson Centre for Biostatistics and Clinical Trials, University of Glasgow, Glasgow, Scotland, UK; National Heart and Lung Institute, Imperial College, London, United Kingdom

Total Words count (excluding Abstract, figures, tables, references): 3,068

Funding: None to report

Disclosures: None to report

### **Address for correspondence**

Dr Ahmad Shoaib

Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University and Royal Stoke Hospital, Stoke-on-Trent

Pone: +44 1782 732958

Fax number: +44 1782 734719

Email: ahmad.shoaib@keele.ac.uk

## **Abstract**

**Background:** Most trials of patients hospitalised for heart failure focus on breathlessness (alveolar pulmonary oedema) but worsening peripheral oedema is also an important presentation. We investigated the relationship between the severity of peripheral oedema on admission and outcome amongst patients with a primary discharge death or diagnosis of heart failure.

**Objectives:** We tested the hypothesis that severity of peripheral oedema is associated with length of hospital stay and mortality.

**Methods:** Patient variables reported to the National Heart Failure Audit for England & Wales between April 2008 and March 2013 were included in this analysis. Peripheral oedema was classified as 'none', 'mild', 'moderate' or 'severe'. Length of stay, mortality during the index admission and for up to three years after discharge are reported.

**Results:** Of 121,214 patients, peripheral oedema on admission was absent in 24%, mild in 24%, moderate in 33% and severe in 18%. Median length of stay was, respectively, 6, 7, 9 and 12 days ( $P < 0.001$ ), index admission mortality was 7%, 8%, 10% and 16% ( $P < 0.001$ ) and mortality at a median follow-up of 344 (IQR 94-766) days was 39%, 46%, 52% and 59%. In an adjusted multi-variable Cox model, the hazard ratio for death was 1.51 for severe ( $P < 0.001$ , CI 1.50-1.53), 1.21 for moderate ( $P < 0.001$ , CI 1.20-1.22) and 1.04 ( $P < 0.001$ , CI 1.02-1.05) for mild peripheral oedema compared to patients without peripheral oedema at presentation.

**Conclusion:** Length of hospital stay and mortality during index admission and after discharge increased progressively with increasing severity of peripheral oedema at admission.

**Key Words:** Acute Heart Failure, Peripheral Oedema, Breathlessness, Mortality.

## **Introduction**

The main symptoms of worsening heart failure are breathlessness, at rest or during slight exertion, or worsening peripheral oedema; many patients admitted to hospital will have both.(1) Surveys suggest that fewer than 50%,(2, 3), perhaps as few as 16% (4), of patients admitted to hospital for heart failure have severe breathlessness at rest, whereas, worsening peripheral oedema may be an important reason for admission in >60% of cases.(5, 6) However, clinical trials of 'acute' heart failure have focussed almost exclusively on breathlessness as a presenting symptom and designed with pulmonary oedema as the pathophysiological target.

Pulmonary oedema is not necessarily accompanied by obvious fluid retention and may develop within minutes or hours. In the context of heart failure, this is due to a rise in left atrial and pulmonary capillary pressure beyond a threshold at which the pulmonary lymphatics can deal with increasing pulmonary venous congestion and interstitial pulmonary oedema, resulting in accumulation of fluid in the alveoli. This may occur due to displacement of fluid from the circulation into the lungs rather than an increase in total body water.(7, 8) Pulmonary oedema is often due to an acute coronary syndrome (ACS), cardiac arrhythmia (usually atrial fibrillation with rapid ventricular response) or uncontrolled hypertension.(9, 10) Severe breathlessness due to alveolar pulmonary oedema is an acute medical emergency that requires treatment within minutes but is relatively well served by existing therapies including oxygen, intravenous diuretics and nitrates and, perhaps, opiates that can resolve symptoms within minutes or hours. As fluid redistribution into the alveoli is the underlying pathophysiological mechanism, vasodilators are, at least theoretically, a first-line treatment.(11, 12)

Peripheral oedema is due to fluid accumulation and typically develops over days, weeks or even months and is often due to a gradual, progressive deterioration in cardiac and renal function. It will usually be accompanied by a rise in left atrial pressure, pulmonary venous congestion, pulmonary hypertension and right ventricular dysfunction leading to a rise in right atrial pressure. It is misleading to think of this problem as acute heart failure in the same way as alveolar pulmonary oedema. Treatment delays of a few hours or even days will make little difference to symptoms and many patients could be managed without hospital admission. Days or weeks of treatment, predominantly with diuretics, are required to correct peripheral oedema. However, low blood pressure and renal dysfunction often make these patients difficult to manage. Peripheral oedema has been associated with longer lengths of stay and higher risks of re-admission and death, although these reports included a relatively small number of patients. (2, 13)

Accordingly, we investigated the clinical characteristics, length of stay and mortality, both during the index admission and after discharge, according to severity of peripheral oedema at presentation in patients enrolled in National Heart Failure Audit (NHFA) for England & Wales.

