

Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry

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Aims

To identify differences in clinical epidemiology, in-hospital management and 1-year outcomes among patients hospitalized for acute heart failure (AHF) and enrolled in the European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) Registry, stratified by clinical profile at admission.

Methods and results

The ESC-HF-LT Registry is a prospective, observational study collecting hospitalization and 1-year follow-up data from 6629 AHF patients. Among AHF patients enrolled in the registry, 13.2% presented with pulmonary oedema (PO), 2.9% with cardiogenic shock (CS), 61.1% with decompensated heart failure (DHF), 4.8% with hypertensive heart failure (HT-HF), 3.5% with right heart failure (RHF) and 14.4% with AHF and associated acute coronary syndromes (ACS-HF). The 1-year mortality rate was 28.1% in PO, 54.0% in CS, 27.2% in DHF, 12.8% in HT-HF, 34.0% in RHF and 20.6% in ACS-HF patients. When patients were classified by systolic blood pressure (SBP) at initial presentation, 1-year mortality was 34.8% in patients with SBP <85 mmHg, 29.0% in those with SBP 85–110 mmHg, 21.2% in patients with SBP 110–140 mmHg and 17.4% in those with SBP >140 mmHg. These differences tended to diminish in the months post-discharge, and 1-year mortality for the patients who survived at least 6 months post-discharge did not vary significantly by either clinical profile or SBP classification.

Conclusion

Rates of adverse outcomes in AHF remain high, and substantial differences have been found when patients were stratified by clinical profile or SBP. However, patients who survived at least 6 months post-discharge represent a more homogeneous group and their 1-year outcome is less influenced by clinical profile or SBP at admission.

Keywords

Acute heart failure • Clinical profile • Outcomes

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Introduction

Acute heart failure (AHF) represents a broad spectrum of disease states, with heterogeneous clinical presentations, but commonly characterized by either a rapid onset or a progressive worsening of signs and symptoms, requiring immediate treatment and leading to urgent hospitalization.¹ The initial clinical presentation is more heterogeneous than the simple description “de novo or worsening heart failure (HF)”, and includes several distinct phenotypes such as acutely decompensated HF (DHF), cardiogenic shock (CS), pulmonary oedema (PO), right HF (RHF), hypertensive HF (HT-HF) and HF in the setting of acute coronary syndromes (ACS-HF).² In addition to clinical profile classification, several other classification schemes have been proposed by the European Society of Cardiology (ESC) guidelines, including classification based on the level of systolic blood pressure (SBP) at initial presentation in the emergency department³ and the most recent one with phenotypes based on clinical signs of congestion and/or hypoperfusion.¹ The identification of more distinct entities with different clinical outcomes would help clinicians to address the immediate life-threatening medical condition and to direct treatment strategies more correctly by targeting specific underlying conditions and precipitating factors,⁴ in order to create pathways for better care of the spectrum of AHF patients.

Several large and well designed registries^{5–12} have been created in recent years to describe more accurately the demographic, clinical, and therapeutic characteristics of AHF patients. However, with very few exceptions,^{12,13} the description of the clinical course of AHF from prior registries was mainly restricted to the inpatient phase or the initial weeks post-discharge. Very often, these registries were not representative, being either a single country description, or having a limited number of centres or clinical settings.

The ESC Heart Failure Long-Term (ESC-HF-LT) Registry is a permanent registry^{14,15} with systematic collection of 1-year follow-up data, capturing the whole spectrum of AHF patients.

The aim of the present analysis of the ESC-HF-LT Registry was to identify differences in clinical characteristics, in-hospital treatment and outcomes among AHF patients stratified according to well specified clinical profiles within the overall descriptor of AHF.²

Methods

Study design and clinical setting

The ESC-HF-LT Registry is a prospective, multicentre, observational study of patients admitted to 211 cardiology centres (*Appendix S1*) from 21 European and Mediterranean countries, all members of the ESC. The number of participating centres per country was chosen in relation to the population of the country (one centre/2 million people, but no more than 25 centres per country) and centre selection took into account the geographical distribution of each country. Moreover, the selection of centres allowed for a 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 which should consist 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.

Periodic consecutive enrollment has been used and patients were included ‘one day per week’. In this 1-year follow-up analysis, patient data of the best 12 consecutive recruitment months for each country were used for the analysis.

The survey was approved by each local Institutional Review Board according to the rules of each participating country. No data were collected before detailed information was provided to the patient and a signed informed consent was obtained.

The EURObservational Research Programme (EORP) Department was appointed to coordinate the project operationally, providing support to the committees, national coordinators and participating centres, and overseeing the implementation of the survey.

Patient population

The ESC-HF-LT Registry included all outpatients with chronic HF seen at the clinics and those admitted to hospital for AHF from selected centres. In the present analysis, all patients admitted for AHF, either *de novo*, or worsening of pre-existing HF, for whom intravenous (i.v.) therapy (inotropes, vasodilators, or diuretics) was needed, were included. There were no specific exclusion criteria, with the exception that all patients had to be older than 18 years.

