# Clinical phenotypes of acute heart failure based on signs and symptoms of perfusion and congestion at emergency department presentation and their relationship with patient management and outcomes

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**ABSTRACT**(250words)

**Objective:**To compare the clinical characteristics and outcomes of patients with acute heart failure (AHF) according to clinical profiles based on congestion and perfusion determined in the emergency department (ED)

**Methods:** 11,261 unselected AHF patients from 41 Spanish EDs were classified according to perfusion (normoperfusion=warm; hypoperfusion=cold) and congestion (not=dry; yes=wet). Baseline and decompensation characteristics were recorded as were the main wards to which patients were admitted. The primary outcome was 1-year all-cause mortality; secondary outcomes were need for hospitalisation during the index AHF event, in-hospital all-cause mortality, prolonged hospitalisation, 7-day post-discharge ED revisitfor AHF and 30-day post-discharge rehospitalisation for AHF.

**Results:** 8,558 patients (76.0%) were warm+wet, 1,929 (17.1%) cold+wet, 675 (6.0%) warm+dry,and 99 (0.9%) cold+dry; hypoperfused(cold) patients were more frequently admitted to intensive care units and geriatrics departments, and warm+wet were discharged home without admission.The four phenotypes differed in most of the baseline and decompensation characteristics. The 1-year mortality was 30.8%, and compared to warm+dry, the adjusted HRs were significantly increased for cold+wet (1.660; 95%CI=1.400-1.968) and cold+dry (1.672; 1.189-2.351). Hypoperfused (cold) phenotypes also showed higher rates of index episode hospitalisation and in-hospital mortality, while congestive (wet) phenotypes had a higher risk of prolonged hospitalisation but decreased risk of rehospitalisation. No differences were observed among phenotypes in ED revisit risk.

**Conclusions:** Bedside clinical evaluation of congestion and perfusion of AHF patients upon ED arrival and classification according to phenotypic profiles proposed by the latest ESC Guidelines provide useful complementary information and help to rapidly predict patient outcomes shortly after ED patient arrival.

**Key words:**congestion, perfusion, clinical profiles, acute heart failure, emergency department

**INTRODUCTION**

Acute heart failure (AHF) is considered a syndrome in which new therapeutic approaches have systematically failed to improve survival[1-3]. One of the most relevant causes proposed to explain this failure is the inclusion of patients with different phenotypes in clinical trials. This lack of patient homogeneity has been partially due to the absence of an adequate form of classification of clinical phenotypes of AHF. While it is well accepted to base the classification of patients with chronic heart failure (CHF) on the left ventricular ejection fraction (LVEF), the classification of the episodes of decompensation has evolved. The most recent European Society of Cardiology (ESC) Guidelines have now changed from the previous clinical classification based on six phenotypical forms (worsening or decompensated CHF, pulmonary oedema, hypertensive heart failure, cardiogenic shock, isolated right heart failure, and acute coronary syndrome and heart failure)[4] to one based on the intensity of congestion and perfusion[5].This latter clinical classification is based on physical bedside evaluation of clinical symptoms/signs of congestion ('wet' vs. 'dry' if present vs. absent) and peripheral perfusion ('cold' vs. 'warm' if hypoperfused vs. normoperfused). The combination of these two conditions identifies four phenotypical groups: warm-wet (well perfused and congested), cold-wet (hypoperfused and congested); cold-dry (hypoperfused without congestion); and warm-dry (compensated, well perfused without congestion). **However, while the prognostic potential of this clinical classification has been well-demonstrated, its possible impact on more personalized medicine remains unclear, and indeed, is an ongoing area of investigation.**

Since the publication of the 2016 ESC Guidelines, the only study assessing the potential role of classification in clinical phenotypes in AHF prognostication is the analysis of the ESC-HF-LT Registry reported by Chioncel *et al.*[6]. Nonetheless, the ESC-HF-LT registry only enrolled AHF patients admitted to 211 cardiology centres, and therefore, generalisation of these findings to the whole universe of AHF patients (including those admitted to other hospital departments or completely managed in the ED without hospitalisation) remains to be elucidated. **In particular, the potential applicability of this classification in the ED setting has not previously been assessed. If prompt classification based on the first ED findings of congestion and perfusion were potentially able to identify different patients with different outcomes, it could be of value to promote its use in this particular setting.** Taking these considerations into account, we evaluated the clinical characteristics and the therapeutic approach of the acute episode of decompensation as well as outcomes in the four different clinical phenotypes defined by the 2016 ESC Guidelines in order to provide evidence about the potential value of this classification in the real world.

## METHODS

### Setting

The present study was a secondary analysis within the EAHFE Registry. The EAHFE Registry was initiated in 2007 and every 2-3 years it carries out a 1-2-month recruitment period of all consecutive patients diagnosed with AHF in Spanish EDs participating in the project. To date, 6 recruitment phases (in 2007, 2009, 2011, 2014, 2016 and 2018) have been performed with the participation of 45 EDs from community and university hospitals across Spain (representing about 15% of the Spanish public health care system hospitals), enrolling a total of 18,370 AHF patients. The present study included data from the 11,360 patients recruited in phases 3 to 5, since data needed to classify AHF patients according to the phenotype defined in the 2016 ESC Guidelines[5] were not recorded in phases 1 and 2, and follow-up data of EAHFE-6 patients were not yet available when this study was designed. Details of patient inclusion have been reported previously[7,8]. The AHF diagnosis was based on the Framingham clinical criteria[9]. **Attending emergency physicians performed the initial patient inclusion and data recording, and all data were obtained within the first 6 hours of ED patient arrival. In some cases, especially patients arriving to the ED at night, data were recorded the next morning, but these data always referred to the time of patient presentation at the ED. Thereafter, the principal investigators of every centre retrospectively reviewed medical reports and made the final diagnostic adjudication at a local level. They revised every case to check the compliance of AHF criteria and to confirm diagnosis by measurement of plasma natriuretic peptides and/or echocardiography during ED or hospital stay, when possible, following the current ESC Guidelines recommendations [5] (available in about 92% of cases).** The EAHFE Registry does not include any planned intervention, and the management of patients is entirely based on the attending ED physician decisions.

### Ethics

The EAHFE Registry protocol was approved by a central Ethics Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain) with the reference numbers 49/2010, 69/2011, 166/13, 160/15 and 205/17. Due to the non-interventional design of the registry, Spanish legislation allows central Ethical Committee approval, accompanied by notification to the local Ethical Committees. All participating patients gave informed consent to be included in the registry and to be contacted for follow up. The present study was carried out in strict compliance with the Declaration of Helsinki principles.

### Design and variables recorded

**The attending physician assessed the presence of clinical signs and symptoms of perfusion and congestion following the 2016 ESC Guidelines[6] during the first patient assessment in the ED. Congestion was accepted by the clinical presence of pulmonary congestion, orthopnoea/paroxysmal nocturnal dyspnoea, peripheral bilateral oedema, jugular venous dilatation, congested hepatomegaly, gut congestion, ascites and/orhepatojugular reflux. Hypoperfusion was considered to be present with cold sweaty extremities, oliguria, mental confusion, dizziness and/or narrow pulse pressure (that was clinically ascertained and**

**accepted based on physician perception of weak pulse) were identified.** Thereafter, patients were classified into one of the four phenotypic groups defined by the ESC Guidelines: 1) warm (no signs or symptoms of hyppoperfusion) and dry (no signs or symptoms of congestion), which was considered as the reference group for comparisons; 2) warm (no hypoperfusion) and wet (presence of any sign or symptom of congestion); cold (presence of any sign or symptom of hypoperfusion) and wet (congestion); and 4) cold (hypoperfusion) and dry (no congestion).