## Methods

The National Heart Failure Audit (NHFA) was established in 2007 for hospitals in England & Wales to assess the quality of care of patients with heart failure by collecting information on their presentation, characteristics, specialist input, investigations and management.(14) Information is collected on hospitalised patients who had heart failure coded in the first position at death or discharge. The number of participating NHS trusts in England and Health Boards in Wales increased from 86 (52%) in 2008-9 to 145 in 2012-13 (97%). For this analysis, data were collected from April 2008 to March 2013. Patients' clinical characteristics and medicines at discharge were extracted from case notes by staff at each hospital. Left ventricular systolic dysfunction was defined as a left ventricular ejection fraction <40% and severity of peripheral oedema classified as "none", "mild", "moderate" or "severe" by local site staff. Haemoglobin and serum creatinine were collected routinely only after 2012. Length of stay and all-cause mortality during hospital admission and after discharge were recorded until March 2013 using hospital information services and tracking by the Medical Research Information Service using an individual's unique National Health Service number.(15, 16)

The analysis was performed using the Stata/MP 13.1 statistical software (College Station, TX). The cohort was stratified into groups according to severity of oedema reported at presentation. Continuous data are presented as median with interquartile ranges. Categorical variables are presented as counts (percentage). We tested for differences amongst groups by using Chi-squared tests for nonparametric data, one-way ANOVA for normally distributed continuous variables and Kruskal Wallis test where continuous variables were not normally distributed. Prognostic models for all-cause mortality were developed using Cox regression. The proportionality of hazards (PH) assumption was verified for all covariates using tests based on Schoenfeld residuals.(17, 18)

There was no departure from the PH assumption for any covariate. Cox metrics included the hazard ratio (HR), 95% confidence intervals (CI), and pseudo  $r^2$  (the square of the correlation coefficient of the actual and predicted values of dependent variable). This is a measure of goodness of fit.(19) Sensitivity analyses were performed on models determined from the imputed data. Multiple imputations with chained equations were used to impute missing data. Ten imputations were generated. Study findings are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.(20)

## **Results**

Of 158,906 administrative records, a diagnosis of heart failure was confirmed by local clinicians for 136,790 patients (Supplement Figure 1). Of 121,214 patients considered for this analysis, peripheral oedema on admission was reported to be absent in 24%, mild in 25%, moderate in 33% and severe in 18% (Table 1). Patients with peripheral oedema tended to be older, were more likely to be women and were more likely to have a history of diabetes, hypertension and valve disease, although not ischaemic heart disease, but none of these differences was large. Patients with severe peripheral oedema were more likely to have symptoms at rest or minimal exertion (NYHA Class IV: 56%) compared to those without peripheral oedema (26%). Patients with severe peripheral oedema had worse renal function and lower haemoglobin but were less likely to have Heart Failure with reduced ejection fraction (HFrEF). Patients with peripheral oedema were less likely to be prescribed angiotensin converting-enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and beta blockers (BB), but more likely to receive mineralocorticoid receptor antagonists (MRA), digoxin, loop and thiazide diuretics (Table 1).

Patients who had no peripheral oedema at presentation had shorter length of hospital stay (6 (IQR 3-13) days compared to 7 ((IQR 3-14), 9 (IQR 5-17) and 12 (IQR 6-21) (P <0.001)) for patients with mild, moderate and severe peripheral oedema respectively (Table 1). Mortality both during the index admission and after discharge increased progressively as the severity of peripheral oedema worsened (Table 2). Mortality during the index admission was 7% for patients without peripheral oedema but 16% for those with severe peripheral oedema and mortality at three years was 39% compared to 59%. Mortality rates were similar for patients with or without HFrEF or in the presence of valve disease (Figure 1).

In univariate analysis, the hazard ratio of death (all-cause at any time) was 1.88 for patients with severe (P <0.001, CI 1.81-1.84), 1.47 for moderate (P<0.001, CI 1.44-1.51) and 1.20 (P<0.001, CI 1.17-1.23) for mild peripheral oedema when compared to those who had none. In multi-variable Cox regression analysis, we considered three models for statistical modelling, first on original and then on imputed data (Table 3 and Supplement Table 2-3). In Cox model 1 (Supplement Table 2), mortality was assessed after adjusting for age, sex, NYHA class (functional capacity), and prior history of diabetes mellitus, hypertension, ischaemic heart disease, valvular heart disease, length of stay during index admission and left ventricular systolic dysfunction. The hazard ratio for death increased progressively with worsening severity of oedema for both complete and imputed data sets. In Cox model 2 (Supplement Table 3), after adjusting for haemoglobin and serum creatinine concentrations in addition to the variables in model 1 for the smaller cohort with available laboratory data, the hazard ratios for all-cause mortality with increasing severity of peripheral oedema were similar to model 1. In Cox model 3 (Table 3), further adjusting for medicines at discharge in addition to the nine variables in model 1 had little impact on the relationship between worsening severity of peripheral oedema and death.

