Acute heart failure congestion and perfusion status – impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA Heart Failure Long-Term Registry

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Abstract

Aims. Classification of acute heart failure (AHF) patients into four clinical profiles defined by evidence of congestion and perfusion is advocated by the 2016 European Society of Cardiology (ESC)guidelines. Based on the ESC-EORP-HFA Heart Failure Long-Term Registry, we compared differences in baseline characteristics, in-hospital management and outcomes among congestion/perfusion profiles using this classification.

Methods and results. We included 7865 AHF patients classified at admission as: 'dry-warm' (9.9%), 'wet-warm' (69.9%), 'wet-cold' (19.8%) and 'dry-cold' (0.4%). These groups differed significantly in terms of baseline characteristics, in-hospital management and outcomes. In-hospital mortality was 2.0% in 'dry-warm', 3.8% in 'wet-warm', 9.1% in 'dry-cold' and 12.1% in 'wet-cold' patients. Based on clinical classification at admission, the adjusted hazard ratios (95% confidence interval) for 1-year mortality were: 'wet-warm' vs. 'dry-warm' 1.78 (1.43–2.21) and 'wet-cold' vs. 'wet-warm' 1.33 (1.19–1.48). For profiles resulting from discharge classification, the adjusted hazard ratios (95% confidence interval) for 1-year mortality were: 'wet-warm' vs. 'dry-warm' 1.46 (1.31–1.63) and 'wet-cold' vs. 'wet-warm' 2.20 (1.89–2.56). Among patients discharged alive, 30.9% had residual congestion, and these patients had higher 1-year mortality compared to patients discharged without congestion (28.0 vs. 18.5%). Tricuspid regurgitation, diabetes, anaemia and high New York Heart Association class were independently associated with higher risk of congestion at discharge, while beta-blockers at admission, de novo heart failure, or any cardiovascular procedure during hospitalization were associated with lower risk of residual congestion.

Conclusión. Classification based on congestion/perfusion status provides clinically relevant information at hospital admission and discharge. A better understanding of the clinical course of the two entities could play an important role towards the implementation of targeted strategies that may improve outcomes.

Keywords

Acute heart failure; Congestión; Perfusion; Forrester classification; Registry•Outcomes

Introduction

Acute heart failure (AHF) includes a wide spectrum of clinical conditions with varied aetiologies and triggers.[1] The pathophysiology of AHF is also diverse, and involves various haemodynamic abnormalities related to elevated ventricular filling pressure and/or reduced cardiac output, clinically manifesting as congestion and hypoperfusion.[2-6]

Classification of AHF patients by evidence of congestion and perfusion was introduced by the 2016 European Society of Cardiology (ESC) heart failure (HF) guidelines with recommended treatment approaches for each category.[1] This classification scheme is based on bedside evaluation and categorization by clinical signs of congestion ('wet' vs. 'dry' if present vs. absent) and hypoperfusion ('cold' vs. 'warm' if present vs. absent),[1] to allow differentiation into four distinct profiles: 'wet-warm' – patients demonstrating congestion and adequate peripheral perfusion; 'wet-cold' – with congestion and hypoperfusion; 'dry-cold' – free of congestion but with hypoperfusion; and 'dry-warm' – free of either congestion or hypoperfusion. The classification was originally proposed by Forrester and Waters[3] and then clinically adapted by Nohria *et al.*[4] Although invasive haemodynamic data could refine classification based on clinical examination and would improve guiding of intravenous (i.v.) therapies, the results of the ESCAPE trial[7] showed no benefit in terms of mortality and HF readmissions from invasive assessment of haemodynamics by pulmonary artery catheter compared to rigorous clinical assessment. Previous studies[4,8] have yielded conflicting evidence about the reliability of congestion/hypoperfusion profiling to offer prognostic information. However, these studies had small sample size, enrolling less than 500 patients, and selectively included only those patients with advanced HF and very low ejection fraction.[4,8] Although proposed by the recent ESC guidelines,[1] this classification has never been validated in an unselected 'real-world' AHF population including patients from the entire continuum of clinical severity and with any range of left ventricular ejection fraction (LVEF).

The ESC-EURObservational Research Programme (EORP)-Heart Failure Association (HFA) Heart Failure Long-Term (HF-LT) Registry is the largest pan-European cohort with systematic collection of baseline, discharge and 1-year follow-up data, providing contemporary information about the whole spectrum of AHF patients, from all regions of Europe and affiliated countries at a mix of primary, secondary and tertiary care centres.[9-

[11] The objectives of this analysis were to use the congestion/hypoperfusion classification in ESC-EORP-HFA HF-LT Registry, and to describe the baseline features, treatment patterns and outcomes associated with each clinical profile, defined at both admission and discharge.

Methods

Study design

The ESC-EORP-HFA HF-LT Registry is an ongoing, prospective, multinational, multicentre, observational study of patients presenting to 211 cardiology centres from 21 European and Mediterranean countries.[9-11] Centre selection took into account the population of each country (one centre/2 million people) and representation of each category of hospitals and hospital facilities according to the distribution of the different types of medical centres in the individual country, approximately 20% of centres providing cardiac surgery, 30% that do not provide cardiac surgery but do provide interventional cardiology, and 50% community centres providing neither cardiac surgery nor interventional cardiology. Patients were included one day per week. Ethics approvals were obtained for all sites and written informed consent was provided by all patients. The EORP Department of the ESC was appointed to coordinate the project operationally, provide support to the committees, national coordinators, and participating centres, and to oversee the methodological concepts of the survey and statistical analysis.

Patients and data

All patients admitted to hospital for AHF (either pre-existing or new-onset HF) were included, and age < 18 years was the only exclusion criterion. A diagnosis of AHF was made by the clinician-investigators at initial presentation and required the presence of signs and symptoms of HF, evidence of cardiac dysfunction, and the need for therapy.[1]
In the ESC-EORP-HFA HF-LT Registry, data from a comprehensive clinical examination were collected at both admission and discharge. Based on the findings from clinical examination at admission, patients were retrospectively classified into four profiles according to the 2016 ESC guidelines[1]: no congestion and no hypoperfusion

('dry-warm'), congestion without hypoperfusion ('wet-warm'), hypoperfusion without congestion ('dry-cold'), and congestion and hypoperfusion ('wet-cold').

To categorize as congestion, at least one of the following clinical signs collected in the case report form should be present: pulmonary rales, peripheral bilateral oedema, jugular venous distension >6 cm, hepatomegaly, hepatojugular reflux. Hypoperfusion was defined by the presence of either cold extremities or other peripheral hypoperfusion signs (oliguria or mental confusion).

Patients who survived during hospitalization were again re-classified into the same four profiles, based this time on clinical signs collected at discharge.

Statistical analysis

All results were summarized overall and then stratified by the four clinical profiles. Baseline continuous variables were reported as mean ± standard deviation or median and interquartile range (IQR), as appropriate. Comparisons among groups were made using *t*-test and Kruskal–Wallis test, as appropriate. Categorical variables were reported as percentages and compared using chi-square test, or Fisher's exact test if any expected cell count was less than five.