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 i.v. therapy.^{14,15} Several training meetings were organized for the study investigators to assure consistency in definition and data collection, and for a random sample of 5% of centres, data source verification was performed by EORP monitors.

Patients were classified into the following six clinical profiles by the clinician-investigators at the time of presentation according to the 2008 ESC guidelines:² DHF, CS, PO, RHF, HT-HF and ACS-HF (see Supplementary material online, *Appendix S2*). Another two classifications, including SBP at presentation (<85 mmHg, 85–110 mmHg, 110–140 mmHg and >140 mmHg)³ and a classification based on the presence of clinical signs of congestion and/or hypoperfusion (no congestion and no hypoperfusion; congestion without hypoperfusion; hypoperfusion without congestion; hypoperfusion and congestion)¹ were used for reporting in-hospital and 1-year adverse outcomes.

A follow-up visit 12 months after the entry visit was used to collect information on morbidity and mortality.

Data collection

All data including demographics, medical history, clinical presentation, laboratory results, inpatient management and in-hospital and 1-year outcomes were collected by chart review and entered into a centrally managed online database using a web-based electronic case report form. Automated electronic data checks were performed to prevent out-of-range or duplicate entries.

In-hospital outcome included all-cause mortality. One-year outcomes included 1-year mortality, 1-year HF readmissions and 1-year death or HF readmission. The cause of death was categorized as cardiac, vascular, non-cardiovascular, and unknown.¹⁶

Statistical analysis

Continuous variables were reported as mean \pm SD, or as median and interquartile range. Among-group comparisons were made using a

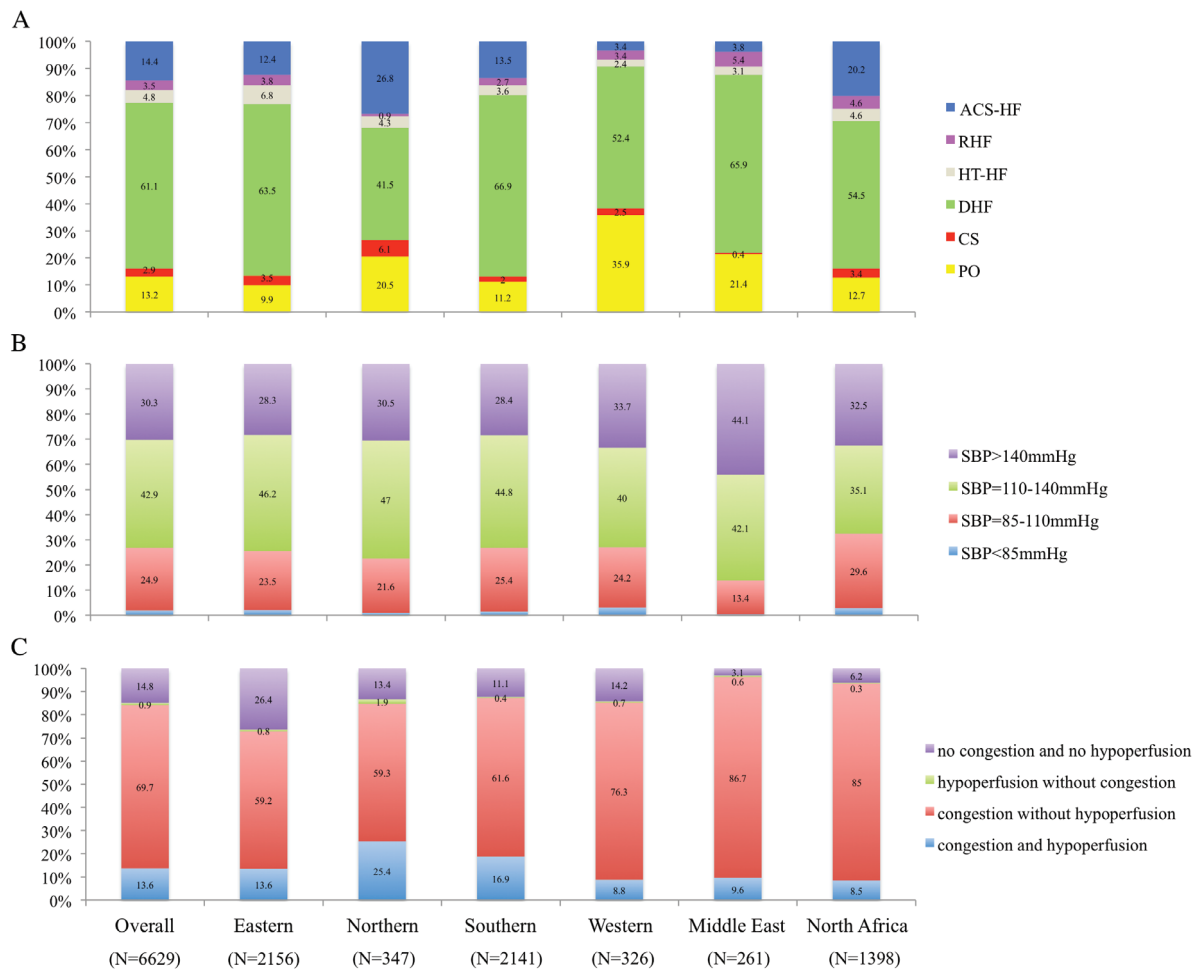


Figure 1 Classification of acute heart failure patients by geographical area. A: clinical profile classification by geographical area. B: systolic blood pressure (SBP) classification by geographical area. C: congestion/hypoperfusion classification by geographical area. ACS-HF, acute heart failure and associated acute coronary syndromes; CS, cardiogenic shock; DHF, decompensated heart failure; HT-HF, hypertensive heart failure; PO, pulmonary oedema; RHF, right heart failure.