Twenty-two independent variables related to demographics (2 variables), comorbidities (13 variables), baseline status (3 variables) and chronic treatments for heart failure (5 variables) that could potentially affect clinical outcomes were recorded to adjust outcomes for potential differences among groups. In addition, 17 variables about the current AHF episode were recorded to delineate characteristics of decompensations of the four clinical phenotypes. These consisted of vitals at ED arrival (3 variables), analytical data at ED (7 variables), and data related to ED management during the acute episode (7 variables) (see **Supplemental Table 1** for definitions). The disposition of the patients after ED care (admission/discharge) was recorded, and when hospitalised, the department to which the patient was admitted was recorded, with special focus on the main departments where AHF patients are usually admitted in Spain: cardiology, internal medicine, geriatrics, short-stay unit and intensive/coronary care unit.

**Outcomes**

The primary outcome in the present study was 1-year all-cause mortality. Five additional secondary outcomes were measured and consisted in:1) need for hospitalisation during the index event;2) in-hospital all-cause mortality during the index event;3) prolonged length of hospitalisation (LOH) during the index event, defined as a hospital stay longer than 7 days counted from the ED visit; 4) ED revisit due to AHF within the 7 days after patients discharge; and 5) hospitalisation due to AHF within 30 days after discharge **(this outcome was only recorded in the EAHFE 4 and 5 phases, but not in EAHFE 3). Follow-up was performed by consultation of medical records electronically accessible in nearly all Spanish communities. In addition, patients were contacted when no clear data was present in the clinical history or access to data was not possible, as at the time of patient inclusion into the EAHFE Registry they provide phone numbers and permission to be called.Death was also determined through the Spanish database of public health insurance, that covers >99% of Spanish population. Upon death patients are immediately withdrawn from the database.**

**Statistical analysis**

Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR) if not normally distributed, and categorical variables as absolute values and percentages. Comparison among the four phenotypical groups was carried out using one-way ANOVA for continuous variables (or by Kruskal Wallis non-parametrical test if not normally distributed) and the chi square test for categorical variables. Curves depicting proportional hazard for 1-year survival for the four clinical phenotypes were plotted using the Cox regression method. Outcomes of patients according to clinical phenotype were

compared to the warm-dry clinical phenotype by means of Cox regression (for the primary outcome) and logistic regression (for secondary outcomes), and the results were expressed as hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (95% CI), respectively. **The HRs and ORs were then adjusted for differences in demographics, comorbidities, baseline status and chronic treatment which were statistically significant (p<0.05) in the univariate analysis.** Missing values in the variables included in the adjusted models were replaced using the multiple imputation technique, generating 5 datasets in which there were no missing values among all the variables included in the adjustment. The signs and symptoms presented during the acute episode of decompensation were not included in the adjusted model, as differences in clinical phenotypes essentially refer to characteristic findings during decompensation. The same concept was used for data regarding patient management in the ED, because it is driven by the clinical phenotypes. Therefore, for all these data regarding acute decompensation, differences among phenotypes were assessed from an unadjusted purely descriptive perspective. **We made a subanalysis of primary and secondary outcomes stratified by the type of AHF episode (de novo vs. acutely-decompensated), the LVEF (below vs. above 50%) and the final destination after ED care (discharge vs. hospitalisation).**Statistical significance was accepted if the 95%CI excluded the value 1, or the p value was less than 0.05. Since this was an exploratory study, a pre-hoc sample size calculation was not made.

## RESULTS

### Patient distribution among phenotype categories

Of the 11,360 patients included in the EAHFE registries 3 to 5, **62 were excluded due to lack of data for phenotype classification and 37 due to lack of follow-up data regarding 1-year mortality (primary outcome); therefore, 11,261 (99.1%) provided the key data included in the present analysis (Supplementary Figure 1).** There were 8,558 patients (76.0%) classified as warm-wet (no hypoperfusion, congestion), 1,929 (17.1%) as cold-wet (hypoperfusion, congestion), 675 (6.0%) as warm-dry (no hypoperfusion, no congestion), and 99 (0.9%) as cold-dry (hypoperfusion, no congestion). This distribution of clinical phenotypes differed according to the main patient destinations after ED care. The intensive care unit and geriatrics department had the highest percentage of patients with hypoperfusion, and cardiology departments and patients discharged home without hospitalisation had the lowest percentages of hypoperfusion phenotypes (**Figure 1**). Patients discharged home without hospitalisation had the highest proportion of warm-wet phenotype (81.7%) among all final destinations after ED care. **On the other hand, there were differences in phenotype distribution between patients with *de novo* and acutely-decompensated heart failure (p<0.001) and between patients with a LVEF below and above 50% (p<0.001). The warm-wet phenotype was more frequent in patients with acutely-decompensated heart failure and LVEF ≥50%, while cold-wet was more frequent in patients with *de novo* AHF and with LVEF <50% (Figure 1).**

### Main patient baseline characteristics

Overall, the mean age of the patients was 80 years (SD:10), and 55.5% were women. The patients had a high number of comorbidities, the most frequent being hypertension, previous episodes of AHF, atrial fibrillation and diabetes mellitus (**Table 1**); 63.9% also presented some degree of limitation in functional class (i.e., Barthel index < 100) and 34.3% had some degree of systolic dysfunction (LVEF <50%). With respect to chronic treatments, 58.8% was receiving renin-angiotensin system (RAS) inhibitors, 42.7% betablockers, and 16.8% mineral corticosterid-receptor antagonists (MRA). The four clinical phenotypes differed in many of these variables (**Table 1**).

### Acute heart failure management according to phenotype

With respect to the current episode, 17 variables were compared across phenotypes (**Table 1**), and all but one significantly differed among the 4 AHF phenotypes. The use of intravenous morphine was higher in the cold-wet and cold-dry groups (14.3% and 13.3%, respectively) compared to the warm-dry and warm-wet groups (5.4% and 4.3%, respectively) (p<0.001). Inotropic drugs and vasopressors were also more frequently used in the former groups (4.9% and 6.1%) compared to the latter groups (0.9% and1.1%) (p<0.001). The cold-wet group presented lower oxygen saturation value, higher NT-proBNP values and greater need for the use of non-invasive mechanical ventilation (16.4%) compared to the other groups (p<0.001).The use of mechanical ventilation was higher in the cold-dry (5.1%) and cold-wet groups (4.9%) compared to the other groups (p<0.001)(**Table 1**).

**Primary and secondary outcomes across clinical phenotypes**

**Since the 37 patients without data for mortality (primary endpoint) were excluded from the final analysis (0.3% of the whole cohort; Supplementary Figure 1), all patients accounted for the analysis of 1-year mortality, which was 30.8% for the whole cohort (warm-dry 23.9%, warm-wet 27.1%, cold-wet 42.0%, cold-dry 42.4%).** Compared to the warm-dry phenotype, the cold-wet and cold-dry phenotypes had a significantly incremented risk of death, while the warm-wet phenotype had a risk very similar to the warm-dry phenotype (**Figure 3**). **Similar patterns were observed in the analysis stratified by *de novo*/acutely-decompensated heart failure, by LVEF below/above 50% and by hospitalised/discharged patients (Figure 2). On analysing each individual phenotype, we observed that warm-dry, warm-wet, and cold-wet patients with acutely-decompensated heart failure had worse prognoses than their comparators with *de novo* AHF;cold-wet patients with LVEF <50% had a worse prognosis than those with LEVF >50%; and hospitalised warm-dry and warm-wet patients had a worse prognosis than those discharged .**

**Regarding secondary outcomes, data was lacking for need of hospitalisation, in-hospital mortality, prolonged hospitalisation, post-discharge ED revisit and post-discharge hospitalisation in 0.1%, 0%, 2.0%, 1.9% and 30.5% of patients, respectively (the latter because post-discharge hospitalisation was not recorded during the EAHFE-3 phase).** Overall, 75.8% of patients required hospitalisation during the index AHF episode, 7.7% died before discharge, 36.0% had prolonged hospitalisation, 11.2% of discharged patients revisited the ED during the 7 following days after discharge, and 14.6% were hospitalised within 30 days after discharge. With the exception of the 7-day ED revisit, there were significant differences in outcomes among the four clinical phenotypes (**Figure 3**).