In-hospital and 1-year outcomes were reported stratified by congestion/hypoperfusion classification. Plots of the Kaplan–Meier curves for time to all-cause death and time to first all-cause death or HF hospitalization were performed for clinical profiles identified at admission and discharge, and survival distributions were compared using the log-rank test. In addition to unadjusted Kaplan–Meier curves, the associations between clinical profiles and in-hospital and 1-year all-cause mortality were assessed using Cox proportional hazard models with multivariable adjustment for baseline relevant variables: age, gender, New York Heart Association (NYHA) class, systolic blood pressure (SBP), LVEF, serum sodium, serum creatinine, and blood urea nitrogen (BUN).

For AHF patients who survived during hospitalization, a multivariable logistic regression analysis was performed to identify independent predictors associated with congestion at discharge. All variables at entry with at least 70% of available data, which were statistically significant at univariate analysis ($P<0.10$) were included, and variables considered of relevant clinical interest were forced into the multivariable model, even if *P*-value was not <0.10 in univariate analysis. A significance level of 0.05 was required to

enter a variable into the model (SLENTRY = 0.05) and a significance level of 0.05 was required for a variable to stay in the model (SLSTAY = 0.05). Missing values were not imputed.

A two-sided *P*-value <0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Clinical profile classification

The registry enrolled 8290 patients hospitalized for AHF, of whom 7865 had detailed physical examination to allow classification into four clinical profiles, thus the study population included 7865 patients hospitalized for AHF.

Classifying patients with AHF by clinical signs of congestion/hypoperfusion collected at admission yielded four mutually exclusive categories: 'dry-warm' (9.9%), 'wet-warm' (69.9%), 'wet-cold' (19.8%), and 'dry-cold' (0.4%) (*Figure* 1). During hospitalization, 417 patients died (5.3%) and classification at discharge was performed in the remaining of 7448 patients who survived. Classification at discharge differed from admission, and patients classified at admission in one of the four clinical profiles frequently had migrated by the time of discharge into other categories (*Figure* 1). The distribution of patients classified at admission by congestion/hypoperfusion status according to the two classification systems recommended by previous guidelines (i.e. clinical phenotypes[11,12] and SBP categories at admission[13]) is presented in the online supplementary *Figure* S1. The 'wet-warm' category was the most prevalent in all clinical profiles, except for cardiogenic shock (CS). Patients with CS presented most commonly as 'wet-cold' (57.8%), but also as 'wet-warm' (13.0%), 'dry and cold' (26.4%), and even 'dry and warm' (2.8%).

Baseline characteristics by congestion/hypoperfusion classification

Detailed baseline characteristics stratified by congestion/perfusion at admission are presented in *Table* 1. Patients classified as 'dry-warm' were younger and more frequently

male and had more commonly a history of percutaneous coronary intervention/coronary artery bypass graft or device implants. Overall, 86.9% of patients classified as ‘wet-warm’ presented at admission with NYHA class III and IV, compared to only 47% for ‘dry-warm’ patients. SBP < 90 mmHg at admission was reported in 6.4% of ‘wet-cold’ and 1.6% of ‘wet-warm’ patients. The lowest haemoglobin levels were reported in ‘wet-warm’ patients. ‘Wet-cold’ patients had more frequently diabetes (41.3%) and baseline renal dysfunction (creatinine > 1.5 mg/dL) (35.4%) and had the highest levels of B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP).

Echocardiography was obtained during hospitalization in 79.8% of patients. On the basis of LVEF categories, HF with reduced (HFrEF), mid-range (HFmrEF) and preserved ejection fraction (HFpEF) was present in 51.1%, 25.1% and 23.8% of patients, respectively. When AHF patients were stratified by LVEF categories, the ‘wet-warm’ profile was identified in 67.3% of HFrEF patients, in 72.7% of HFmrEF patients and in 73.4% of HFpEF patients (online supplementary *Figure* S2). The ‘wet-cold’ profile was more common in HFrEF patients (22.7%).

Moderate to severe mitral and tricuspid regurgitation were reported in 65.7% and 50.6% of ‘wet-cold’ patients, respectively.

In-hospital therapies and procedures

Utilization of i.v. treatments, interventional procedures and cardiovascular therapies is presented in *Table* 2. The proportion of patients treated with i.v. diuretics varied among the four groups, between 30% and 88%. Overall, inotropes and vasopressors were used in 11.7% of patients, and the highest proportion was observed in the ‘wet-cold’ profile (27.8%). Interestingly, invasive procedures were not more common among the cold profiles. Utilization of cardiovascular therapies increased during hospitalization in the warm profiles, and decreased in the cold profiles. During hospitalization, the highest implant rates of cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) was in ‘dry-warm’ patients.

In-hospital course

During hospitalization, 417 (5.3%) patients died, and classification performed at discharge in alive patients showed that 30.9% of discharged patients still had signs of residual congestion (*Figure* 1). Using a multivariable logistic regression model (*Table* 3), moderate to severe tricuspid regurgitation, diabetes and worse NYHA class were independent risk markers for congestion at discharge. In contrast, beta-blocker at admission, high haemoglobin levels at admission, de novo HF and any procedure during hospitalization were associated with lower risk of residual congestion.

During hospitalization, body weight decreased in 65.2% of patients and 24.4% were discharged with NYHA class III and IV (*Table* 4). In-hospital all-cause mortality was 5.3%, and the highest rate was noted in 'wet-cold' patients (12.1%) vs. 9.1%, 2.0% and 3.8% in the 'dry-cold', 'wet-warm' and 'dry-warm' categories, respectively (*Table* 4). Of the total number of deaths occurring during hospitalization, the 'wet-warm' profile was associated with 50.3% of deaths and the 'wet-cold' profile with 45.1% of deaths (online supplementary *Figure* S3). For the deaths collected between discharge and 1-year follow-up, 82.1% of deaths were associated with the 'wet-warm' profile and 11.2% were associated with the 'wet-cold' profile.

Cox proportional hazard model for in-hospital all-cause mortality (*Figure* 2) showed that although in the unadjusted model 'wet-warm' patients had higher mortality than 'dry-warm' patients, mortality rates did not differ significantly by pairwise comparison in the adjusted model. In both unadjusted and adjusted models, in-hospital mortality of 'wet-cold' patients was significantly higher compared to other groups.

Clinical profiles and one-year outcomes

Figure 3 shows the Kaplan–Meier curves for all-cause mortality, and the composite event of all-cause mortality and HF hospitalization for AHF patients stratified by clinical profiles assessed at admission and discharge (again excluding the 'dry-cold' profile because of the few patients in this group). One-year all-cause mortality ranged from 12.1% in 'dry-warm' to 26.4% in 'wet-cold' patients, and most of deaths were due to cardiovascular causes (*Table* 4). AHF patients presenting as 'wet-warm' and 'wet-cold' had the highest 1-year HF hospitalization rate. Patients free of congestion at discharge

had a significantly lower 1-year mortality compared to patients with residual congestion (18.5 vs. 28.0%; $P < 0.001$) (online supplementary *Table* S1).