non-parametric test (Kruskal–Wallis test). 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 5. For categorical variables with more than two possible values, exact *P*-values were estimated according to the Monte Carlo method. Univariable analysis was applied to both continuous and categorical variables.

Baseline characteristics and type of treatments were reported by clinical profile classification. In-hospital and 1-year post-discharge outcomes were also reported stratified by clinical profile, SBP classification and congestion/hypoperfusion. Plots of the Kaplan–Meier curves for time to all-cause death, time to HF hospitalization and time to all-cause death or HF hospitalization were performed for each clinical profile and for each SBP category. In addition to unadjusted Kaplan–Meier curves, Cox proportional hazard models with multivariable adjustment by clinical relevant variables such as age, gender, chronic kidney disease, chronic obstructive pulmonary disease and cancer, have been performed.

Furthermore, for each outcome, Kaplan–Meier curves have been generated for a different time point (T₀): moment of admission, 1 month post-discharge, and 3, 6 and 12 months post-discharge, and

outcomes in each group were compared using log-rank test. A Tukey’s adjustment of log-rank has been performed and all clinical profiles and SBP categories were pairwise compared for each time point and each outcome.

A two-sided *P*-value of <0.05 was considered statistically significant.

All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

From April 2011 to June 2015, 16 012 patients were enrolled in the ESC-HF-LT Registry. Of these, 6629 patients (41.4% of the total database) were hospitalized with a primary diagnosis of AHF and 9383 patients (58.6%) were ambulatory patients with chronic HF. At 1 year, 411 AHF patients were lost to follow up, representing 6.2% of the study population. Median follow-up time was 378 (288–415) days.

Clinical classifications

Of the AHF patients enrolled in the registry, 13.2% presented with PO, 2.9% with CS, 61.1% with DHF, 4.8% with HT-HF, 3.5% with RHF, and 14.4% with ACS-HF.

The variation in classifications by geographical area is depicted in *Figure 1*. Considering SBP classification, 1.9% of AHF patients presented with SBP <85 mmHg, 24.9% with SBP 85–110 mmHg, 42.9% with SBP 110–140 mmHg, and 30.3% with SBP >140 mmHg. Phenotyping AHF patients by clinical signs of congestion/hypoperfusion showed four mutually exclusive categories: no congestion and no hypoperfusion (14.8%), congestion without hypoperfusion (69.7%), congestion and hypoperfusion (13.6%), and hypoperfusion without congestion (0.9%) (*Figure 1*).

Baseline characteristics and clinical profiles on admission

The group with PO had the highest proportion of patients older than 75 years, while the proportion of females was highest in RHF, HT-HF and PO (*Table 1*).

Ischaemic aetiology was common in patients with CS (68.2%), while valvular aetiology was most frequent in RHF patients (27.0%). Large variations in reported aetiologies were noted in patients admitted with DHF (*Table 1*). Patients admitted with HT-HF and ACS-HF had fewer co-morbidities than patients with CS and RHF (*Table 1*).

At presentation, SBP differed markedly among clinical profiles and varied from 101.9 ± 29 mmHg in CS patients to 168.3 ± 31 mmHg in HT-HF patients. Patients with CS retained distinguishing clinical features in terms of low SBP and signs of hypoperfusion, while most of the clinical characteristics were similar in patients with PO and DHF. Patients presenting with RHF had a constellation of clinical signs, including jugular venous pressure >6, peripheral oedema and hepatomegaly.

Haemoglobin level <12 g/dL was found in 39% of patients and was more frequently observed in patients admitted with RHF and CS. A significantly higher proportion of CS patients presented with baseline renal dysfunction (creatinine >1.5 mg/dL). Hyperglycaemia (blood glucose >120 mg/dL) at presentation was reported in 41% of patients and in more than half of patients admitted with PO, CS and ACS-HF (*Table 1*).

A more elevated level of natriuretic peptides was found in patients with CS and PO compared with other clinical profiles. High troponin levels on admission were a distinctive feature of patients with ACS-HF and were also common in patients with CS and PO (*Table 1*).

The proportion of patients with atrial fibrillation (AF) varied widely between the clinical profiles, with the highest AF prevalence being documented in patients with RHF. A proportion of 26% of patients had QRS duration >120 ms. QRS duration was larger in patients with CS and DHF, and the prevalence of left bundle branch block was highest in PO patients. Particularly, for patients admitted with CS, a longer QT interval duration was noted (*Table 1*).