The unadjusted and adjusted risks for primary and secondary outcomes for the rest of the phenotypes, compared to the warm-cold phenotype, are shown in **Figure 4**, and these unadjusted and adjusted risks remained consistent in both, direction and magnitude of associations for every outcome. Regarding mortality, groups with hypoperfusion showed a clear increased risk (66% and 67% of increments depending on the presence or absence of congestion, respectively). Hypoperfusion was also associated with the need for hospitalisation at the index AHF episode and death during this index hospitalisation. Phenotypes including congestion were associated with a higher risk of prolonged hospitalisation (27% and 52% increase depending on the absence or presence of hypoperfusion, respectively), and a decreased risk of hospitalisation due to AHF during the 30 days following discharge (31% and 27% of reduction, respectively). Finally, no statistically significant differences were observed among phenotypes in the risk of ED revisit due to AHF during the 7 days following patient discharge. **The stratified analysis showed very similar estimations for all subgroups of patients (Table 2).**

**DISCUSSION**

**The present study is the first to describe the characteristics of a wide sample of patients with AHF at ED arrival according to the phenotype classification proposed by the 2016 ESC Guidelines on AHF, which is based on clinical evaluation of congestion and perfusion. Of note, this approach contains a higher representation of patients with HFpEF (close to two thirds in our study) in comparison with other series of patients hospitalised in cardiology departments.** Remarkably, this new phenotypic classification based on clinical evaluation of congestion and perfusion is very helpful in the initial evaluation of patients with AHF which usually takes place in the ED and can be performed at bedside without the need for time consuming invasive measures or techniques requiring previous training, providing useful prognostic information for the initial clinical decision making.

The first main finding of the current study is that the predominant phenotypic group in the ED is warm-wet (in which 3 out of 4 patients with AHF are classified) while the least frequent group is cold-dry (with 1% of the cases), and this distribution is very similar to that reported by Chioncel *et al*.[6]. However, our results extend this phenotype distribution to the whole spectrum of patients with AHF and not only to those admitted to cardiology wards. Notably, slight, albeit statistically significant, differences were found in the distribution of patients according to the final destination after ED management. Thus, patients discharged directly from the ED without admission are mainly warm-wet (82%), while the percentage of hypoperfused patients (cold; with or without congestion) increases in internal medicine (21%), geriatric (26%) and especially in intensive care wards (39%). In the latter department, the largest percentage of these patients is likely related to the haemodynamic profiles of these patients at ED arrival, since this group usually presents more episodes of cardiogenic shock. However, it should be highlighted that not all patients with hypoperfusion are in cardiogenic shock. In this regard, Chioncel *et al*.'s paper showed that hypoperfusion was present in more than 10% of cases included in the hypertensive category. This fact probably explains the high presence of hypoperfusion in internal medicine and geriatric wards and represents very advanced forms of chronic heart failure in elderly patients, most of whom could receive palliative care[10]**. Remarkably, in both our series and that of Chioncel *et al*., a few AHF patients were warm-dry (15% and 6%, respectively) and probably represent the mildest forms of AHF, with very subtle clinical signs of congestion or hypoperfusion. These patients are diagnosed with AHF based by echocardiography or natriuretic peptides rather than clinical findings, and could be treated in specialised units or at walk-in centres. Nonetheless, in universal public health systems such as those in Europe, most of these patients spontaneously come to the ED and are even hospitalised.**

The use of intravenous diuretics in the ED was very frequent, in 85% of the cases, in agreement with the 93% of patients who presented congestion, and the use of these drugs was also more frequent in the warm-wet and cold-wet groups than in the other two categories. Likewise, oxygen was more frequently administered to the congestive categories (wet), possibly reflecting a higher difficulty of oxygen diffusion in congestive lungs. The use of morphine and non-invasive mechanical ventilation was more frequent in the hypoperfusion phenotypes (cold), possibly indicating the greater severity of these patients. Although vasopressors are not

frequently used in the ED (2%), their use was concentrated, as expected, in hypoperfused patients. On the other hand, vasodilatators were more frequently used in cold+wet congestive patients, likely because their use in hypoperfused but hypovolemic patients carries an elevated risk of hypotension which, in turn, is associated with a high risk of increasing hypoperfusion. Although current guidelines support the generalised use of vasodilators in congestive patients who are not hypoperfused[5], it should be highlighted that this did not occur in our series. Unfortunately, we were unable to find studies comparing the characteristics of patient management in the ED based on the phenotypic profile of the patients, and therefore, we cannot generalise our results.

It is clear that the different phenotypic categories carry different outcomes. The presence of hypoperfusion (cold) is related to a greater in-hospital and one-year mortality, and these increases do not depend on the different basal profile or patient comorbidities, as our results remained consistent after adjustment for these differences. **This worse prognosis for patients with hypoperfusion was observed in the analysis of the whole cohort, as well as in the separated analysis for patients with *de novo* or acutely-decompensated heart failure, LVEF below or above 50% and for patients admitted or discharged after ED care. While the subanalysis based on LVEF showed similar curves for both patient categories based on LEVF in every phenotypic group (except for cold-wet group), admitted patients had a worse prognosis than those discharged from ED to home, probably indicating that emergency physicians admitted the sickest patients of each phenotypic category, and differences were statistically significant for the warm-dry and warm-wet phenotypes. Similarly, patients with acutely-decompensated heart failure had worse prognoses in each phenotype (except for the cold-dry) than patients with *de novo* AHF.** In our study, the in-hospital mortality for the cold-wet group was 15% and the mortality at one year increased 66% compared to the control group (warm-dry). This increase in mortality is due, in part, to the fact that these patients presented a lower mean blood pressure than the other 3 groups. This inverse relation between blood pressure value and mortality has been largely demonstrated and, indeed, is included in most risk stratification scales in patients with AHF[6,7,11-13]. In addition, in our study hypoperfused patients more frequently required admission, possibly demonstrating that management of congestion is easier than hypoperfusion for emergency medicine physicians.

In contrast, it seems that congestion (wet) affects the outcomes of patients with AHF differently from hypoperfusion, as it does not impact mortality. **This was observed despite the majority of patients, irrespective of the phenotype, receiving drugs directed to reduce congestion (diuretics and vasodilators). Currently, it is widely accepted that while clearly improving symptoms in patients with AHF, these drugs have no impact on patient survival[14-16].** Remarkably, in the current study, the presence of congestion conditioned onger hospital stay, with increases of 27% and 52% of prolonged admissions depending on the concomitant absence or presence of hypoperfusion, respectively, compared to the warm-dry group. In previous studies which analysed the length of hospitalisation in patients with AHF, it was observed that patients with a larger number of comorbidities had longer hospitalisation periods[17-20], and similarly, in our study comorbidities were generally more prevalent in patients with congestion. However, it is of note that

despite adjustment for differences in comorbidity, the increase in prolonged admissions was maintained and thus, future studies are needed to determine the real causes of this increase. On the other hand, we also observed that patients with congestion had a lower risk of rehospitalisation for AHF after discharge following the index episode (reduction of 31% and 27% in risk compared to the dry-warm group based on the absence or presence of hypoperfusion, respectively). However, the study of Chioncel *et al*.[6] showed that around one out of every five patients with AHF admitted to cardiology units still present peripheral and pulmonary congestion at hospital discharge. As our AHF patients with congestion had longer hospital stay, perhaps the possibility of effectively continuing in-hospital treatment of congestion with diuretics would favour this better outcome of patients in this particular aspect. Finally, it is of note that no clinical phenotype was related to an increased or decreased risk of reconsultation to the ED for AHF during the week following discharge. This should be placed into the context of the public healthcare system such as that in Spain, in which many factors not directly related to the morbid process determine the use of EDs.