Since there were significant differences in baseline characteristics among clinical profiles, Cox proportional hazard models with multivariable adjustment were performed, and 1-year mortality rates of each profile resulting from both admission and discharge classification, were pairwise compared by adjusted Cox regression analysis (again excluding 'dry-cold' patients) (*Figure* 2). Comparing 1-year mortality of each profile resulting from admission and discharge classifications, the 'wet-cold' profile had the highest risk, followed by the 'wet-warm' profile and with the 'dry-warm' profile having the lowest risk. All these pairwise differences were highly statistically significant.

Discussion

In the ESC-EORP-HFA HF-LT Registry, classification of patients hospitalized for AHF based on clinical signs obtained at bedside physical examination can be used to detect four distinct phenotypes with different baseline characteristics, different in-hospital therapies and significantly different outcomes. An additional strength of the present analysis is the re-classification at discharge. Using classification at admission, hypoperfusion, but not congestion, was associated with in-hospital mortality, while for discharge classification, hypoperfusion but also congestion were associated with 1-year mortality, suggesting that congestion at discharge is a particularly important treatment target.

This classification scheme was used more than 15 years ago in two previous studies that classified AHF patients prospectively[4] and retrospectively.[8] In both studies, the distribution of the four clinical profiles was similar to the present analysis, with a majority of patients ascertained as 'wet-warm' and only a small minority classified as 'dry-cold'. The 'dry-warm' category represented 9.9% of the study population in the present analysis, compared to 27.2% and 16.6%, respectively, in the two previous studies.[4,8] These differences may reflect changes in medical care patterns over time with an increasing threshold for hospital admission in favour of ambulatory visits or emergency department treatments, as well as differences in the methodologies of the two studies.

Similarly to previous studies,[4,8] 'dry-warm' patients were less symptomatic compared to other phenotypes. Since physical assessment can only detect a moderate to high level of

congestion,[5] it cannot be excluded that these patients may have mild signs of congestion, potentially undetected at initial evaluation but causing sufficient symptoms for patients to seek acute care and to be admitted to hospital. Also, some 'dry-warm' patients may be treated with vasoactive drugs before hospitalization in the ambulance or in the emergency department with resolution of signs/symptoms of HF by the time they were enrolled in the registry. In ESC-EORP-HFA HF-LT Registry, 'dry-warm' patients had the highest rate of CRT/ICD implants, suggesting that some of these patients are 'suitcase' patients with a planned but expedited procedure during acute admission, since elective admissions for procedures are excluded from the registry. Of note, AHF patients classified as 'dry-warm' have a similar echocardiographic pattern as 'wet -warm' patients, in terms of LVEF, left ventricular end-diastolic diameter and left atrial volume, suggesting comparable cardiac structural abnormalities, but with different clinical presentations.

In the ESC-EORP-HFA HF-LT Registry, 'wet-warm' represented the largest category (69.9%), similar to previous reports.[4,8] This category of patients had a dynamic in-hospital course, 39% presented residual congestion at discharge, whereas 59.2% were free of congestion. Furthermore, they had the highest in-hospital decrease in natriuretic peptides (NPs), but the highest proportion of in-hospital worsening renal function (WRF).

Patients classified at admission as 'dry-cold' represented a minority of those admitted with AHF in the ESC-EORP-HFA HF-LT Registry (0.4%). Additionally, when considering discharge classification, only 1.6% of patients were categorized as 'dry-cold'. 'Dry-cold' was also poorly represented in previous studies with proportions ranging from 3.5% to 4.1%.[4,8] This phenotype may represent some hypovolemic patients as a result of dehydration or pre-hospital vasoactive therapies. Some patients may fit into the 'wet-cold' phenotype when clinical signs of congestion at admission are obscure and unnoticed.

The 'wet-cold' profile represented 19.9% of patients enrolled in the ESC-EORP-HFA HF-LT Registry. The 'wet-cold' group includes more diverse entities, with CS at the end-spectrum of severity, representing only 7.8% of 'wet-cold' patients. This suggests that hypoperfusion signs are not completely specific to CS, being reported in other clinical phenotypes such as pulmonary oedema and decompensated HF. Also, utilization of i.v. inotropes in 'wet-cold' patients is lower than in patients with CS,[11] suggesting that the

two entities are not equivalent, and in 'wet-cold' patients hypoperfusion is not always accompanied by SBP < 90 mmHg or by markers of end-organ injury.[14]

Alternatively, CS patients have diverse clinical presentations varying from 'wet-cold' (57.8%) to 'dry-warm' (2.8%), demonstrating the existence of the diverse sub-phenotypes within CS, rather than a singular clinical presentation.[15] Our results are similar to those obtained in the SHOCK trial,[16] where CS patients have been classified as: 'wet-cold' (64%), 'dry-cold' (28%), 'wet-warm' (6%) and 'dry-warm' (3%).

One novel aspect of our work is the assessment by LVEF (HFrEF, HFmrEF and HFpEF) categories. These LVEF categories presented at admission with similar proportion of congestion, suggesting that high filling pressure is a common finding in these phenotypes despite the diverse cardiac abnormalities. Similar proportions of patients free of congestion at discharge, among the three phenotypes, suggest that i.v. vasoactive therapies are equally effective in decreasing filling pressures, regardless of baseline LVEF.

More surprisingly, the considerable prevalence of hypoperfusion in the HFpEF group suggests that LVEF has a low accuracy to identify a specific clinical phenotype. Of note, peripheral hypoperfusion is much closer related to stroke volume and vascular resistance rather than LVEF. In clinical practice, various HFpEF pathologies such as hypertrophic cardiomyopathy, acute mitral regurgitation or massive pulmonary embolism, may clinically manifest with clinical hypoperfusion as a consequence of low stroke volume.

In-hospital outcomes

Despite a relatively long in-hospital stay, a high proportion (30.9%) of patients from the ESC-EORP-HFA HF-LT Registry were discharged with clinical signs suggestive of persistent congestion, which confers a significant risk of 1-year death, similar to the EVEREST[17] and PROTECT[18] trials. Also, in a post-hoc analysis including patients from DOSE-AHF and CARESS-HF, 48% of patients had signs of congestion at discharge, and in particular had higher mortality and rehospitalization rates at 60 days.[19] Ensuring decongestion is an essential goal during AHF hospitalization, but there is no standardized method for evaluating congestion before discharge and what defines adequate decongestion is currently unclear.[20] Although clinical trials[17,21] proposed a 'definition for decongestion', assessment of decongestion based strictly on trial pre-defined clinical

signs may be non-sensitive and non-specific, and has not been investigated in real-life clinical practice. Furthermore, clinicians often limit decongestion interventions due to fear of WRF, but growing evidence suggests that apparent WRF that is due to decongestion is both reversible and not associated with harm.[22,23] In addition, very few studies described the factors associated with residual congestion that may contribute to the understanding of clinical course of congestion during hospitalization.