During hospitalization, echocardiography was performed in 78.3% of patients. A proportion of 53.2% of patients had an ejection fraction (EF) <40%, 25.2% had EF 40–50% and 21.6% had EF >50%. Mitral regurgitation was more often detected in patients admitted with ACS-HF, DHF and CS, while tricuspid regurgitation was common in patients admitted with RHF (69.6%) (*Table 1*).

In-hospital management

The use of i.v. treatments and interventional procedures in the different clinical profiles are reported in *Table 2*. In clinical profiles consistent with more severe HF, such as CS and PO, coronary angiography, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) and intra-aortic balloon pump insertion were more frequently used.

In-hospital outcomes

The highest rate of in-hospital all-cause mortality was noted in CS patients (36.1%) and the lowest in HT-HF patients (1.8%) (*Table 3*). When patients were stratified by SBP at admission, the highest in-hospital mortality was observed in patients with SBP <85 mmHg (26.6%) and the lowest in patients with SBP >140 mmHg (2.7%). Considering the congestion/hypoperfusion classification, the highest mortality was noted in patients with presence of both congestion and hypoperfusion signs (16.5%) and lowest in patients without congestion and without hypoperfusion (1.7%). Most of the in-hospital deaths were cardiac in origin.

For patients hospitalized with CS, of the total number of deaths during hospitalization, 49% occurred in the first 24 hours from presentation, while for patients with PO, 16.3% of deaths occurred in the first 24 hours. For the remaining clinical profiles, the rate of death in the first 24 hours represented less than 10% of total number of deaths occurring during hospitalization.

Between admission and discharge, New York Heart Association (NYHA) class and clinical signs and symptoms suggestive of HF showed substantial variation (*Figure 2*).

Of patients discharged alive, worsening renal function was documented in 12.5% of patients, and it was reported more often in patients hospitalized for CS (21.0%). Patients classified as CS and RHF had more frequent hyponatraemia at discharge as compared with other clinical profiles (*Table 3*).

One-year outcomes

One-year mortality rate was 26.7% and 1-year HF hospitalization was 25.9% (*Table 4*). Cardiovascular deaths represented 57.2% of total deaths in the overall population. Similar to in-hospital mortality, the highest 1-year mortality rate was observed in patients with CS (54.0%), low SBP at admission (34.8%) and in patients with both congestion and hypoperfusion (29.8%).

Figures 3 and 4 show the Kaplan–Meier curves for all-cause mortality, and the combined event of all-cause mortality and HF hospitalization for AHF patients stratified by clinical profiles, at different time points (at admission, and 1, 3, 6 and 12 months post-discharge). One-year outcome rates of each clinical profile

Table 1 Epidemiology and baseline characteristics by clinical profile at admission