Our study has some limitations. First, this was an observational study and causal relationships between phenotypes and outcomes cannot be inferred. The retrospective assessment of the classification into the four phenotypes might introduce some degree of bias**. Moreover, although signs and symptoms were prospectively recorded by attending physicians, classification into clinical phenotypes was retrospectively performed at the time of data exploration for the present study. Indeed, no ED clinical manoeuvre or treatment was influenced by the clinical phenotype beyond the potential use of attending physicians in their usual practice. Therefore, our findings are not a result of the impact of using the clinical phenotype classification during ED care by emergency physicians, but rather merely describe how these different phenotypes are currently being managed in the ED and demonstrate the feasibility of phenotype classification in the ED setting. Second, since this study is observational and the number of patients analysed was large, it is possible that some findings may be statistically significant but not clinically relevant.** Third, in this real life cohort without intervention, attending physicians followed their usual local protocols and did not receive any specific instructions about the precise time for ED or hospital discharge and patient transition. Although this imposes limitations in some of our conclusions, it otherwise makes our findings more generalizable. **Fourth, the use of clinical criteria could determine, to some extent, patient distribution across phenotype categories, as most of the Framingham major criteria and some of the minor criteria are signs and symptoms of congestion. Additionally, in patients without signs of congestion or hypoperfusion (warm-dry, 6%), AHF diagnosis was mainly made by the presence of dyspnoea (referred by the patient), elevated natriutetic peptides and exclusion of other alternative diagnoses, leaving the possibility that a few of these patients could have had a diagnosis other than AHF. On the other hand, subtle data of congestion or hypoperfusion could have remained unidentified during ED evaluation in patients erroneously classified as warm-dry phenotype.** Fifth, the patients were from a single country with a universal public healthcare system, and since international heterogeneity in organizational and transition processes is high[21], our results should be confirmed in other countries with different healthcare system models. **In particular, we report 24% of direct discharge home after ED care, which is higher than that observed in other countries, such as the United States[22].** And sixth, the diagnosis of AHF was based on

clinical criteria, and the final diagnosis of AHF was not supported in all cases by natriuretic peptide or echocardiographic results.

In view of the results of the present study, clinical evaluation of congestion and perfusion at the bedside of patients with AHF at arrival at the ED and the classification of patients into the four phenotypic profiles proposed by the last ESC Guidelines provide complementary information about patient management in the ED. Moreover, destination after ED healthcare differs according to clinical phenotypes. Finally, the classification into the four categories based on perfusion and congestion signs and symptoms is associated with outcomes. **The clinical implications of all these findings are that the phenotypic classification of the 2016 ESC Guidelines could be used at a very early stage when patients are diagnosed with AHF in the ED, and could help to better estimate patient prognosis and, eventually, provide more individually-guided therapy.**

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**Table 1**: Baseline (above) and decompensation (below) characteristics of the patients and comparison according to the clinical phenotype.

| | Total N=11,261 n (%) | Warm-dry N=675 n (%) | Warm-wet N= 8,558 n(%) | Cold-wet N=1,929 n (%) | Cold-dry N=99 n (%) | p value | Missing values n (%) |
|---|---|---|---|---|---|---|---|
| **BASELINE CHARACTERISTICS** | | | | | | | |
| **Demographic data** | | | | | | | |
| **Age (years)** (mean (SD)) | 80 (10) | 79 (12) | 80 (10) | 82 (10) | 82 (10) | **<0.001** | 8 (0.1) |
| **Female** | 6,229 (55.5) | 353 (52.6) | 4,676 (54.9) | 1,146 (59.6) | 54 (54.5) | **0.001** | 45 (0.4) |
| **Comorbidities** | | | | | | | |
| **Hypertension** | 9,447 (84.0) | 528 (78.2) | 7,205 (83.4) | 1,635 (84.8) | 79 (79.8) | **<0.001** | 13 (0.1) |
| **Diabetes mellitus** | 4,721 (42.0) | 252 (37.3) | 3,579 (41.9) | 845 (43.9) | 45 (45.5) | **0.026** | 14 (0.1) |
| **Ischaemic heart disease** | 3,243 (28.8) | 178 (26,4) | 2,428 (28.4) | 601 (31.2) | 36 (36.4) | **0.014** | 13 (0.1) |
| **Chronic kidney failure (creatinine>2 mg/mL)** | 3,012 (26.8) | 151 (22.4) | 2,237 (26.2) | 595 (30.9) | 29 (29.3) | **<0.001** | 12 (0.1) |