In the present study, multivariable analysis identified the presence of moderate to severe tricuspid regurgitation as the most important independent predictor of residual congestion. Since the right ventricle is preload-dependent and afterload-sensitive, the presence of functional tricuspid regurgitation signifies a dilated and dysfunctional right ventricle or severe pulmonary hypertension.[24] The association between beta-blocker use at admission and lower risk of residual congestion is not clearly understood. However, these patients may represent a lower-risk group with less contraindications to therapy and more clinically stable over time.[25] Low haemoglobin was also associated with residual congestion. In the EVEREST analysis,[26] anaemic patients had more clinical signs of fluid overload (jugular vein distension and higher level of NPs) and a higher rate of HF readmissions, suggesting that anaemia may be a reflection of haemodilution (or lack of haemoconcentration).[22,23,26] As an effect of hyperinsulinaemia or insulin treatment,[27] diabetes is associated with weight gain, sodium and fluid retention, accounting for the increased probability of residual congestion observed in our study.

The lowest and highest in-hospital mortality rates were reported in the ‘dry-warm’ and ‘wet-cold’ groups, respectively, in both unadjusted and adjusted models. When pairwise compared in an adjusted Cox proportional hazard model, in-hospital mortality of ‘wet-warm’ patients did not differ significantly from mortality of ‘dry-warm’ patients, suggesting that congestion may be an important target of therapy and alleviating congestion during hospitalization is associated with improved outcomes.

One-year outcomes

The Kaplan–Meier curves showed that the highest rates of both 1-year death and the composite of 1-year death and HF readmissions were observed in patients classified at admission as ‘wet-cold’. When pairwise compared in the adjusted Cox model, 1-year mortality differed significantly by each profile. Patients classified at admission as ‘wet-

warm' had higher 1-year mortality than 'dry-warm' patients, in contrast to in-hospital mortality. 'Wet-warm' patients may have been inadequately decongested during hospitalization, or even if decongested they may experience a recurrence of congestion during post-discharge follow-up, which may trigger subsequent deaths or readmissions in the post-discharge phase. These findings may account for the association between congestion at admission and 1-year mortality, despite of lack of association with in-hospital mortality. In a previous study, 65% of decongested AHF patients had recurrence of congestion at 60-day follow-up,[19] suggesting that the clinical benefit of in-hospital decongestive therapies does not extend beyond hospitalization. Taken together, our findings suggest that although it is crucial to achieve adequate decongestion during hospitalization, medical efforts should not be only limited to decongestion, and is further important to treat co-morbidities, to optimize therapies and to follow up patients after discharge.

Analysis of the specific contribution of each clinical profile to the total number of deaths and the Kaplan–Meier curves showed that the vast majority of 'wet-cold' patients died during hospitalization or within the first few months after discharge. In order to improve outcomes in this category, medical therapies, including vasoactive agents and invasive procedures, should be initiated early in the course of decompensation and these patients should be closely monitored during hospitalization. Early recognition of hypoperfusion signs, even in the absence of hypotension, may help to identify in an appropriate therapeutic window the 'high-risk' patients who will develop CS and require mechanical circulatory assistance or specific organ function support.

Previous studies yielded conflicting information about the reliability of the congestion/hypoperfusion classification to predict outcomes. Our results are similar to those reported by Nohria *et al.*[4] revealing significant differences in outcomes by clinical profiles. In another study,[8] although outcomes did not differ significantly among the four profiles, the trend for survival was similar to that seen in the present analysis.

Notably, similar to the classification obtained at admission, phenotyping alive AHF patients based on clinical signs at discharge identified significant differences in mortality among groups. Kaplan–Meier curves based on discharge classification showed that 'wet-cold' patients had an abrupt increase in mortality in the early months post-discharge. Furthermore, comparing 1-year mortality rates in Cox proportional hazard model, patients

with congestion at discharge (‘wet-warm’) had significantly higher 1-year mortality than patients without congestion (‘dry-warm’). In terms of residual clinical congestion, our results are similar to other studies,[17-19] indicating residual congestion as a factor associated with higher rehospitalization and mortality rates, and supporting the risk stratifying properties of congestion at discharge. Indeed, the clinical profile classification at the time of planned discharge will both identify patients at distinctly higher risk and alert clinicians to residual congestion. Persisting congestion should be more aggressively addressed prior to discharge, perhaps even at the expense of delaying discharge. Also, these patients should be more closely followed up during the post-discharge period. Furthermore, other biological variables as surrogate markers of haemodynamic congestion, a $< 30\%$ change in NP concentrations[28] or decreased haematocrit during hospitalization,[29] add significant prognostic information beyond residual clinical congestion. This underscores the need to integrate all data available from in-hospital monitoring acquired with different tools.[30]

Clinical phenotyping of AHF patients, in conjunction with biological variables, may facilitate early decision-making regarding appropriate triage, novel targeted treatment of high-risk populations and may mediate improvements in quality of care and outcomes. However, the impact of AHF classification on current clinical practice should be further evaluated in prospective studies.

Limitations

This analysis retrospectively evaluated physical examinations performed as part of an observational study. Because of the variety of type of centres and participating investigators, the degree of clinical acumen in the examination may have varied. Although a training meeting was organized for all clinical investigators, the diagnosis and classification were made at the point of care by each clinician-investigator and this process may not have been readily reproducible or may have resulted in inconsistent classification. The very low prevalence of in-hospital utilization of pulmonary artery catheter reflects real-life practice typical for an observational study, and consequently these data were not used to validate the clinical classification.

Other potentially important variables, with well-known prognostic importance, such as NP levels, were not selected in the multivariable models or in adjusted analyses, as data were not available in many patients.
Finally, the limited number of patients with a 'dry-cold' profile precluded meaningful statistical analysis of this category.

Conclusions

Classifying AHF patients based on evaluation of clinical signs of congestion/perfusion at baseline and discharge identified significant differences in 1-year mortality and rehospitalizations among groups. 'Wet-cold' patients had the worst outcomes, confirming that hypoperfusion is a marker of severity of HF and is associated with poor prognosis. 'Wet-warm' was not worse than 'dry-warm' for in-hospital mortality, suggesting congestion can be addressed in hospital. However, at discharge, 'wet-warm' had a higher 1-year mortality than 'dry-warm', suggesting residual congestion is associated with poor outcomes. Assessment of congestion and hypoperfusion status is therefore important throughout hospitalization, and a better understanding of the clinical course of the two entities could play an important role towards the implementation of targeted strategies that may improve outcomes.