## **Discussion**

Analysis of this large registry suggests that peripheral oedema at admission is common amongst patients admitted for heart failure and is associated with many clinical characteristics and differences in therapy that portend a poor prognosis. However, none of these clinical features appear to account for the worse outcome associated with peripheral oedema. Whether more effective treatment of peripheral oedema and its causes can improve outcome is uncertain and will remain so until trials targeting this problem are designed and completed.

Although the age-adjusted prognosis of patients with stable chronic heart failure is improving, the mortality rate for patients with worsening symptoms and signs requiring admission to hospital remains high in our large and contemporary national registry. This is despite high rates of implementation of treatments known to be effective for HFrEF.(16) In this audit, 87% of patients with HFrEF received either an ACEi or ARB, 77% received a beta-blocker and 40% received an MRA compared to 72%, 57% and 32% of patients who had Heart failure with preserved ejection fraction (HFpEF) (who had left ventricular ejection greater than 40%). Patients with severe peripheral oedema were more likely to have HFpEF with valve disease underlying their heart failure, but adjusting for these differences did not account for the association between peripheral oedema on outcome.

Apart from OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure n= 48,612) and ADHERE (Acute Decompensated Heart Failure National, number in derivation cohort = 33,046 and validation cohort 32,229 ) registries, most prognostic models for acute heart failure were developed based on relatively small cohorts of highly selected patients. (21-23) Both models were designed solely to study in-hospital

mortality.(24) In OPTIMIZE-HF, age, race, heart rate, systolic blood pressure, serum creatinine and sodium concentrations, heart failure as the primary cause of admission, liver disease, previous stroke, peripheral vascular disease, hyperlipidaemia, smoking, HFrEF, chronic obstructive pulmonary disease (COPD), ACEi and BB at admission predicted in-hospital mortality. In ADHERE, blood urea nitrogen (BUN), serum creatinine and systolic blood pressure predicted in hospital mortality.

Only 4,402 patients were followed for up to 90 days beyond discharge in OPTIMIZE-HF. Systolic blood pressure was the strongest predictor of death, followed by age, weight, COPD, depression, serum sodium and creatinine, liver disease and peripheral oedema. In a multi-variable analysis, the hazard ratio for death after discharge for lower extremity oedema was 1.36 (P 0.019, CI 1.05-1.77)(25), which is similar to our findings. The European Society of Cardiology Heart Failure Long-Term Registry enrolled 5,039 patients between 2011 and 2013 but unfortunately did report the proportion admitted with peripheral oedema.(26)

More data are available for patients enrolled in randomised trials but these are inevitably highly-selected individuals.(23) A post-hoc analysis of PROTECT study (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); age, previous heart failure hospitalization, peripheral oedema, SBP, serum sodium, urea, creatinine and albumin were selected for final model to predict 180 days mortality. However, in this study no variable had a c-index >0.70, few had values >0.60 and peripheral oedema had a c-index of only 0.58 for 30-day mortality and 0.54 for 180 mortality in univariable analysis (an index of 0.5 reflects an association no better than by

chance). A post hoc analysis of the RELAXin in Acute Heart Failure (RELAX-AHF) trial classified 1,161 patients into those with no/mild oedema and moderate/severe oedema. Patients with moderate/severe oedema had a worse prognosis as compared to no/mild oedema but had similar relative but possibly greater absolute benefit from administration of serelaxin. (13)

There are many possible reasons for the higher mortality amongst those with more severe peripheral oedema. It is likely that they have higher right atrial pressures, reflecting more severe pulmonary hypertension, due in part to more severe left heart disease, more severe right ventricular dysfunction and more tricuspid regurgitation. (27) The prognosis of patients with heart failure may be more strongly related to right than to left ventricular dysfunction. (28) Thus, the severity of peripheral oedema may be a surrogate for more severe right heart disease.

Moreover, a rise in renal vein pressure may contribute to renal dysfunction, diuretic resistance and a worse prognosis and hepatic congestion will impair degradation of aldosterone and reduce synthesis of albumin, both of which may exacerbate oedema. (29) Low arterial pressure and renal dysfunction and a high prevalence of atrial fibrillation may all confound the effective implementation and/or benefits of effective therapies.

Very few sizeable trials have targeted patients with peripheral oedema. (30) In the Ultrafiltration versus intravenous diuretics for patients hospitalized for Acutely decompensated HF (UNLOAD; n = 200) trial, patients with hypervolemia were randomized to Ultrafiltration (UF) or intravenous (IV) diuretics. After 48 hours, net fluid and weight loss was greater in the UF group. A lower rehospitalisation rate was observed in those assigned to UF without a significant effect on renal function or mortality. (31) In contrast, in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF; n = 188) trial, stepped pharmacological therapy and UF were