| **Cerebrovascular disease** | 1,488 (13.2) | 84 (12.4) | 1,098 (12.8) | 286 (14.8) | 20 (20.2) | **0.019** | 14 (0.1) |
| **Atrial fibrillation** | 5,587 (49.7) | 313 (46.4) | 4,318 (50.5) | 911 (47.3) | 45 (45.5) | **0.014** | 11 (0.1) |
| **Peripheral artery disease** | 1,060 (9.4) | 56 (8.3) | 762 (8.9) | 233 (12.1) | 9 (9.1) | **<0.001** | 16 (0.1) |
| **Heart valve disease** | 3,020 (26.8) | 158 (23.4) | 2,329 (27.2) | 512 (26.6) | 21 (21.2) | 0.092 | 13 (0.1) |
| **Chronic obstructive pulmonary disease** | 2,705 (24.1) | 145 (21.5) | 2,071 (24.2) | 470 (24.4) | 19 (19.2) | 0.262 | 14 (0.1) |
| **Dementia** | 1,454 (12.9) | 82 (12.2) | 943 (11.0) | 400 (20.8) | 30 (30.3) | **<0.001** | 14 (0.1) |
| **Active neoplasia** | 1,581 (14.1) | 62 (9.2) | 1,211 (14.2) | 293 (15.2) | 15 (15.2) | **0.001** | 17 (0.2) |
| **Hepatic cirrhosis** | 166 (1.5) | 4 (0.6) | 133 (1.6) | 28 (1.5) | 1 (1.0) | 0.247 | 27 (0.2) |
| **Prior episodes of acute heart failure** | 6,471 (57.9) | 327 (49.2) | 4,921 (58.0) | 1,175 (61.3) | 48 (48.5) | **<0.001** | 93 (0.8) |
| **Baseline status** | | | | | | | |
| **Barthel Index (points)** (mean (SD)) | 79 (25) | 80 (27) | 81 (24) | 71 (27) | 70 (31) | **<0.001** | 1,401 (12.4) |
| **NYHA class III-IV** | 2,570 (24.3) | 125 (20.1) | 1,856 (23.1) | 566 (31.2) | 23 (25.3) | **<0.001** | 702 (6.2) |
| **Left ventricular ejection fraction (%)**(mean (SD)) | 52 (15) | 51 (15) | 52 (15) | 50 (16) | 47 (15) | **0.001** | 5,053 (44.9) |
| Heart failure with reduced ejection fraction (<40%) | 1,273 (20.5) | 70 (21.9) | 915 (19.1) | 275 (26.0) | 13 (33.3) | | |
| Heart failure with mid-range ejection fraction (40-49%) | 856 (13.8) | 41 (12.8) | 665 (13.9) | 143 (13.5) | 7 (17.9) | | |
| Heart failure with preserved ejection fraction (<40%) | 4079 (65.7) | 209 (65.3) | 3,212 (67.0) | 639 (60.5) | 19 (48.7) | | |
| **Chronic treatments at home** | | | | | | | |
| **Diuretics (any)** | 8,164 (74.6) | 421 (63.4) | 6,285 (75.4) | 1,394 (75.6) | 64 (65.3) | **<0.001** | 322 (2.9) |
| **ACE inhibitor or ARB** | 6,218 (56.8) | 366 (55.1) | 4,751 (57.0) | 1,058 (57.4) | 43 (43.9) | **0.049** | 323 (2.9) |
| **Beta-blocker** | 4,669 (42.7) | 299 (45.0) | 3,574 (42.9) | 757 (41.1) | 39 (39.8) | 0.267 | 327 (2.9) |
| **Mineralocorticoid-receptor antagonist** | 1,842 (16.8) | 91 (13.7) | 1,434 (17.2) | 305 (16.5) | 12 (12.2) | 0.073 | 323 (2.9) |
| **Digoxin** | **1,654 (15.1)** | **86 (13.0)** | **1,272 (15.3)** | **282 (15.3)** | **14 (14.3)** | **0.441** | 332 (2.9) |
| **DECOMPENSATION CHARACTERISTICS** | | | | | | | |
| **Vitals at ED during acute episode** (mean (SD)) | | | | | | | |
| **SBP (mmHg)** | 141 (27) | 141 (27) | 142 (26) | 139 (32) | 125 (30) | **<0.001** | 168 (1.5) |
| **Heart rate (bpm)** | 88 (24) | 89 (25) | 88 (23) | 91 (25) | 88 (24) | **<0.001** | 234 (2.1) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Room air oxygen saturation (%)** | 92 (7) | 93 (6) | 93 (6) | 90 (8) | 91 (7) | **<0.001** | 352 (3.1) |
| **Results of blood tests at ED** | | | | | | | |
| **Glucose (mg/dL)**(mean (SD)) | 149 (85) | 152 (73) | 145 (79) | 164 (110) | 167 (85) | **<0.001** | 191 (1.7) |
| **Creatinine (mg/dL)**(mean (SD)) | 1.35 (0.84) | 1.33 (0.94) | 1.32 (0.80) | 1.48 (0.96) | 1.42 (0.84) | **<0.001** | 136 (1.7) |
| **Haemoglobin (g/L)**(mean (SD)) | 120 (23) | 125 (21) | 120 (20) | 116 (23) | 121 (23) | **<0.001** | 303 (2.7) |
| **Potassium (mmol/L)**(mean (SD)) | 4.42 (0.70) | 4.43 (0.71) | 4.40 (0.67) | 4.53 (0.79) | 4.62 (0.76) | **<0.001** | 688 (6.1) |
| **Sodium (mmol/L)**(mean (SD)) | 138.1 (5.1) | 138.1 (4.9) | 138.2 (4.9) | 137.3 (5.3) | 137.3 (5.3) | **<0.001** | 235 (2.1) |
| **Raised troponin (>99th percentile)** | 3,538 (56.2) | 219 (53.2) | 2,624 (55.7) | 661 (59.1) | 34 (64.2) | 0.066 | 4,971 (44.1) |
| **NT-proBNP (pg/mL)** (median (RIC)) | 3,868 (1,880-8,309) | 3,561 (1,619-8,946) | 3,643 (1,777-7,675) | 5,205 (2,406-11,766) | 4,012 (2,095-16,639) | **<0.001** | 6,259 (55.6) |
| **Management at ED** | | | | | | | |
| **Need for oxygen supplementation** | 8,010 (71.6) | 415 (62.8) | 6,109 (71.8) | 1,423 (74.1) | 63 (64.3) | **<0.001** | 71 (0.6) |
| **Need for intravenous diuretics** | 9,468 (84.6) | 469 (71.0) | 7,257 (85.3) | 1,675 (87.1) | 67 (69.1) | **<0.001** | 72 (0.6) |
| **Need for intravenous/subcutaneous morphine** | 686 (6.1) | 36 (5.4) | 363 (4.3) | 274 (14.3) | 13 (13.3) | **<0.001** | 70 (0.6) |
| **Need for intravenous nitrates** | 1,512 (13.5) | 53 (8.0) | 996 (11.7) | 453 (23.6) | 10 (10.2) | **<0.001** | 70 (0.6) |
| **Need for inotropics/vasopressors** | 197 (1.8) | 6 (0.9) | 91 (1.1) | 94 (4.9) | 6 (6.1) | **<0.001** | 74 (0.7) |
| **Need for non-invasive ventilation** | 719 (6.4) | 24 (3.6) | 377 (4.4) | 315 (16.4) | 3 (3.1) | **<0.001** | 71 (0.6) |
| **Need for mechanical ventilation** | 320 (5.1) | 8 (1.2) | 212 (2.5) | 95 (4.9) | 5 (5.1) | **<0.001** | 70 (0.6) |

*ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; ED: emergency department; AHF: acute heart failure.*

*Bold p values denote statistical significance.*

**Table 2**: **Multivariate analysis of outcomes adjusted by differences among groups for the whole cohort and stratified by type of episode (*de novo*/acutely-decompensated), left ventricular ejection fraction (below/above 50%), and final disposition after emergency department care (discharged/hospitalised).**

| | Warm-dry N=675 n (%) | Warm-wet N= 8,558 n(%) | Cold-wet N=1,929 n (%) | Cold-dry N=99 n (%) |
|---|---|---|---|---|
| **1-year all-cause mortality (HR)** | | | | |
| **ALL PATIENTS** | 1 (reference) | 1.29 (0.96-1.32) | **1.66 (1.40-1.97)** | **1.67 (1.19-2.35)** |
| *De novo* acute heart failure | 1 (reference) | 1.20 (0.93-1.56) | **1.83 (1.38-2.41)** | **2.21 (1.36-2.41)** |
| Acutely-decompensated patients | 1 (reference) | 1.08 (0.88-1.33) | **1.54 (1.24-1.91)** | 1.22 (0.74-1.99) |
| LVEF <50% | 1 (reference) | 1.18 (0.88-1.59) | **2.00 (1.50-2.67)** | 1.60 (0.80-3.19) |
| LVEF ≥50% | 1 (reference) | 1.10 (0.88-1.37) | **1.45 (1.16-1.83)** | **1.72 (1.00-2.95)** |
| Discharged home | 1 (reference) | 1.02 (0.70-1.50) | **1.98 (1.30-3.00)** | 2.70 (0.94-7.79) |
| Hospitalised | 1 (reference) | 1.16 (0.97-1.38) | **1.56 (1.30-1.89)** | **1.53 (1.06-2.19)** |
| **Need for hospitalisation (OR)** | | | | |
| **ALL PATIENTS** | 1 (reference) | 1.16 (0.97-1.38) | **2.02 (1.64-2.50)** | **2.56 (1.36-4.82)** |
| *De novo* acute heart failure | 1 (reference) | **1.37 (1.08-1.74)** | **2.65 (1.95-3.61)** | **2.46 (1.20-5.48)** |
| Acutely-decompensated patients | 1 (reference) | 0.94 (0.72-1.24) | **1.54 (1.13-2.09)** | **3.07 (1.06-8.90)** |
| LVEF <50% | 1 (reference) | 1.17 (0.85-1.61) | **2.13 (1.49-3.05)** | 4.11 (0.77-21.81) |
| LVEF ≥50% | 1 (reference) | 1.14 (0.90-1.44) | **1.96 (1.49-2.57)** | 2.19 (0.92-5.23) |
| Discharged home | NA | NA | NA | NA |
| Hospitalised | NA | NA | NA | NA |
| **In-hospital all-cause mortality (OR)** | | | | |
| **ALL PATIENTS** | 1 (reference) | **1.52 (1.02-2.26)** | **3.47 (2.31-5.22)** | **5.70 (3.05-10.65)** |
| *De novo* acute heart failure | 1 (reference) | 1.48 (0.82-2.68) | **3.61 (1.96-6.66)** | **6.15 (2.50-15.10)** |
| Acutely-decompensated patients | 1 (reference) | 1.57 (0.92-2.70) | **3.44 (1.98-5.98)** | **5.21 (2.15-12.66)** |
| LVEF <50% | 1 (reference) | 1.21 (0.63-2.35) | **3.56 (1.80-7.04)** | **4.42 (1.38-14.12)** |
| LVEF ≥50% | 1 (reference) | **1.80 (1.02-3.18)** | **3.44 (1.90-6.22)** | **7.12 (2.85-17.82)** |
| Discharged home | NA | NA | NA | NA |
| Hospitalised | NA | NA | NA | NA |
| **Prolonged length of stay (>7 days) (OR)** | | | | |
| **ALL PATIENTS** | 1 (reference) | **1.27 (1.06-1.51)** | **1.52 (1.25-1.85)** | 1.05 (0.66-1.66) |
| *De novo* acute heart failure | 1 (reference) | **1.40 (1.09-1.81)** | **1.66 (1.24-2.22)** | 0.98 (0.50-1.92) |
| Acutely-decompensated patients | 1 (reference) | 1.16 (0.91-1.48) | **1.40 (1.07-1.82)** | 1.18 (0.62-2.23) |
| LVEF <50% | 1 (reference) | 1.23 (0.91-1.65) | **1.40 (1.00-1.97)** | 1.02 (0.47-2.21) |
| LVEF ≥50% | 1 (reference) | 1.29 (1.02-1.62) | **1.61 (1.24-2.08)** | 1.06 (0.55-2.05) |
| Discharged home | NA | NA | NA | NA |
| Hospitalised | NA | NA | NA | NA |
| **7-day post-discharge ED revisit due to AHF (OR)** | | | | |
| **ALL PATIENTS** | 1 (reference) | 0.82 (0.60-1.13) | 0.98 (0.69-1.40) | 0.93 (0.37-2.33) |
| *De novo* acute heart failure | 1 (reference) | 0.96 (0.58-1.57) | 1.03 (0.58-1.84) | 1.20 (0.32-4.45) |
| Acutely-decompensated patients | 1 (reference) | 0.74 (0.49-1.12) | 0.93 (0.59-1.47) | 0.73 (0.20-2.65) |
| LVEF <50% | 1 (reference) | 0.73 (0.43-1.23) | 0.80 (0.42-1.51) | 0.86 (0.18-4.10) |
| LVEF ≥50% | 1 (reference) | 0.88 (0.58-1.33) | 1.11 (0.69-1.79) | 1.00 (0.26-3.80) |
| Discharged home | 1 (reference) | 0.83 (0.50-1.37) | 1.36 (0.73-2.52) | 0.97 (0.10-9.49) |
| Hospitalised | 1 (reference) | 0.84 (0.56-1.26) | 1.01 (0.64-1.58) | 1.05 (0.38-2.62) |
| **30-day post-discharge hospitalisation due to AHF (OR)** | | | | |
| **ALL PATIENTS** | 1 (reference) | **0.69 (0.54-0.88)** | **0.73 (0.55-0.97)** | 0.86 (0.38-1.93) |
| *De novo* acute heart failure | 1 (reference) | 0.69 (0.46-1.03) | 0.86 (0.54-1.39) | 0.73 (0.20-2.66) |
| Acutely-decompensated patients | 1 (reference) | **0.68 (0.50-0.93)** | **0.69 (0.49-0.98)** | 0.90 (0.32-2.57) |
| LVEF <50% | 1 (reference) | 0.73 (0.46-1.15) | 0.81 (0.48-1.38) | 0.80 (0.21-2.99) |
| LVEF ≥50% | 1 (reference) | **0.66 (0.48-0.92)** | 0.69 (0.47-1.01) | 0.95 (0.30-3.04) |
| Discharged to home | 1 (reference) | 1.02 (0.60-1.74) | 1.23 (0.65-2.33) | 2.05 (0.21-20.01) |
| Hospitalised | 1 (reference) | **0.60 (0.45-0.80)** | **0.63 (0.45-0.86)** | 0.72 (0.30-1.71) |

*LVEF: left ventricular ejection fraction.*

*Bold numbersdenote statistical significance*

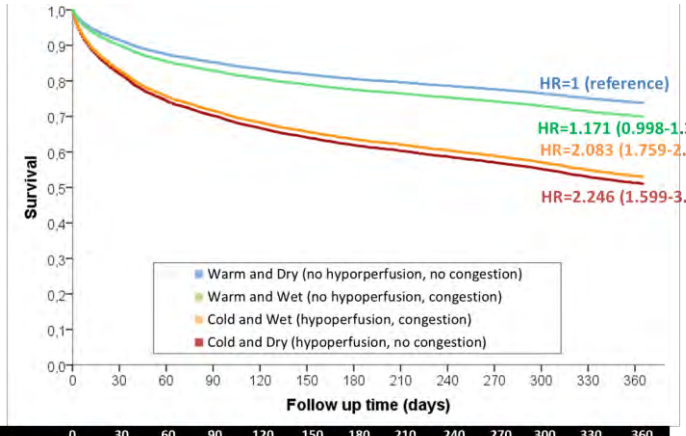
**Figure 1:** Distribution of clinical phenotypes of acute heart failure, overall and according to the department where the patient was hospitalised for the whole cohort (upper panel) **and stratified (lower panels) by the type of decompensation (*de novo*/acutely-decompensated) and left ventricular ejection fraction (below/above 50%).**


*P values in bold letters denote statistical significance.*

*In the upper panel, P values for each phenotype refer to comparison of distribution among the main patient destinations after emergency care presented in the figure.*

*In the middle and lower panel, P values for each final patient destination after emergency department care refer to comparison of distribution between patients with de novo (DN) or acutely-decompensated heart failure (ADHF; middle) and patients with left ventricular ejection fraction below and above 50% (lower).*

**Figure 2:** Unadjusted proportional hazard curves for all-cause mortality for the whole cohort (upper panel) **and stratified (lower panels) according to type of decompensation (*de novo*/acutely-decompensated), left ventricular ejection fraction (below/above 50%) and disposition after emergency department care (discharge/admission).**




| Time (days) | 0 | 30 | 60 | 90 | 120 | 150 | 180 | 210 | 240 | 270 | 300 | 330 | 360 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients at risk | 675 | 625 | 588 | 555 | 543 | 531 | 521 | 515 | 508 | 503 | 497 | 486 | 471 |
| Number of events | 0 | 46 | 66 | 90 | 96 | 108 | 118 | 124 | 131 | 136 | 142 | 153 | 161 |
| Patients at risk | 8558 | 7821 | 7218 | 6844 | 6609 | 6426 | 6309 | 6209 | 6127 | 6035 | 5923 | 5784 | 5588 |
| Number of events | 0 | 688 | 1058 | 1258 | 1443 | 1583 | 1694 | 1791 | 1873 | 1965 | 2076 | 2204 | 2309 |
| Patients at risk | 1929 | 1560 | 1404 | 1311 | 1253 | 1206 | 1164 | 1153 | 1127 | 1103 | 1080 | 1049 | 988 |
| Number of events | 0 | 358 | 473 | 541 | 693 | 628 | 669 | 680 | 706 | 730 | 753 | 783 | 806 |
| Patients at risk | 99 | 70 | 66 | 64 | 61 | 60 | 59 | 59 | 58 | 56 | 56 | 55 | 54 |
| Number of events | 0 | 29 | 33 | 35 | 36 | 37 | 38 | 38 | 39 | 41 | 41 | 42 | 42 |