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Appendix 1

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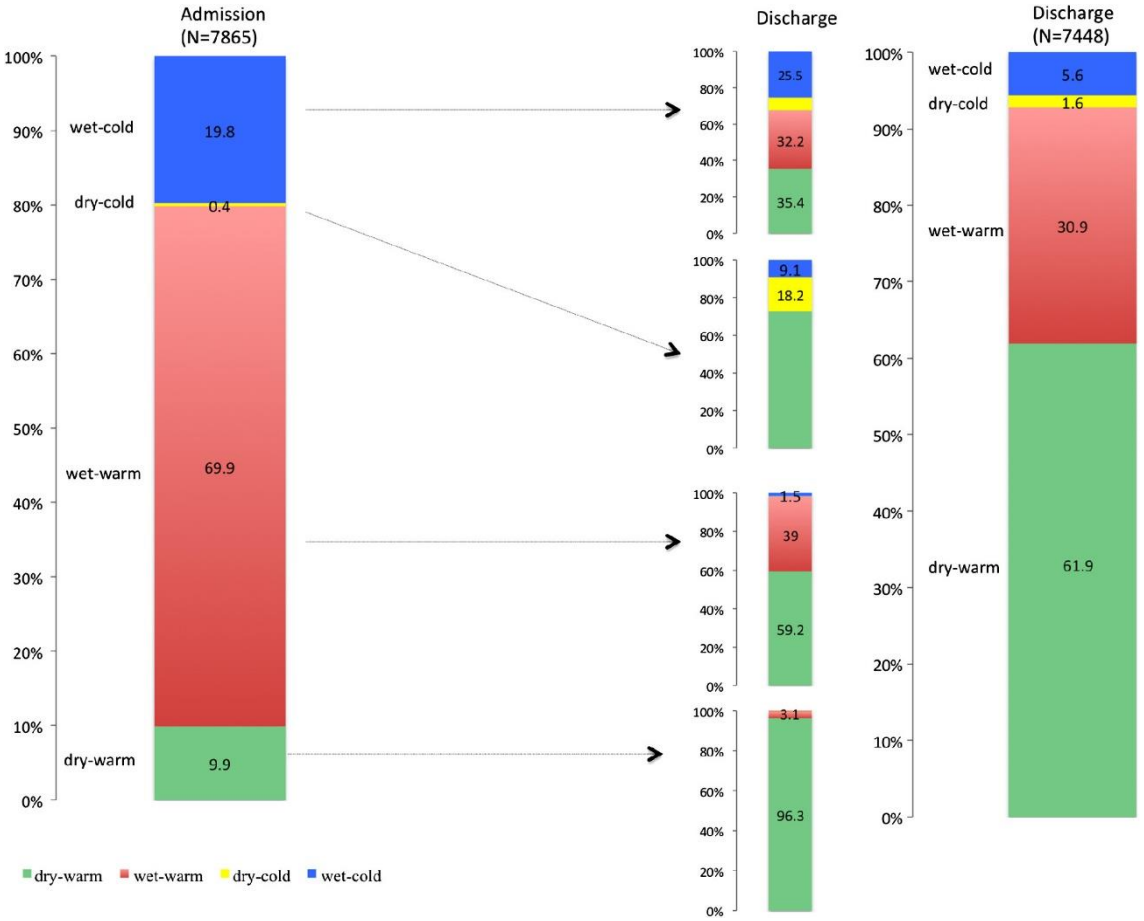

Figure 1. Classification based on congestion/hypoperfusion status assessed by clinical examination performed at admission and discharge. Classification at discharge was used in 7448 patients discharged alive.

Table 1. Epidemiology and baseline characteristics by congestion and hypoperfusion status at admission

	Overall (n = 7865)	Dry-warm (n = 785)	Wet-warm (n = 5492)	Dry-cold (n = 33)	Wet-cold (n = 1555)	P-value
Age (years)	69.0 ± 12.9	65.8 ± 12.2	69.2 ± 13.2	70.8 ± 11.9	70.1 ± 12.1	<0.001
Male sex	62.9	67.3	62.8	57.6	61.2	0.033
History						
Diabetes	39.0	31.6	39.4	36.4	41.3	<0.001
Previous MI	53.4	54.8	51.4	81.8	59.1	<0.001
PCI	20.3	30.2	18.8	36.4	20.3	<0.001
CABG	10.0	10.6	9.8	6.1	10.5	0.629
PM	6.4	6.7	6.4	3.0	6.4	0.865
CRT-P	0.7	0.9	0.7	3.0	0.6	0.353
CRT-D	2.9	4.4	2.5	0.0	3.7	0.004
ICD	4.7	9.5	4.0	0.0	4.9	<0.001
Valvular surgery	5.6	3.8	6.1	6.1	4.6	0.014
PAD	15.1	7.3	12.1	6.1	30.1	<0.001
Stroke/TIA	12.6	8.3	10.7	12.1	21.6	<0.001
VTE	5.3	4.0	3.3	3.0	12.9	<0.001
CKD	26.3	11.4	25.8	21.2	35.4	<0.001
Hepatic dysfunction	7.7	1.7	6.7	3.0	14.5	<0.001
Cancer	4.9	1.8	4.8	0.0	6.8	<0.001
COPD	20.2	8.8	18.2	24.2	33.1	<0.001
Sleep apnoea	3.0	1.0	3.1	3.0	3.5	0.007
Parkinson's disease	1.2	0.6	0.7	3.0	3.2	<0.001

Table 1. Epidemiology and baseline characteristics by congestion and hypoperfusion status at admission

	Overall (n = 7865)	Dry-warm (n = 785)	Wet-warm (n = 5492)	Dry-cold (n = 33)	Wet-cold (n = 1555)	P-value
Depression	7.8	2.6	5.9	12.1	17.5	<0.001
Primary aetiology						
Ischaemic heart disease	56.6	58.1	54.4	75.8	63.5	<0.001
Hypertension	8.1	7.8	8.9	6.1	5.2	<0.001
Dilated cardiomyopathy	13.6	15.0	13.1	12.1	14.7	0.266
Valve disease	12.0	7.6	13.0	6.1	10.6	<0.001
Other	9.7	11.5	10.6	0.0	6.0	<0.001
Precipitants						
ACS	18.6	19.4	16.2	45.5	26.0	<0.001
Myocardial ischaemia	30.9	34.1	27.3	42.4	41.7	<0.001
AF	31.1	21.9	30.3	18.2	38.8	<0.001
Ventricular arrhythmias	8.0	9.2	4.7	12.1	18.8	<0.001
Bradyarrhythmias	3.9	3.6	2.8	9.1	7.6	<0.001
Infection	19.7	6.8	19.6	12.1	26.7	<0.001
Uncontrolled HTN	17.6	9.6	16.4	15.2	26.0	<0.001
Noncompliance	5.5	1.0	5.8	3.0	6.6	<0.001
Renal dysfunction	18.6	7.8	16.7	15.2	31.1	<0.001
Anaemia	15.4	6.8	14.8	18.2	21.7	<0.001
Iatrogenic	1.3	1.5	1.1	0.0	1.8	0.191
Clinical presentation						
New onset (%)	29.7	31.5	31.2	18.2	23.6	