similarly effective at short-term correction of fluid overload but there were more adverse events in those assigned to UF and no differences were observed on rehospitalisation or mortality.(32-34) The Aquapheresis Versus Intravenous Diuretics & Hospitalizations for Heart Failure (AVOID-HF; n = 224) is the most recent randomized trial comparing UF and pharmacological therapy. (35) During the hospital admission, more fluid was removed by UF but weight loss was similar in each arm 72 hours after randomization. During a 90-day follow-up, patients assigned to UF had a lower rate of re-hospitalisation for heart failure, although no difference in all-cause rehospitalisation or mortality was observed. A large proportion of patients in these trials had substantial peripheral oedema (UNLOAD; 80%, CARRESS-HF; not reported, AVOID-HF; 87%). In summary, although it is clear that UF can off-load fluid in diuretic-resistant patients and might be a useful bridging-procedure to a definitive therapy or recovery, it is unclear whether UF substantially alters outcome for patients who have severe irreversible cardiac dysfunction.

Current clinical practice lacks a standardized approach to the classification of ‘acute’ heart failure. Classification based on the needs of the patient and choice of therapy is one possible approach which may vary according to aetiology, left ventricular ejection, heart rhythm, blood pressure, renal function, precipitating factors and the acuity and nature of the presentation. However, current clinical practice lacks a standardized approach to evaluate and grade either pulmonary or peripheral congestion. Accurate methods of assessing pulmonary congestion are impractical for routine clinical use.(36) Pulmonary congestion may be assessed on a chest X-ray but has low sensitivity and specificity. Assessment by lung ultrasound may be more sensitive and quantitative but use is limited to a few enthusiasts and there is limited experience of its use in multi-centre studies.(37) Ultrasound measurement of the inferior vena cava is objective and strongly related to prognosis but is rarely used in clinical practice .(38) Objective methods of

assessing the severity of peripheral oedema are also rarely employed in clinical practice. Better scoring systems and clinical tools are needed for routine clinical assessment and grading of both pulmonary and peripheral congestion.

## **Limitations**

There are many limitations to this analysis. The severity of peripheral oedema and NYHA class were assessed by many clinicians in a semi-quantitative fashion often based on case-note review. This could account for the anomaly that some patients were admitted without evidence of either severe breathlessness or peripheral oedema. However, some patients will have been admitted with other diagnoses and only subsequently had their admission dominated by the development of heart failure. Some clinical variables were not collected routinely, such as prior history of heart failure, signs of pulmonary congestion, heart rate, blood pressure, urea and natriuretic peptides, although the registry has now started to do so. Detailed assessments of cardiac function, especially of the right heart, by echocardiography or other imaging methods, are not available. More general aspects of health such as frailty, mood, social network and cognitive function were not collected. In common with other large registries, some data were missing although this was mostly driven by the year of collection (older data was more likely to be missing). We used multiple imputations to avoid potential bias caused by excluding patients with missing data. Heart Failure with Mid-range ejection fraction (HFmrEF) is a recently defined entity in the European Society of Cardiology (ESC) 2016 HF guidelines, which encompass those patients who have a LVEF of 40-49%, elevated plasma concentrations of natriuretic peptides and either left ventricular hypertrophy, left atrial enlargement or diastolic dysfunction. In the NHFA, LVEF is simply classified as above or below 40% or not recorded for the majority of patients.

## **Conclusion**

Many patients admitted to hospital for worsening heart failure have peripheral oedema. However, the term acute heart failure may be misleading when applied to such patients. Peripheral oedema often develops over a period of days or weeks and, unless accompanied by severe symptoms at rest, does not constitute a medical emergency. Moreover, these patients are unlikely to benefit from the acute interventions of short duration that were investigated in recent trials of acute heart failure. However, patients with severe peripheral oedema have prolonged hospital stays and a poor prognosis. Unfortunately, very few clinical trials have been conducted in this population to determine what treatments might address their unmet needs. This analysis provides the rationale for designing trials with peripheral oedema as the primary therapeutic target in appropriately selected patients.

## **Acknowledgments**

The National Heart Failure Audit is managed by the National Institute for Cardiovascular Outcomes Research (NICOR) and commissioned by The Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme.

Specialist clinical knowledge and leadership is provided by the British Society for Heart Failure (BSH). The strategic direction and development of the audit is determined by the audit Project Board. This includes representatives of major stakeholders in the audit including cardiologists, the BSH, Heart Failure specialist nurses, Clinical Audit and Effectiveness Managers, patients, NICOR and HQIP.

We would especially like to thank the contribution of all NHS Trusts, Welsh Health Boards and the individual nurses, clinicians and audit teams who collect data and participate in the audit.