	Overall (n = 6629)	PO (n = 875)	CS (n = 195)	DHF (n = 4052)	HT-HF (n = 320)	RHF (n = 233)	ACS-HF (n = 954)	P-value
Age >75 years, %	34.0	42.0	31.8	34.9	32.5	35.2	23.7	<0.0001
Male, %	63.0	56.9	60.0	65.2	50.0	54.1	66.7	<0.0001
History, %								
Diabetes	39.1	42.1	33.8	37.9	35.6	39.9	43.2	0.0062
Previous MI	53.6	52.1	60.0	48.1	37.8	21.0	90.1	<0.0001
PCI	20.2	20.4	23.1	18.1	13.7	8.1	33.5	<0.0001
CABG	9.5	8.7	5.6	10.7	5.3	7.3	8.4	0.0014
PM	6.0	6.0	5.7	6.6	4.1	10.3	2.7	<0.0001
CRT-P	0.6	0.2	0.0	0.9	0.0	0.4	0.4	0.0674
CRT-D	3.0	1.9	1.5	4.2	0.0	2.1	0.4	<0.0001
ICD	5.1	3.8	5.6	6.4	1.2	3.8	2.1	<0.0001
Valvular surgery	5.3	4.4	3.6	6.6	2.5	12.0	0.5	<0.0001
PAD	13.9	15.9	14.3	13.5	12.2	13.8	14.1	0.05267
Stroke/TIA	12.0	13.6	16.4	11.5	14.4	9.4	11.8	0.0812
VTE	4.3	4.1	6.6	3.9	2.8	9.9	4.9	0.0002
CKD	26.3	26.7	29.2	28.1	22.9	28.7	18.2	<0.0001
Hepatic dysfunction	7.8	7.5	14.3	7.9	3.7	20.1	4.6	<0.0001
Cancer	4.8	5.5	4.6	4.9	5.9	6.4	2.5	0.0136
COPD	19.1	19.7	16.4	18.9	17.6	29.2	17.9	0.0032
Sleep apnoea	2.9	2.5	1.0	3.4	3.8	4.8	1.1	0.0007
Parkinson's disease	1.1	1.1	2.0	1.0	0.9	0.0	1.3	0.4211
Depression	7.1	8.9	12.3	6.4	7.5	8.1	6.9	0.0070
Primary aetiology, %								
Ischaemic heart disease	56.5	58.4	68.2	50.2	31.5	16.3	97.2	<0.0001
Hypertension	8.2	13.9	1.0	6.0	50.3	3.4	0.4	<0.0001
Dilated cardiomyopathy	13.6	9.7	18.4	18.5	3.1	7.7	0.6	<0.0001
Valve disease	11.8	11.2	5.1	14.2	6.9	27.0	1.1	<0.0001
Other	5.2	2.9	6.1	5.3	2.5	36.5	0.3	<0.0001
Precipitants, %								
Myocardial ischaemia	30.0	34.7	57.9	17.3	21.2	3.4	93.4	<0.0001
AF	30.3	27.3	26.15	34.3	29.3	34.7	16.3	<0.0001
Ventricular arrhythmias	7.1	5.8	18.9	6.2	5.3	2.1	11.1	<0.0001
Bradyarrhythmias	3.6	2.4	9.2	3.3	4.7	3.8	4.2	0.0002
Infection	20.0	22.1	24.6	21.4	11.8	22.7	13.2	<0.0001
Uncontrolled HTN	16.5	26.5	5.6	9.6	81.5	6.4	23.1	<0.0001
Noncompliance	5.8	6.8	4.1	6.4	8.1	2.5	2.3	<0.0001
Renal dysfunction	18.5	18.4	25.1	19.5	17.2	18.9	13.5	0.0002
Anaemia	15.7	14.1	16.4	19.2	13.1	26.1	12.9	<0.0001
Iatrogenic	1.2	1.5	1.0	1.3	0.6	0.8	0.7	0.5343
Other	8.3	8.9	10.2	8.7	11.5	15.0	3.0	<0.0001
Clinical presentation								
New onset, %	29.3	38.7	40.0	18.8	51.1	27.9	56.4	<0.0001
Worsening, %	70.6	61.3	60.0	81.1	48.9	72.1	43.6	<0.0001
SBP, mmHg (median [IQR])	130.0 [110–150]	140.0 [120–161]	95.0 [80–120]	130.0 [110–140]	170.0 [150–190]	120.0 [110–140]	138.5 [120–156]	
HR, b.p.m. (median [IQR])	88.0 [73–104]	95.0 [79–110]	100.0 [79–117]	85.0 [70–100]	87.5 [74–108]	85.0 [70–100]	90.0 [75–108]	
Pulmonary rales, %	73.6	93.7	77.9	72.1	66.7	53.2	67.7	<0.0001
JVP >6, %	35.2	40.8	50.2	36.3	20.6	58.8	21.0	<0.0001
Peripheral oedema, %	55.4	46.2	48.2	63.7	40.9	84.9	27.6	<0.0001
Hepatomegaly, %	25.4	23.3	25.2	27.8	18.2	52.6	13.0	<0.0001
S3, %	30.5	34.3	48.7	25.8	26.2	25.4	46.0	<0.0001
Peripheral hypoperfusion, %	17.8	22.4	56.4	15.0	10.7	13.8	20.9	<0.0001
Peripheral congestion, %	56.0	61.8	64.9	59.1	38.2	76.3	36.1	<0.0001
Pulmonary congestion, %	73.6	93.7	77.9	72.1	66.7	53.2	67.7	<0.0001
Congestion without hypoperfusion, %	69.7	68.3	16.0	73.4	73.1	72.3	60.3	<0.0001
Congestion and hypoperfusion, %	13.6	19.5	54.8	10.5	1.9	12.1	15.7	<0.0001
Hypoperfusion without congestion, %	0.9	9.3	26.4	0.8	0.2	1.0	1.7	<0.0001
No congestion and no hypoperfusion, %	14.8	2.9	2.8	14.3	24.8	14.6	22.3	<0.0001
Laboratory values								
Creatinine, mg/dL (median [IQR])	1.2 [0.9–1.5]	1.2 [0.9–1.5]	1.4 [1.0–2.1]	1.2 [0.9–1.6]	1.0 [0.8–1.4]	1.2 [0.9–1.5]	1.1 [0.9–1.4]	
Sodium, mmol/L (median [IQR])	139 [135–141]	138 [135–141]	136 [133–140]	139 [135–141]	140 [137–142]	138 [134–141]	139 [136–141]	