Table 1. Epidemiology and baseline characteristics by congestion and hypoperfusion status at admission

	Overall (n = 7865)	Dry-warm (n = 785)	Wet-warm (n = 5492)	Dry-cold (n = 33)	Wet-cold (n = 1555)	*P*-value
Worsening	70.3	68.5	68.8	81.8	76.4	<0.001
NYHA class						<0.001
II	16.4	53.3	13.0	51.5	9.3	
III	52.1	38.3	57.3	33.3	41.1	
IV	31.5	8.4	29.6	15.2	49.6	
CS	2.8	2.8	1.3	15.2	7.8	<0.001
SBP < 90 mmHg	2.5	1.1	1.6	0.0	6.4	
SBP 90–140 mmHg	67.1	73.9	66.7	69.7	65.1	<0.001
SBP > 140 mmHg	30.4	25.0	31.7	30.3	28.5	
Pulse pressure (mmHg)	50.0 [40.0–65.0]	50.0 [40.0–60.0]	50.0 [40.0–66.0]	49.0 [40.0–70.0]	35.0 [30.0–55.0]	<0.001
Proportional pulse pressure (%)	39.8 [33.6–45.5]	40.0 [35.7–45.6]	40.0 [34.6–45.5]	33.7 [26.0–46.2]	28.8 [23.3–41.4]	<0.001
HR (b.p.m.)	87.0 [72.0–104.0]	76.0 [65.0–90.0]	88.0 [73.0–104.0]	80.0 [72.0–88.0]	90.0 [75.0–110.0]	<0.001
Pulmonary rales	74.6	0.0	82.8	0.0	85.0	<0.001
Peripheral oedema	55.0	0.0	60.8	0.0	63.5	<0.001
JVD > 6 cm	34.4	0.0	35.4	0.0	50.3	<0.001
Hepatomegaly	24.6	0.0	25.2	0.0	35.7	<0.001
Hepatojugular reflux	22.8	0.0	24.8	0.0	32.3	<0.001
Cold extremities	18.3	0.0	0.0	75.7	91.0	<0.001
Other hypoperfusion signsa	16.4	0.0	0.0	45.4	82.1	<0.001
Biology						
Creatinine (mg/dL)	1.2 [0.9–1.5]	1.0 [0.9–1.2]	1.2 [0.9–1.5]	1.2 [0.9–1.5]	1.3 [1.0–1.7]	<0.001

Table 1. Epidemiology and baseline characteristics by congestion and hypoperfusion status at admission

	Overall (n = 7865)	Dry-warm (n = 785)	Wet-warm (n = 5492)	Dry-cold (n = 33)	Wet-cold (n = 1555)	P-value
BUN (mg/dlL)	25.0 [19.0–39.0]	23.0 [19.0–35.0]	25.0 [18.3–36.0]	18.3 [15.6–20.9]	28.1 [21.0–46.0]	0.022
Sodium (mmol/L)	139 [135–141]	139.0 [137–141]	139 [135–141]	137 [135–140]	138.0 [135.0–141.0]	<0.001
Glycaemia (mg/dL)	110 [92–150]	101 [89–123]	111 [93–150]	107 [96–156]	115 [93–161]	<0.001
Haemoglobin (g/dL)	12.8 [11–14]	13.7 [12–15]	12.6 [11–14)	12.7 [10–14]	12.8 [11–14]	<0.001
BNP (pg/mL) (available for 822 patients)	745 [339–1374]	527 [168–869]	756 [354–1315]	339 [246–532]	898 [415–2145]	<0.001
NT-proBNP (pg/mL) (available for 1769 patients)	3937 [1736–8839]	1639 [582–3701]	4144 [1837–9429]	3200 [2500–8270]	5000 [2500–10 590]	<0.001
Troponin (mg/L) (available for 3564 patients)	0.1 [0.0–0.4]	0.1 [0.0–0.5]	0.1 [0.0–0.3]	0.1 [0.0–0.3]	0.1 [0.0–1.2]	<0.001
ECG						
AF	32.3	21.0	33.2	21.4	34.8	<0.001
QRS duration	110.2 ± 31.0	116.6 ± 31.4	109.1 ± 30.6	100.6 ± 35.4	111.2 ± 31.8	<0.001
QT duration	380.4 ± 71.8	397.8 ± 58.1	374.6 ± 75.0	377.1 ± 58.4	391.2 ± 63.9	<0.001
LBBB	15.0	13.2	14.3	3.7	18.3	<0.001
Echo						
LVEF	39.8 ± 14.8	38.9 ± 14.1	39.8 ± 14.4	44.6 ± 15.0	40.4 ± 16.4	0.165
LVEF < 40%	51.0	54.4	50.5	40.0	51.2	
LVEF 40–49%	25.1	26.5	26.0	15.0	21.5	<0.001
LVEF ≥ 50%	23.8	19.1	23.5	45.0	27.2	
LVEDD (mm)	58.7 ± 11.2	58.3 ± 11.9	58.7 ± 11.2	59.3 ± 12.5	59.2 ± 10.7	0.431
LA volume (mL)	69.4 ± 40.7	73.1 ± 36.6	74.4 ± 44.3	42.2 ± 14.5	57.4 ± 28.6	<0.001

Table 1. Epidemiology and baseline characteristics by congestion and hypoperfusion status at admission

	Overall (n = 7865)	Dry-warm (n = 785)	Wet-warm (n = 5492)	Dry-cold (n = 33)	Wet-cold (n = 1555)	P-value
Mitral regurgitation, moderate-severe	52.5	38.2	50.9	63.6	65.7	<0.001
Tricuspid regurgitation, moderate-severe	36.3	19.3	34.8	50.0	50.6	<0.001

Values are expressed as mean ± standard deviation, percentages, or median [interquartile range].

ACS, acute coronary syndrome; AF, atrial fibrillation; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; CS, cardiogenic shock; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; HTN, hypertension; JVD, jugular venous distension; LA, left atrial; LBBB, left bundle brunch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PM, pacemaker; SBP, systolic blood pressure; VTE, venous thromboembolism; TIA, transient ischaemic attack.

[a] Oliguria < 30 mL/h or mental confusion.