## References

1. Clark AL, Cleland JG. Causes and treatment of oedema in patients with heart failure. *Nat Rev Cardiol*. 2013;10(3):156-70.
2. Shoaib A, Waleed M, Khan S, Raza A, Zuhair M, Kassianides X, et al. Breathlessness at rest is not the dominant presentation of patients admitted with heart failure. *European journal of heart failure*. 2014;16(12):1283-91.
3. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *European heart journal*. 2003;24(5):442-63.
4. Harjola VP, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, et al. Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. *European journal of heart failure*. 2010;12(3):239-48.
5. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. *J Am Coll Cardiol*. 2013;61(4):391-403.
6. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol*. 2007;50(8):768-77.
7. Roguin A, Behar D, Ben Ami H, Reisner SA, Edelstein S, Linn S, et al. Long-term prognosis of acute pulmonary oedema--an ominous outcome. *European journal of heart failure*. 2000;2(2):137-44.
8. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure — Re-distribution and other mechanisms beyond fluid accumulation. *European journal of heart failure*. 2008;10(2):165-9.
9. Michalsen A, Konig G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure. *Heart (British Cardiac Society)*. 1998;80(5):437-41.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *Revista espanola de cardiologia (English ed)*. 2016;69(12):1167.
11. Cotter G, Felker GM, Adams KF, Milo-Cotter O, O'Connor CM. The pathophysiology of acute heart failure--is it all about fluid accumulation? *American heart journal*. 2008;155(1):9-18.
12. Clark AL. Almanac 2013: heart failure. *Heart (British Cardiac Society)*. 2013;99(21):1562-6.
13. Gimpelewicz C, Metra M, Cleland JGF, Szecsody P, Chang Wun CC, Boer-Martins L, et al. 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;190:113-22.
14. McDonagh T, Cleland J, Dargie HJ, Whittaker T, Standing M, Mitchell M, et al. National Heart Failure Audit April 2010-March 2011. National Institute For Cardiovascular Outcomes Research (NICOR); 2011 2012.
15. Emdin CA, Hsiao AJ, Kiran A, Conrad N, Salimi-Khorshidi G, Woodward M, et al. Referral for Specialist Follow-up and Its Association With Post-discharge Mortality Among

Patients With Systolic Heart Failure (from the National Heart Failure Audit for England and Wales). *The American journal of cardiology*. 2017;119(3):440-4.

16. Cleland JG, McDonagh T, Rigby AS, Yassin A, Whittaker T, Dargie HJ. The national heart failure audit for England and Wales 2008-2009. *Heart (British Cardiac Society)*. 2011;97(11):876-86.

17. Cain KC, Lange NT. Approximate case influence for the proportional hazards regression model with censored data. *Biometrics*. 1984;40(2):493-9.

18. Lee YH, Bang H, Kim DJ. How to Establish Clinical Prediction Models. *Endocrinology and metabolism (Seoul, Korea)*. 2016;31(1):38-44.

19. Devarajan K, Ebrahimi N. Goodness-of-Fit Testing for the Cox Proportional Hazards Model. In: Huber-Carol C, Balakrishnan N, Nikulin MS, Mesbah M, editors. *Goodness-of-Fit Tests and Model Validity*. Boston, MA: Birkhäuser Boston; 2002. p. 237-54.

20. Vandembroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology*. 2007;18(6):805-35.

21. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Predictors of in-hospital mortality in patients hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Journal of the American College of Cardiology*. 2008;52(5):347-56.

22. Adams KF, Jr., Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2005;149(2):209-16.

23. Nagai T, Sundaram V, Shoaib A, Shiraishi Y, Kohsaka S, Rothnie KJ, et al. Validation of U.S. mortality prediction models for hospitalized heart failure in the United Kingdom and Japan. *Eur J Heart Fail*. 2018;20(8):1179-90.

24. Fonarow GC, Adams KF, Jr., Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA : the journal of the American Medical Association*. 2005;293(5):572-80.