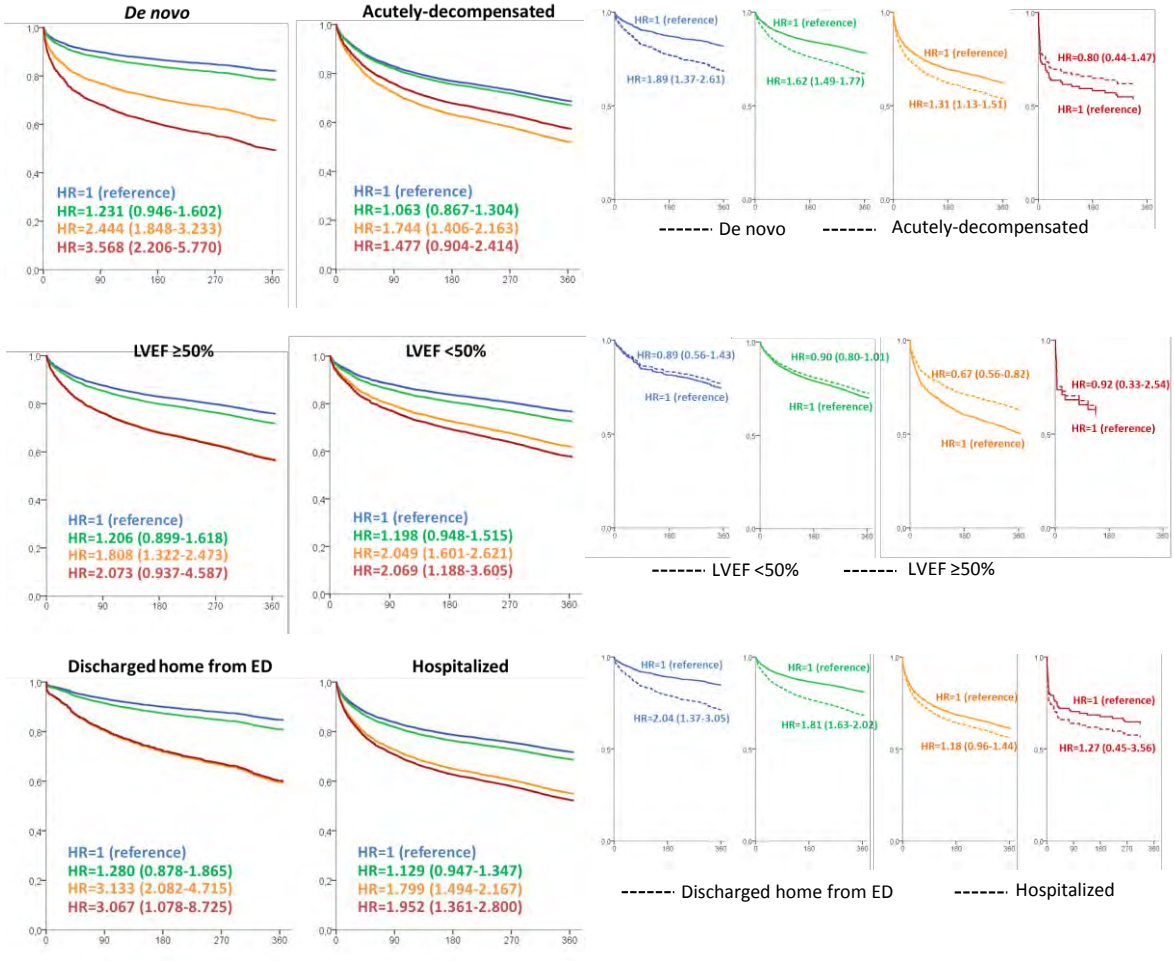


**Figure 3:**Percentage of patients developing the secondary endpoints in every clinical phenotype.

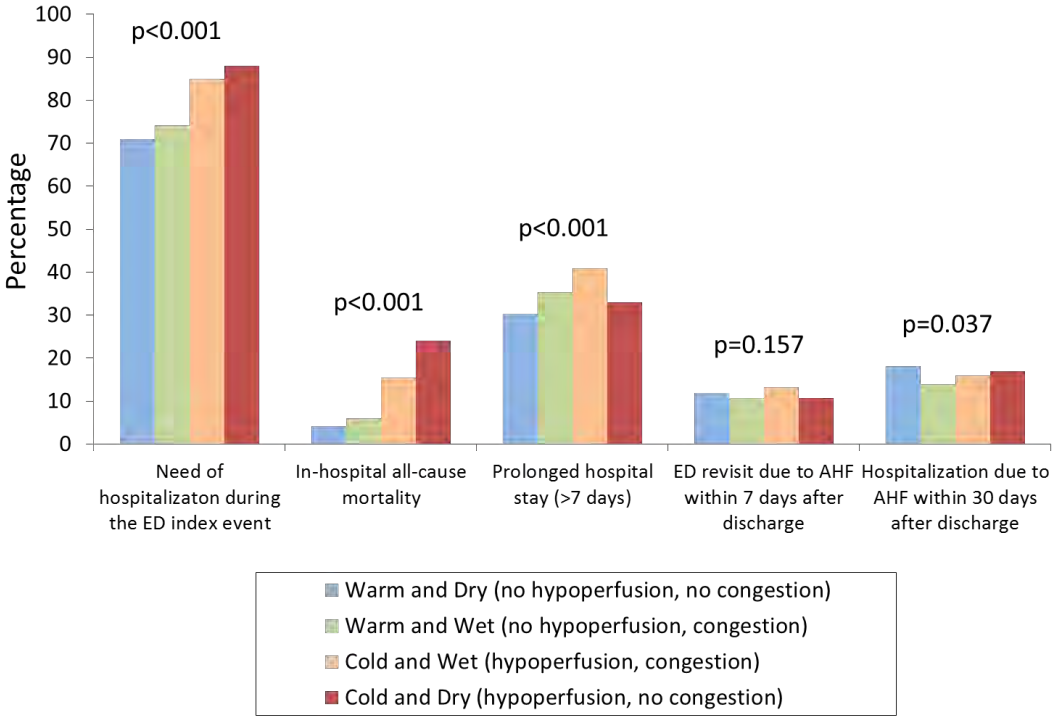
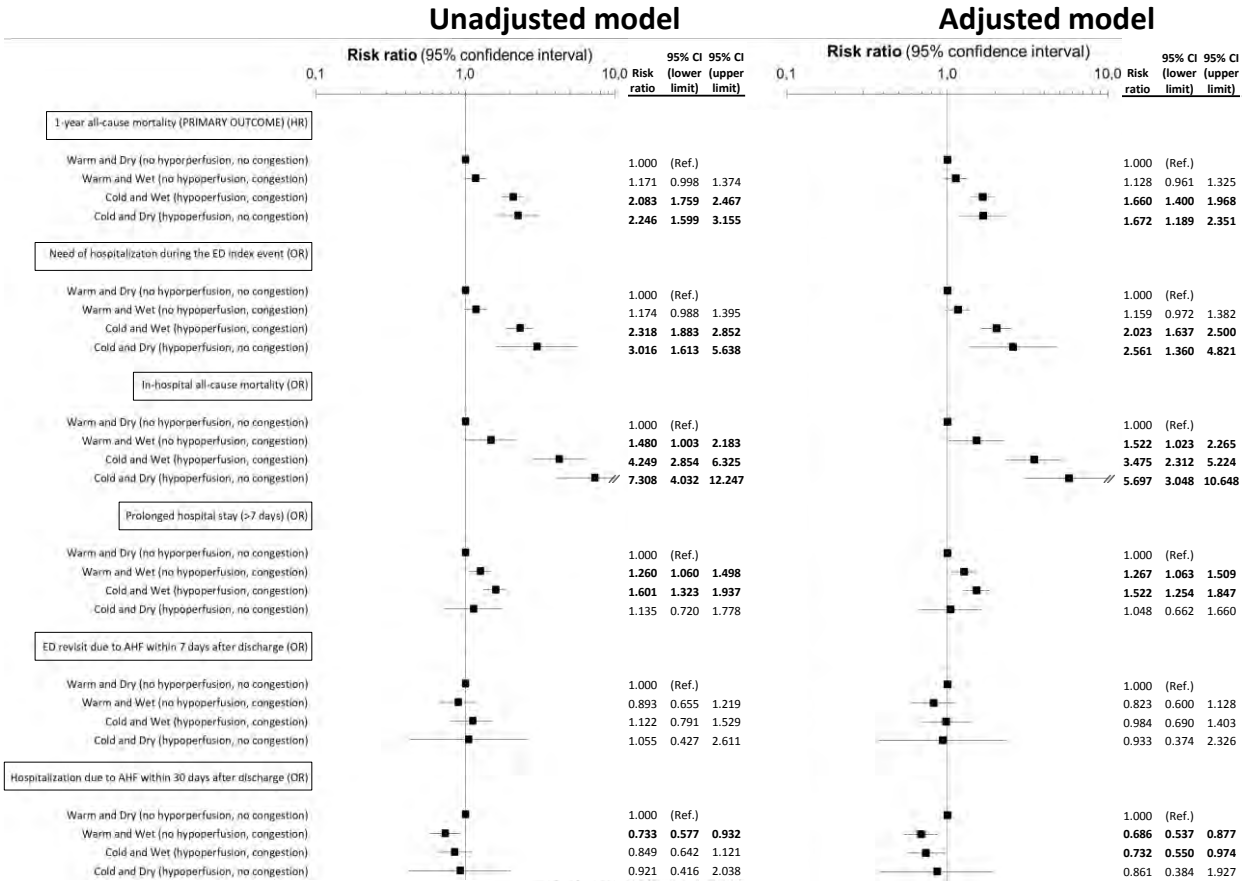