Table 2. Intravenous vasoactive therapies, interventions and cardiovascular oral therapies during hospitalization according to profile at admission

	Overall(*n* = 7865)	Dry-warm (*n* = 785)	Wet-warm (*n* = 5492)	Dry-cold (*n* = 33)	Wet-cold (*n* = 1555)	*P*-value
Intravenous therapies						
Inotropes	11.7	5.0	8.2	9.1	27.8	<0.001
Vasodilators	19.3	7.0	20.6	28.1	20.7	<0.001
Diuretics	81.1	30.5	87.7	54.5	83.8	<0.001
Interventions						
Coronary angiography	21.7	41.5	20.2	15.2	17.0	<0.001
PCI/CABG	10.1	17.9	9.3	12.1	8.6	<0.001
EPS	0.6	1.2	0.6	0.0	0.2	0.029
Transcatheter ablation	0.7	1.5	0.6	0.0	0.3	0.006
Right heart catheterization	1.9	2.5	1.9	0.0	1.9	0.610
IABP	0.9	1.2	0.7	6.1	1.4	0.001
CRT	3.8	5.4	3.2	3.0	4.9	0.001
ICD	6.4	11.9	5.3	0.0	7.5	<0.001
Oral CV therapies						
BB admission	72.4	82.8	71.8	60.6	69.8	<0.001
BB discharge	73.9	84.6	74.0	63.6	68.2	<0.001
ACEi/ARB admission	77.7	84.5	78.7	75.8	71.3	<0.001
ACEi/ARB discharge	79.1	84.6	78.7	69.7	69.5	<0.001
MRA admission	55.9	53.0	57.2	27.3	53.6	<0.001
MRA discharge	54.7	53.9	56.1	27.3	50.8	<0.001
Ivabradine admission	3.2	1.3	3.2	3.0	4.0	0.05

Table 2. Intravenous vasoactive therapies, interventions and cardiovascular oral therapies during hospitalization according to profile at admission

	Overall(*n* = 7865)	Dry-warm (*n* = 785)	Wet-warm (*n* = 5492)	Dry-cold (*n* = 33)	Wet-cold (*n* = 1555)	*P*-value
Ivabradine discharge	3.1	1.4	3.3	3.0	3.4	0.033
Diuretics admission	80.3	71.6	81.9	54.5	79.8	<0.001
Diuretics discharge	83.2	73.1	86.3	54.5	77.8	<0.001
Digoxin admission	25.9	16.8	25.6	15.2	31.5	<0.001
Digoxin discharge	23.7	15.7	24.3	18.2	25.7	<0.001

Values are expressed as percentages.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; CV, cardiovascular; EPS, electrophysiological study; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrilator; MRA, mineralocorticoid receptor antagonist.

Table 3. Independent predictors of residual congestion at discharge in multivariable analysis

	OR (95% CI)	*P*-value
Tricuspid regurgitation, moderate-severe (hospital entry)	2.085 (1.850;2.350)	<0.001
Diuretics i.v.	1.601 (1.357;1.889)	<0.001
Diabetes	1.270 (1.129;1.429)	<0.001
NYHA class		
NYHA class IV vs. II	2.563 (2.103;3.124)	<0.001
NYHA class III vs. II	1.702 (1.412;2.052)	<0.001
PCI/CABG/CRT/ICD at discharge	0.706 (0.605;0.824)	<0.001
Beta-blockers (hospital entry)	0.711 (0.624;0.810)	<0.001
Haemoglobin (g/dL) (hospital entry)	0.931 (0.907;0.956)	<0.001
HF status (new onset vs. worsening)	0.621 (0.546;0.706)	<0.001

CABG, coronary artery bypass graft; CI, confidence interval; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; i.v., intravenous; NYHA, New York Heart Association; OR, odds ratio; PCI, percutaneous coronary intervention.

Table 4. In-hospital and 1-year adverse outcomes by classification at admission

	Overall (n = 7865)	Dry-warm (n = 785)	Wet-warm (n = 5492)	Dry-cold (n = 33)	Wet-cold (n = 1555)	P-value
In-hospital outcomes						
All-cause death	5.3	2.0	3.8	9.1	12.1	<0.001
Cardiac	80.6	62.5	75.2	100.0	87.8	
Vascular	5.0	6.3	4.3	0.0	5.9	
Non-cardiovascular	10.6	25.0	14.8	0.0	4.8	
Unknown	3.8	6.3	5.7	0.0	1.6	–
Hospital length of stay (days)	10.7 ± 25.4	8.6 ± 17.9	10.6 ± 26.5	8.2 ± 4.1	12.0 ± 24.6	<0.001
Admitted in ICCU (%)	47.7	38.5	45.4	45.5	60.0	<0.001
ICCU length of stay (days)	2.6 ± 4.6	2.0 ± 4.4	2.5 ± 4.6	3.0 ± 4.3	3.2 ± 4.4	<0.001
NYHA class III/IV at discharge	24.4	18.7.	22.9	20.0	33.4	0.063
Body weight at discharge						
Decrease >3 kg	22.5	8.0	23.5	6.7	27.0	<0.0001
Decrease 0–3 kg	42.7	29.8	43.3	50.0	47.6	
Stable	29.3	56.9	28.2	23.3	17.9	
Increase	5.5	5.4	5.0	20.0	7.5	
WRF at discharge[a]	14.5	9.9	15.2	7.4	13.9	0.008
Hyponatremia at discharge[b]	17.2	16.7	17.0	17.2	18.0	0.845
Decrease ≥ 40% BNP	38.2	26.3	42.0	16.7	31.3	0.163
Decrease ≥ 25% NT-proBNP	56.3	45.9	57.0	50.0	57.1	0.600
1-year outcomes						
1-year all-cause death	22.2	12.1	22.6	28.0	26.4	<0.001

Table 4. In-hospital and 1-year adverse outcomes by classification at admission

	Overall (n = 7865)	Dry-warm (n = 785)	Wet-warm (n = 5492)	Dry-cold (n = 33)	Wet-cold (n = 1555)	*P*-value
Cardiac	47.8	46.4	43.4	71.4	63.2	
Vascular	3.4	6.0	3.1	0.0	3.6	
Non-cardiovascular	13.2	6.0	14.4	14.3	10.7	
Unknown	35.7	41.7	39.1	14.3	22.5	–
1-year all-cause hospitalization	43.6	37.0	43.6	41.7	47.2	<0.001
1-year HF hospitalization	25.6	14.2	26.3	16.7	29.4	<0.001
1-year all-cause death and/or HF hospitalization	44.7	26.2	44.7	48.1	54.1	<0.001

Values are expressed as percentages, or mean ± standard deviation.

BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease formula); HF, heart failure; ICCU, intensive coronary care unit; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; WRF, worsening renal function.

[a] Hyponatremia: Na < 135 mEq/L.

[b] Creatinine (discharge) – Creatinine (baseline) ≥ 0.3 or [1-eGFR (discharge)]/eGFR (baseline) ≥ 0.25.