25. O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2008;156(4):662-73.

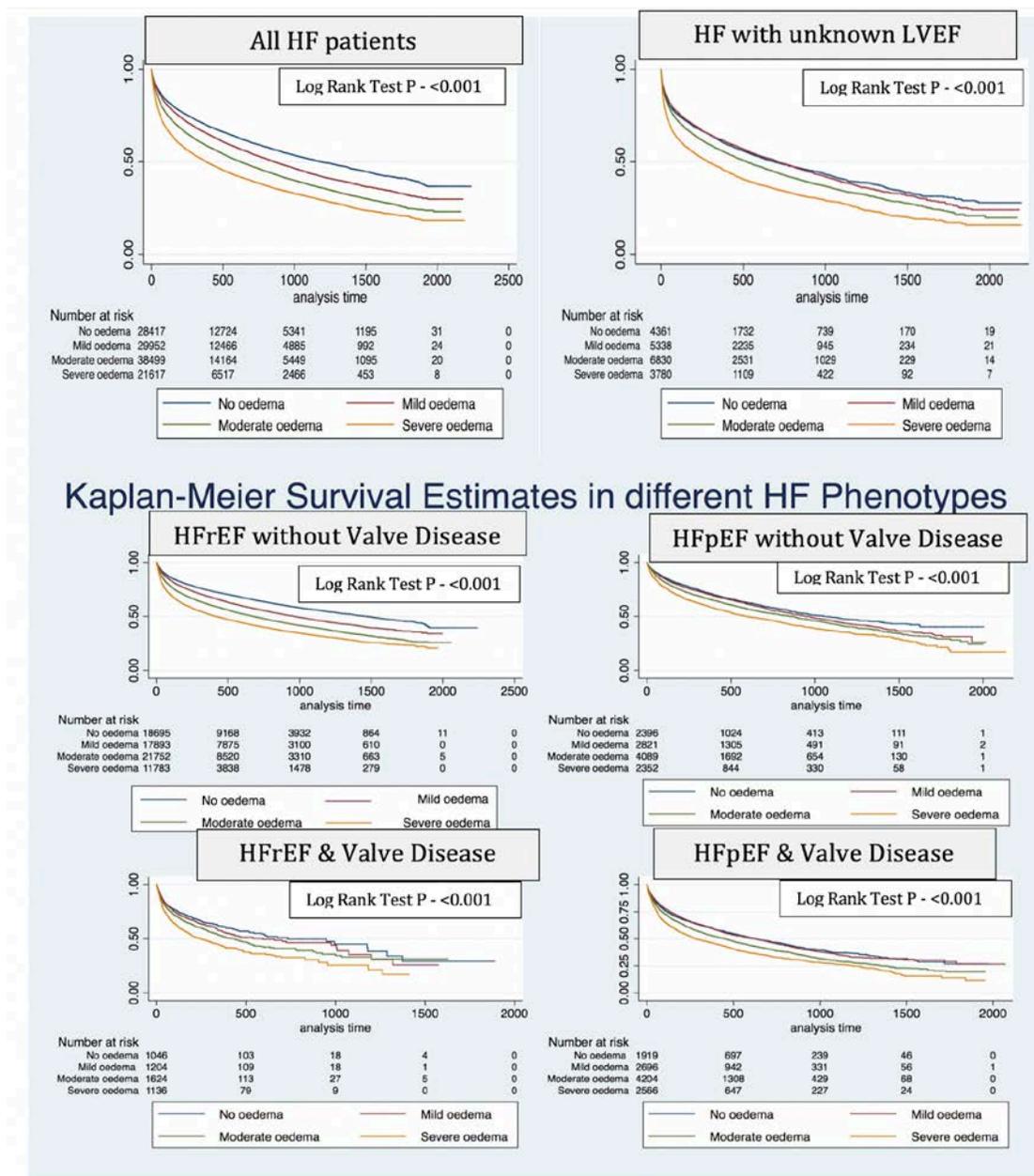
26. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2013;15(10):1173-84.

27. Damy T, Kallvikbacka-Bennett A, Goode K, Khaleva O, Lewinter C, Hobkirk J, et al. Prevalence of, Associations With, and Prognostic Value of Tricuspid Annular Plane Systolic Excursion (TAPSE) Among Out-Patients Referred for the Evaluation of Heart Failure. *Journal of cardiac failure*. 18(3):216-25.

28. Bourantas CV, Loh HP, Bragadeesh T, Rigby AS, Lukaschuk EI, Garg S, et al. Relationship between right ventricular volumes measured by cardiac magnetic resonance imaging and prognosis in patients with chronic heart failure. *European journal of heart failure*. 2011;13(1):52-60.

29. Cleland JG, Carubelli V, Castiello T, Yassin A, Pellicori P, Antony R. Renal dysfunction in acute and chronic heart failure: prevalence, incidence and prognosis. *Heart failure reviews*. 2012;17(2):133-49.
30. Koratala A, Kazory A. Extracorporeal Ultrafiltration for Acute Heart Failure: Lost Battle or Lasting Opportunity? *Blood purification*. 2017;43(1-3):1-10.
31. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *Journal of the American College of Cardiology*. 2007;49(6):675-83.
32. Bart BA, Goldsmith SR, Lee KL, Redfield MM, Felker GM, O'Connor CM, et al. Cardiorenal rescue study in acute decompensated heart failure: rationale and design of CARRESS-HF, for the Heart Failure Clinical Research Network. *Journal of cardiac failure*. 2012;18(3):176-82.
33. Lala A, McNulty SE, Mentz RJ, Dunlay SM, Vader JM, AbouEzzeddine OF, et al. Relief and Recurrence of Congestion During and After Hospitalization for Acute Heart Failure: Insights From Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF). *Circulation Heart failure*. 2015;8(4):741-8.
34. Grodin JL, Carter S, Bart BA, Goldsmith SR, Drazner MH, Tang WHW. Direct comparison of ultrafiltration to pharmacological decongestion in heart failure: a per-protocol analysis of CARRESS-HF. *European journal of heart failure*. 2018.
35. Costanzo MR, Negoianu D, Jaski BE, Bart BA, Heywood JT, Anand IS, et al. Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure. *JACC Heart failure*. 2016;4(2):95-105.
36. Lange NR, Schuster DP. The measurement of lung water. *Critical care (London, England)*. 1999;3(2):R19-r24.
37. Li H, Li YD, Zhu WW, Kong LY, Ye XG, Cai QZ, et al. A Simplified Ultrasound Comet Tail Grading Scoring to Assess Pulmonary Congestion in Patients with Heart Failure. *BioMed research international*. 2018;2018:8474839.
38. Pellicori P, Carubelli V, Zhang J, Castiello T, Sherwi N, Clark AL, et al. IVC diameter in patients with chronic heart failure: relationships and prognostic significance. *JACC Cardiovasc Imaging*. 2013;6(1):16-28.