Table 1 Continued

	Overall (n = 6629)	PO (n = 875)	CS (n = 195)	DHF (n = 4052)	HT-HF (n = 320)	RHF (n = 233)	ACS-HF (n = 954)	P-value
Glycaemia, mg/dL (median [IQR])	110 [93–150]	128 [100–188]	124 [100–179]	106 [90–138]	110 [93–150]	105 [91–147]	120 [98–171]	
Haemoglobin, g/dL (median [IQR])	12.7 [11.2–14.1]	12.4 [11.0–13.9]	12.6 [10.7–14.0]	12.6 [11.1–14.0]	12.9 [11.5–14.1]	11.7 [10.2–13.6]	13.2 [11.9–14.4]	
BNP, pg/mL (median [IQR]) (available for 701 pts)	765 [355–1398]	969 [516–1502]	1719 [692–2134]	805 [376–1492]	493 [218–872]	578 [286–912]	680 [350–1398]	
NT-proBNP, pg/mL (median [IQR]) (available for 1599 pts)	3825 [1658–8960]	6044 [2523–12317]	5000 [2220–9809]	3872 [1674–8839]	2125 [982–4510]	2096 [1023–9970]	2537 [1114–6364]	
Troponin, mg/L (median [IQR]) (available for 2895 pts)	0.10 [0.03–0.37]	0.10 [0.04–1.0]	0.77 [0.08–27.0]	0.06 [0.02–0.20]	0.10 [0.02–0.10]	0.04 [0.02–0.10]	0.35 [0.30–4.60]	
ECG								
AF, %	42.7	38.8	34.8	48.5	39.4	54.9	21.4	<0.0001
QRS duration, ms (mean ± SD)	109.6 ± 30	107.1 ± 28	110.4 ± 31	113.1 ± 31	101.0 ± 25	105.6 ± 29	102.2 ± 26	<0.0001
QT duration, ms (mean ± SD)	376.9 ± 72	378.3 ± 73	385.4 ± 67	380.8 ± 71	369.5 ± 70	362.2 ± 82	365.6 ± 74	<0.0001
LBBB, %	15.0	18.6	16.7	16.3	9.8	5.1	10.3	<0.0001
Echo								
EF, % (mean ± SD)	39.2 ± 14.5	39.9 ± 14.7	34.8 ± 14.0	37.3 ± 14.3	50.9 ± 13.7	49.1 ± 13.3	40.3 ± 12.5	<0.0001
EF <40%, %	53.2	52.0	67.3	58.8	20.6	22.7	48.0	<0.0001
EF 40–50%, %	25.2	24.9	18.0	22.6	26.1	31.3	34.4	<0.0001
EF >50%, %	21.6	23.1	14.7	18.5	53.4	46.0	17.7	<0.0001
Mitral regurgitation, %	45.9	41.0	42.8	47.8	36.2	31.0	49.6	<0.0001
Tricuspid regurgitation, %	35.4	26.1	34.0	40.2	21.6	69.6	22.9	<0.0001

ACS-HF, acute heart failure and associated acute coronary syndromes; AF, atrial fibrillation; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CS, cardiogenic shock; DHF, decompensated heart failure; EF, ejection fraction; HR, heart rate; HT-HF, hypertensive heart failure; HTN, hypertension; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; JVP, jugular venous pressure; LBBB, left bundle branch block; MI, myocardial infarction; NT-proBNP, N-terminal proBNP; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PM, pacemaker; PO, pulmonary oedema; RHF, right heart failure; SBP, systolic blood pressure; VTE, venous thromboembolism; TIA, transient ischemic attack.

Table 2 Intravenous vasoactive therapies and interventions during hospitalization

	Overall (n = 6629)	PO (n = 875)	CS (n = 195)	DHF (n = 4052)	HT-HF (n = 320)	RHF (n = 233)	ACS-HF (n = 954)	P-value
Intravenous therapies, %								
Inotropes	12.3	14.2	81.0	9.8	1.5	9.8	11.2	<0.0001
Vasodilators	21.2	46.1	14.0	10.7	36.9	3.9	43.6	<0.0001
Diuretics	81.7	96.4	78.2	81.3	73.3	80.5	73.47	<0.0001
Interventions, %								
Coronary angiography	20.8	23.5	37.1	14.7	14.5	9.9	45.9	<0.0001
PCI/CABG	9.8	10.8	25.7	4.1	5.0	0.8	33.9	<0.0001
EPS	0.6	0.4	0.0	0.7	0.0	0.8	0.4	0.3255
Transcatheter ablation	0.6	0.3	1.0	0.7	0.0	1.3	0.5	0.3063
Right heart catheterization	1.9	0.3	3.1	2.4	0.6	4.7	0.4	<0.0001
IABP	1.1	1.5	14.9	0.3	0.0	0.8	1.5	<0.0001
CRT-D*	6.8	7.9	4.5	8.5	5.3	3.1	2.0	<0.0001
CRT-P*	1.9	0.6	4.4	2.1	0.0	0.3	1.2	<0.0001
ICD*	9.6	10.2	15.8	11.1	5.3	1.7	5.1	<0.0001

ACS-HF, acute heart failure and associated acute coronary syndromes; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; CS, cardiogenic shock; DHF, decompensated heart failure; EPS, electrophysiological study; HT-HF, hypertensive heart failure; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; PO, pulmonary oedema; RHF, right heart failure.

*CRT-D, CRT-P and ICD are mutually exclusive terms.

have been pairwise compared for each outcome at each time point (see Supplementary material online, *Table S1*). Adjusted Cox proportional hazard models for each outcome are presented in the Supplementary material online, *Table S2*.