**Figure 4:** Unadjusted and adjusted risk ratios for the four clinical phenotypes of acute heart failure defined in the 2016 ESC Guidelines[6]. Adjustment was performed by age, sex, comorbidities (hypertension, diabetes mellitus, ischemic heart disease, chronic kidney failure, cerebrovascular disease, atrial fibrillation, peripheral artery disease, dementia, active neoplasia, and prior episodes of acute heart failure), baseline status (Barthel index, NYHA class, and left ventricular ejection fraction) and chronic treatments at home (diuretics and renin-angiotensin system inhibitors).



**Supplemental Table 1:** Dictionary of the variables included in the present study.

| | |
|---|---|
| **DEMOGRAPHICS** | |
| **Age** | Age calculated as the difference in decimal years between the date of inclusion in the study and the date of birth. |
| **Sex** | Male/Female |
| **COMORBIDITIES** | |
| **Hypertension** | Indicate if the patient has arterial hypertension because this is shown under previous clinical history or the patient is receiving specific treatment. |
| **Diabetes Mellitus** | Indicate if the patient has diabetes mellitus because this is shown under previous clinical history or the patient is receiving specific treatment. |
| **Ischemic heart disease** | Indicate if the patient has any form of ischemic heart disease (SCASEST, SCACEST, unstable angina, stable angina, ACI, etc.) because this is shown under previous clinical history or the patient is receiving specific treatment. |
| **Chronic kidney disease** | Indicate if the patient has chronic renal insufficiency or chronic kidney disease or if analyses over the previous year show creatininevalues >2 mg/dL. |
| **Cerebrovascular disease** | Indicate if the patient has had a previous cerebrovascular accident or cerebrovascular disease because this is described in the clinical history or shown in CT or MR imaging studies within the previous year and reported as cerebrovascular disease. |
| **Atrial fibrillation** | Indicate if the previous history describes permanent or chronic atrial fibrillation or an ECG performed within the previous year shows atrial fibrillation and this continues to be present. |
| **Peripheral artery disease** | Indicate if the patient has peripheral artery disease in either the lower extremities or carotid artery, and if the patient is receiving specific treatment, has undergone specific surgery (by-pass of lower extremities, endarterectomy, etc.) or there is previous history of an ankle brachial index <0.90. |
| **Heart valve disease** | Indicate if the patient has any type of clinically significant heart valve disease according to an ultrasound or hemodynamic study reported in the previous clinical history. |
| **Chronic obstructive pulmonary disease** | Indicate if the patient has chronic obstructive pulmonary disease because this is described in the clinical history, the patient has undergone spirometry which was not normal or is receiving chronic treatment with specific drugs. |
| **Dementia** | Indicate if the patient has a previous clinical diagnosis of dementia performed by a doctor. |
| **Active neoplasia** | Indicate if the patients has an active neoplasm |
| **Hepatic cirrhosis** | Indicate if the patient has a previous clinical diagnosis of hepatic cirrhosis performed by a doctor. |
| **Prior episode of heart failure** | Indicate if the patient has heart failure, is receiving specific treatment or the clinical history reports previous episodes of AHF. |
| **BASELINE STATUS** | |
| **Baseline Barthel index** | Barthel index value of the patient at least 15 days prior to the date seen in the ED. |
| **Baseline functional grade for dyspnea according to the NYHA scale** | Indicate the functional grade of basal dyspnea (in the 15 days prior to the exacerbation episode) of the patient according to the NYHA scale. |
| **Left ventricular ejection fraction** | Indicate left ventricular ejection fraction determined by echocardiography during admission of current episode or, if not determined, the last one determined during the six previous months |
| **CHRONIC TREATMENT AT HOME** | |
| **Diuretics** | Receiving chronic treatment with diuretics, either loop-diuretics, thiazide diuretics or mineralocorticoid receptor antagonists |
| **Angiotensin-converter enzyme (ACE) inhibitors or angiotensin-II receptor blocker** | Receiving chronic treatment with ACE inhibitors or angiotensin-II receptor blocker |
| **Beta-blocker** | Receiving chronic treatment with beta-blocker |
| **Mineralocorticoid-receptor antagonists** | Receiving chronic treatment with aldosterone-receptor antagonists |
| **Digoxin** | Receiving chronic treatment with Digoxin |
| **VITAL SIGNS AT EMERGENCY DEPARTMENT ARRIVAL** | |
| **Systolic blood pressure** | Systolic blood pressure (SBP) measured in mmHg of the patient on arrival to the ED. This value can be that obtained during triage or the first taken on initiating care. |
| **Heart rate** | Central heart rate measured as beats per minute of the patient on arrival to the ED. V This value can be that obtained during triage or the first taken on initiating care . |
| **Arterial oxygen saturation** | Oxygen saturation expressed as percentage obtained by capillary pulsioxymetry on arrival to the ED. This value can be that obtained during triage or the first taken on initiating care. |
| **BLOOD TESTS AT EMERGENCY DEPARTMENT ARRIVAL** | |
| **Glucose** | In mg/dL |
| **Creatinine** | In mg/dL |

| | |
|---|---|
| **Hemoglobin** | In g/dL |
| **Potassium** | In mmol/L |
| **Sodium** | In mmol/L |
| **Raised troponin** | Indicate if troponin is above the 99th percent provided by the manufacturer |
| **NT-proBNP** | In pg/mL |
| **MANAGEMENT TREATMENT AT EMERGENCY DEPARTMENT** | |
| **Oxygen supplementation** | Receiving oxygen supplementation, irrespective of the form of administration and concentration. |
| **Intravenous diuretics** | Receiving intravenous treatment with any kind of diuretic either, in boluses or in continuous infusion |
| **Morphine** | Receiving treatment with subcutaneous or intravenous morphine in the ED |
| **Intravenous nitrates** | Receiving treatment with intravenous nitrates during the first care given in the ED |
| **Vasoactive drugs** | Receiving treatment with vasoactive drugs (dopamine, dobutamine, levosimendan, noradrenalin, adrenalin) during the first care given in the ED |
| **Non-invasive ventilation** | Receiving treatment with non-invasive ventilation during the first care fiven in the ED |
| **Invasive (mechanical) ventilation** | Receiving treatment with Invasive (mechanical) ventilation nitrates during the first care given in the ED |

**Supplementary Figure 1:** Flow chart for patient inclusion