# Figures



**Figure 1:** Kaplan-Meier survival estimates for all-cause mortality according to severity of peripheral oedema for the overall population and four phenotypic groups

HF; Heart Failure, LVEF; Left ventricular ejection fraction, HFrEF; Heart failure with reduced ejection fraction, HFpEF; Heart failure with preserved ejection fraction



## Tables

**Table 1:** Clinical Characteristics and treatment at discharge

Variable	Data available	No Oedema	Mild Oedema	Moderate Oedema	Severe Oedema	P-value
Numbers	121,214	29,150(24%)	30,587(25%)	39,351(33%)	22,126(18%)	
Age (years)	121,212 (99.9%)	77 (67-85)	80 (72-86)	80 (72-86)	79 (70-86)	<0.0001
Women	121,134 (99.9%)	11,700 (40%)	13,978 (46%)	17,345 (44%)	8,591 (39%)	<0.0001
Previous DM	117,691 (97%)	7,103 (25%)	8,879 (30%)	12,478 (33%)	7,566 (35%)	<0.0001
Previous HTN	116,191 (96%)	13,404 (48%)	16,375 (56%)	21,664 (58%)	11,902 (56%)	<0.0001
Previous IHD	115,648 (95%)	13,591 (49%)	15,140 (52%)	19,165 (51%)	10,232 (49%)	<0.0001
Previous Valve heart disease	113,481 (94%)	5,375 (19%)	6,555 (23%)	9,541 (26%)	5,886 (28%)	<0.0001
<b>NYHA Class 117,117(97%)</b>						
Class I	6,449 (6%)	4,098 (15%)	1,034 (3%)	815 (2%)	502 (2%)	<0.0001
Class II	19,027 (16%)	6,472 (23%)	7,274 (24%)	4,033 (11%)	1,248 (6%)	<0.0001
Class III	50,937 (43%)	10,215 (36%)	12,998 (44%)	20,017 (53%)	7,707 (36%)	<0.0001
Class IV	40,704 (35%)	7,216 (26%)	8,402 (28%)	13,264 (35%)	11,822 (56%)	<0.0001
Creatinine (mmol/L)	36,961 (30%)	104 (82-139)	108 (84-145)	113 (87-156)	126 (93-174)	0.0001
Haemoglobin (g/L)	33,540 (28%)	12.5 (11-14)	12 (10.8-13.5)	12 (10.6-13.2)	11.7 (10.3-13)	0.0001
Anaemia **	33,540 (28%)	4,009 (47%)	4,454 (55%)	6,222 (59%)	4,166 (65%)	<0.001
<b>Echocardiogram with LVEF available: 100,313 (83%)</b>						
HFpEF. No Valve Dis.	11,870	2,436 (10%)	2,877 (11%)	4,151 (13%)	2,406 (13%)	0.001
HFrEF. No Valve Dis.	71,670	19,164 (78%)	18,253 (73%)	22,218 (69%)	12,035 (66%)	<0.001
HFpEF & Valve Dis.	11,638	1,967 (8%)	2,749 (11%)	4,291 (13%)	2,631 (15%)	<0.001
HFrEF & Valve Dis.	5,135	1,070 (4%)	1,227 (5%)	1,672 (5%)	1,166 (6%)	0.001
Unknown LVEF	20,309	4,361 (15%)	5,338 (17%)	6,830 (17%)	3,780 (17%)	0.001
Length of stay in days	121,030 (99.9%)	6 (3-13)	7 (3-14)	9 (5-17)	12 (6-21)	0.0001
<b>Treatment at discharge</b>						
ACE inhibitor	105,706 (87%)	16,971/25,923 (65%)	16,699/27,226 (61%)	20,172/34,318 (59%)	9,994/18,239 (55%)	<0.0001

ARB	96,269 (79%)	3,723/23,324 (16%)	4,271/24,894 (17%)	5,098/31,386 (16%)	2,484/16,665 (15%)	<0.0001
Beta blocker	106,756 (88%)	18,565/26,176 (71%)	18,143/27,441 (66%)	21,705/34,648 (63%)	11,184/18,941 (60%)	<0.0001
MRA	105,032 (87%)	9,037/25,289 (36%)	9,742/26,888 (36%)	13,994/34,249 (41%)	9,121/18,606 (49%)	<0.0001
Digoxin	104,847 (86%)	4,768/25,290 (19%)	5,957/26,749 (22%)	8,446/34,013 (25%)	4,996/18,795 (27%)	<0.0001
Loop diuretics	112,166 (93%)	21,872/27,003 (81%)	26,012/28,825 (90%)	33,715/36,653 (92%)	18,113/19,775 (92%)	<0.0001
Thiazide like diuretics	102,484 (85%)	564/24,599 (2%)	884/26,177 (3%)	2,114/33,382 (6%)	2,209/18,326 (12%)	<0.0001

Data are percentages or median and inter-quartile range.