When analysis of Kaplan–Meier curves was performed between 6 and 12 months post-discharge, all six clinical profiles have

comparable 1-year outcomes. Patients with CS showed the highest 1-year mortality rate during hospitalization and the first month after discharge. Patients with HT-HF and ACS-HF had the lowest 1-year Kaplan–Meier mortality regardless of the time point of analysis. Kaplan–Meier curves performed without these two clinical profiles showed no significant differences in 1-year

Table 3 In-hospital outcomes

	Overall (n = 6629)	PO (n = 875)	CS (n = 195)	DHF (n = 4052)	HT-HF (n = 320)	RHF (n = 233)	ACS-HF (n = 954)	P-value
All-cause death, %	5.5	6.4	36.1	4.2	1.8	9.4	4.2	<0.0001
Cardiac	80.3	80.3	90.0	76.6	83.3	72.7	82.5	0.2534
Vascular	5.5	3.6	8.6	5.2	0.0	4.5	5.0	0.8346
Non-cardiovascular	10.4	14.3	1.4	12.9	16.6	13.64	7.5	0.1122
Unknown	3.8	1.8	0.0	5.26	0.0	9.1	5.0	
Time in hospital, days (median [IQR])	7 [4–11]	7 [5–11]	7 [2–13]	7 [4–10]	6 [3–9]	8 [5–13]	6 [4–11]	
NYHA class IV at discharge, %	2.6	3.2	8.2	2.8	0.9	1.9	1.3	<0.0001
Body weight status at discharge, %								
Decrease >3 kg	22.2	23.4	28.3	23.8	20.4	25.7	13.5	<0.0001
Decrease 0–3 kg	72.9	71.1	66.7	71.5	75.4	70.4	81.1	<0.0001
Increase	4.8	5.3	5.0	4.7	4.1	3.9	5.4	0.8612
WRF at discharge*, %	12.5	16.5	21.0	11.8	10.1	9.8	11.3	0.0001
Hyposodaemia at discharge**, %	17.9	17.3	24.4	18.9	11.3	22.8	14.1	0.0002
Increase BNP, %	14.4	5.3	25.0	14.4	14.3	20.0	10.0	0.0921
Decrease BNP <40%, %	35.1	36.6	45.1	35.1	13.7	38.0	25.5	0.0439
Increase NT-proBNP, %	21.6	24.5	32.5	19.1	14.4	18.9	13.0	0.1319
Decrease NT-proBNP <25%, %	16.1	23.8	9.1	16.3	9.1	12.4	10.7	0.0921

ACS-HF, acute heart failure and associated acute coronary syndromes; BNP, brain natriuretic peptide; CS, cardiogenic shock; DHF, decompensated heart failure; HT-HF, hypertensive heart failure; IQR, interquartile range; NT-proBNP, N-terminal proBNP; NYHA, New York Heart Association; PO, pulmonary oedema; RHF, right heart failure; WRF, worsening renal function.

*Serum creatinine difference between hospitalization and discharge >0.3.

**Na <135 mEq/L.

all-cause mortality between PO, DHF, RHF and CS patients, even from 1-month post-discharge (see Supplementary material online, Figure S1).

A similar analysis has been performed for SBP categories (see Supplementary material online, Figures S2 and S3), showing that between 6 and 12 months post-discharge there were no significant differences in subsequent 1-year mortality among the four SBP categories.

For 1-year HF hospitalization, 6-month post-discharge analysis showed reduced differences among clinical profiles and SBP groups, and at 1-year post-discharge there were no differences in outcomes among all clinical profiles and SBP groups.

Discussion

The present analysis describes the classification of patients with AHF, covering the entire spectrum of patients with AHF. Classification of AHF patients may facilitate an early decision-making regarding appropriate triage and targeted treatment of high-risk populations.

Although DHF was the most common clinical presentation, similar to other registries,^{6–10,14} considerable differences in the prevalence of clinical profiles have been found across geographical regions. Furthermore, when considering other classification schemes, such as the most recent one based on congestion and hypoperfusion, substantial geographical variability has been found. The explanations for these geographical differences may be ‘investigator-related’ and ‘system-related’. ‘Investigator-related’

differences reflect variations in interpreting the definitions and different cultural perceptions of severity with different thresholds for hospital admissions, whereas ‘system-related’ differences are due to the absence of objective criteria for hospital admission, as well as differences in patterns of medical care across regions. In contrast to clinical profile and congestion/hypoperfusion classifications, the classification based on initial SBP shows less geographic variation supporting its larger applicability in clinical practice.

Our analysis shows that different clinical profiles may have similar clinical presentations, making the 2008 ESC clinical classification² challenging. Similar to other studies,^{17,18} an elevated SBP at admission and signs of pulmonary congestion are common findings at presentation in PO, DHF and HT-HF patients, leading to misclassification and overlap between these AHF phenotypes.

Patients with CS were significantly different from the other clinical profiles for all clinical characteristics and should therefore be considered separately.¹⁹ In CS patients, overall utilization of i.v. inotropes during hospitalization (81.0%) exceeds the proportion of patients presenting with hypoperfusion signs at admission (56.4%). However, clinical signs vary rapidly during presentation²⁰ and for some CS patients, hypoperfusion signs may not be apparent at presentation and become manifest later during hospitalization, suggesting ongoing clinical worsening despite the use of initial therapies.