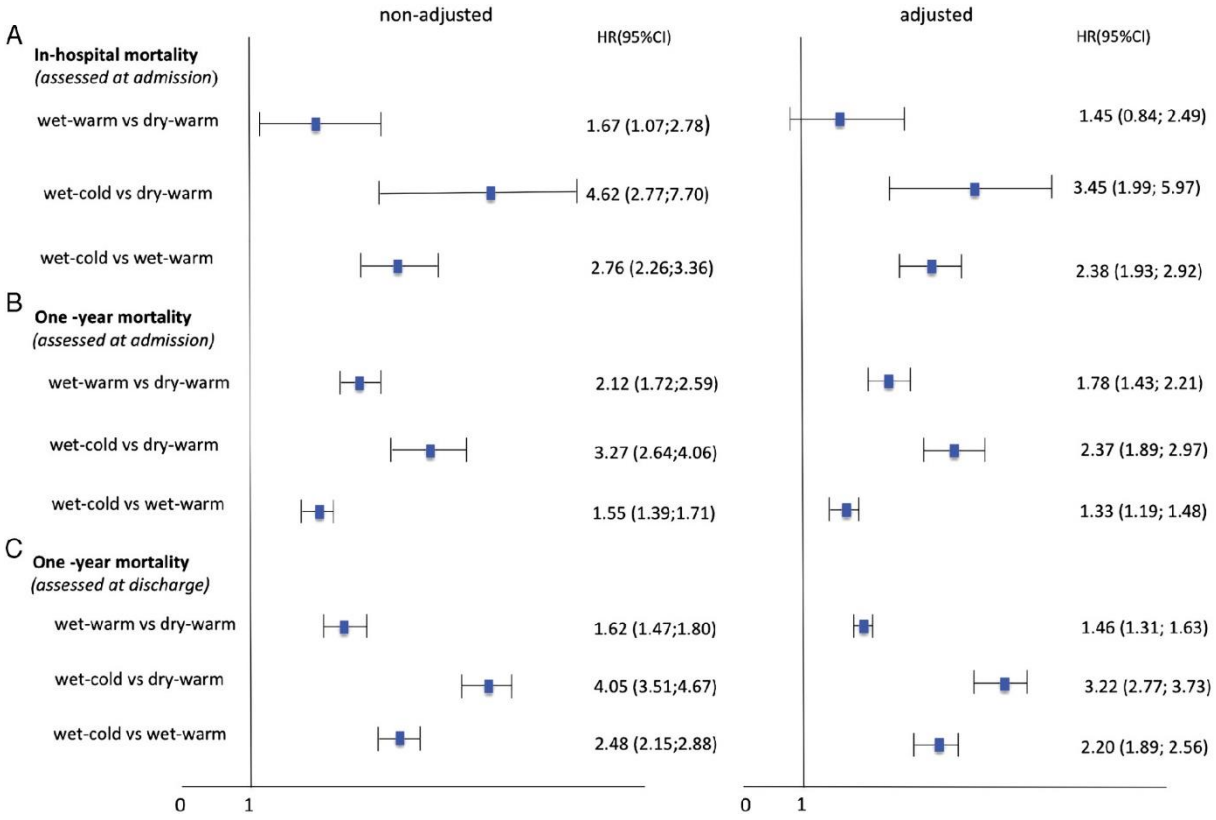

Figure 2. Forest plot of clinical outcomes, in-hospital mortality (*A*) and 1-year mortality using classification at admission *(B)* and at discharge *(C)*. 'Dry-warm', 'wet-warm' and 'wet-cold' profiles were pairwise compared by Cox regression analysis in unadjusted and adjusted model (adjusted for age, gender, New York Heart Association class, systolic blood pressure, left ventricular ejection fraction, serum sodium, serum creatinine and blood urea nitrogen). CI, confidence interval; HR, hazard ratio.

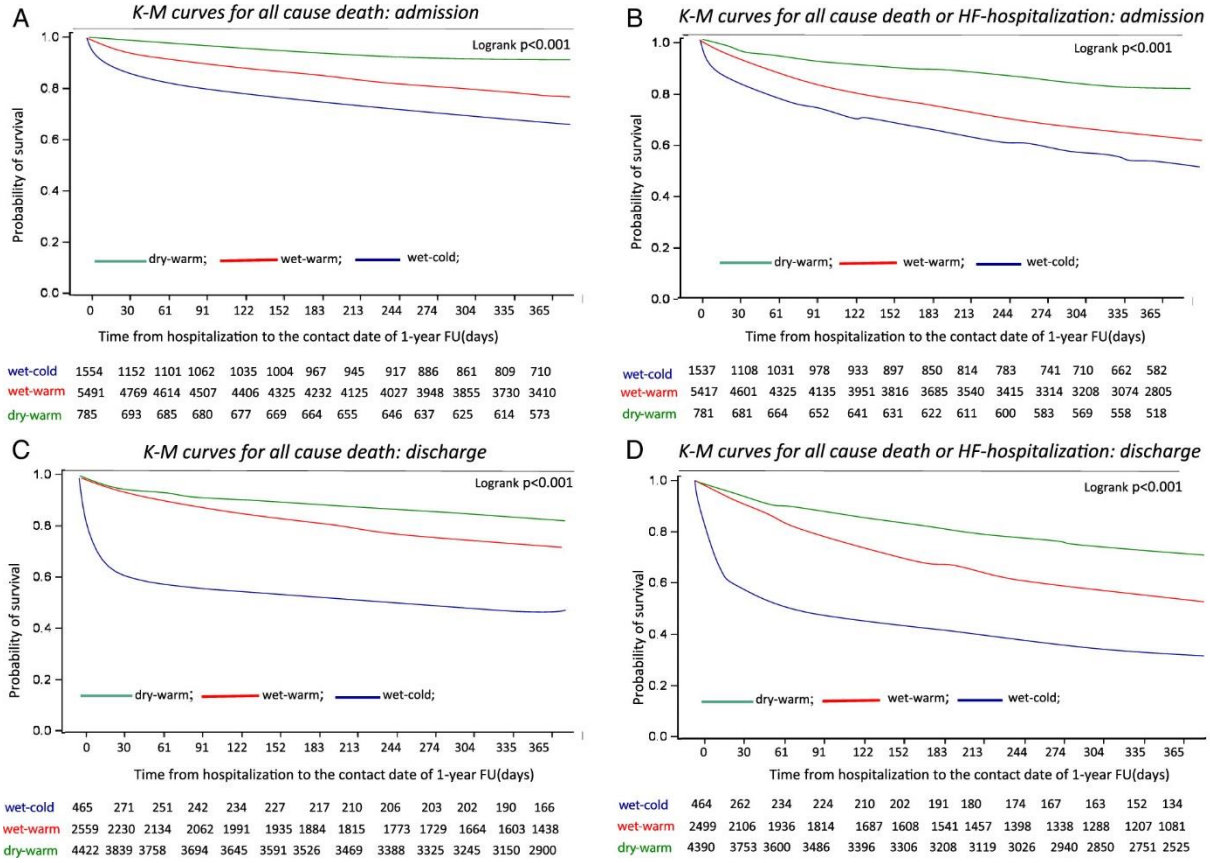

Figure 3. Kaplan–Meier (K-M) curves for 1-year all-cause death and all-cause death or heart failure (HF) hospitalization by clinical profile classification performed at admission (*A*, *B*) and at discharge (*C*, *D*). FU, follow-up.