All proportions according to severity of oedema in brackets are calculated from available data

DM; Diabetes Mellitus, g/l; Gram per litre, HTN; Hypertension, IQR; Interquartile range, IHD; Ischaemic Heart disease, HFrEF = heart failure and left ventricle ejection fraction < 40%, HFpEF = heart failure and left ventricle ejection fraction >40%, NYHA; New York Heart Association, ACE; Angiotensin Converting Enzyme Inhibitor, ARB; Angiotensin receptor blocker, MRA; Mineralocorticoid Receptor antagonist.

\*\* Anaemia = Haemoglobin <13 for men and <12 for women

Table 2: Mortality & Univariate Analysis

Variable	No Oedema	Mild Oedema	Moderate Oedema	Severe Oedema	P-value
Numbers	29,150	30,587	39,351	22,126	
Deaths during index admission	2,150 (7%)	2,427 (8%)	3,981 (10%)	3,432 (16%)	<0.0001
Hazard ratio of death from discharge to census	Ref	1.24 (P <0.0001, CI 1.21-1.28)	1.50 (P <0.0001, CI 1.46-1.54)	1.80 (P <0.0001, CI 1.75-1.86)	
Total deaths	11,507 (39%)	13,929 (46%)	20,377 (52%)	13,003 (59%)	<0.0001
Hazard ratio of death from admission to census	Ref	1.20 (P <0.001, CI 1.17-1.23)	1.47 (P <0.0001, CI 1.44-1.51)	1.88 (P <0.0001, CI 1.84-1.94)	
Hazard ratio of death from admission to census on Imputed data	Ref	1.15 (P < 0.0001, CI 1.14-1.16)	1.41 (P <0.0001, CI 1.40-1.42)	1.83 (P <0.0001, CI 1.81-1.84)	

Table 3: Multi Variable Cox Regression Model 3 on original and imputed data

<u>Variables</u>	Cox Model based on Original data (P < 0.0001)		Cox Model based on Imputed data (P < 0.0001)	
	<u>Hazard Ratio</u>	<u>P-value &amp; CI</u>	<u>Hazard Ratio</u>	<u>P-value &amp; CI</u>
<b>Oedema*</b>				
Mild	1.13	<0.001 1.09-1.18	1.06	<0.001 1.05-1.07
Moderate	1.31	<0.001 1.27-1.37	1.24	<0.001 1.22-1.25
Severe	1.57	<0.001 1.51-1.63	1.55	<0.001 1.53-1.57
Age	1.04	<0.001 1.03-1.05	1.04	<0.001 1.03-1.04
Male Gender	1.13	<0.001 1.10-1.15	1.12	<0.001 1.11-1.13
<b>NYHA Class<sup>+</sup></b>				
Class II	1.08	<0.02 1.01-1.15	0.90	<0.001 0.88-0.91
Class III	1.22	<0.001 1.15-1.30	0.99	<0.81 0.98-1.01
Class IV	1.34	<0.001 1.26-1.42	1.17	<0.001 1.15-1.19
H/O Diabetes Mellitus	1.08	<0.001 1.08-1.11	1.09	<0.001 1.08-1.10
H/O Hypertension	0.93	<0.001 0.90-0.95	0.91	<0.001 0.90-0.92
H/O of IHD	1.25	<0.001 1.22-1.28	1.17	<0.001 1.16-1.18
H/O Valvular heart disease	1.22	<0.001 1.18-1.25	1.21	<0.001 1.20-1.22
Length of stay	1.005	<0.001 1.004-1.006	1.004	<0.001 1.003-1.005
HFrEF	1.21	<0.001 1.17-1.24	1.14	<0.001 1.13-1.15
ACI	0.58	<0.001 0.56-0.59	0.65	<0.001 0.64-0.66
ARB	0.57	<0.001 0.54-0.59	0.64	<0.001 0.63-0.65
MRA	0.95	<0.001 0.93-0.98	1.02	<0.001 1.01-1.03
Beta blockers	0.70	<0.001 0.69-0.72	0.76	<0.001 0.75-0.77
Digoxin	0.99	<0.66 0.97-1.02	0.93	<0.001 0.92-0.94
Loop diuretics	0.70	<0.001 0.68-0.73	0.73	<0.001 0.72-0.74
Thiazide diuretics	1.26	<0.001 1.20-1.32	1.16	<0.001 1.15-1.18

\* Compare to No Oedema at presentation + Compare to NYHA class 1 at presentation.

CI; 95% Confidence Interval, H/O; History of, IHD; Ischaemic heart disease, NYHA; New York Heart Association,