Right HF was also distinguishable from the other scenarios in terms of clinical characteristics and high 1-year readmissions (48.3%). The clinical picture is dominated by signs of systemic congestion (jugular venous pressure >6, peripheral oedema and hepatomegaly) resulting from impaired right ventricular

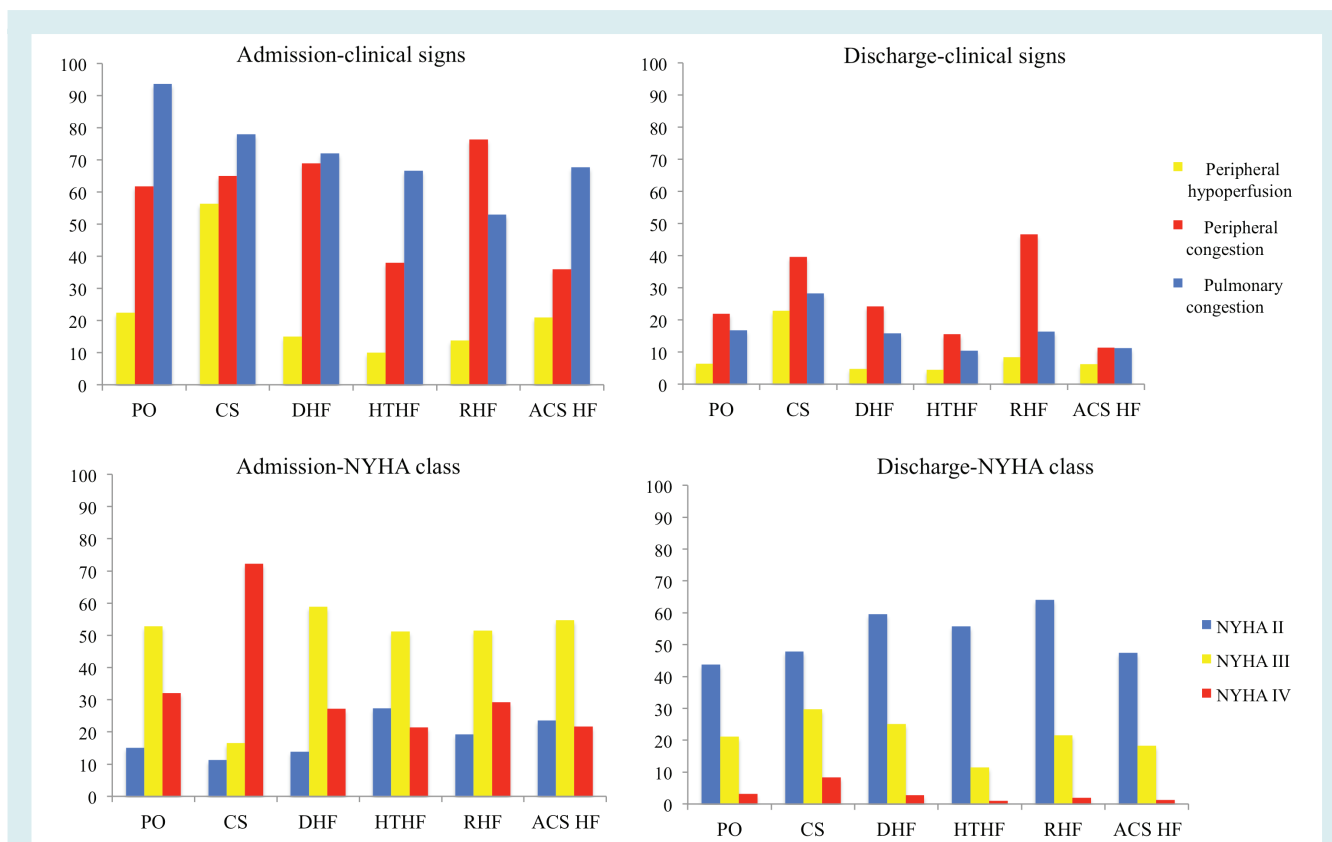


Figure 2 New York Heart Association (NYHA) class and clinical signs: variation between admission and discharge for each clinical profile. ACS-HF, acute heart failure and associated acute coronary syndromes; CS, cardiogenic shock; DHF, decompensated heart failure; HT-HF, hypertensive heart failure; PO, pulmonary oedema; RHF, right heart failure.

filling and/or reduced right ventricular output.²¹ Furthermore, patients with RHF have many co-morbidities, which may prevent the optimization of HF evidence-based therapies. Addressing non-cardiac co-morbidities may be particularly important, since a vast proportion of re-hospitalizations are not HF-related.

The ESC-HF-LT Registry is one of the few registries to describe AHF in the setting of ACS, and its reported prevalence of 14.4% was similar to that found in the Italian IN-HF Outcome registry.⁹ ACS-HF patients present with clinical signs indicative of high left ventricular filling pressures (pulmonary rales, S3 sound, mitral regurgitation murmur) suggesting the impact of acute ischaemia on diastolic and systolic properties of the left ventricle.

The prevalence of moderate-to-severe mitral and tricuspid regurgitation is similar to that reported in previous registries.¹² Different from chronic settings, the prevalence of mitral and tricuspid regurgitation may be overestimated in AHF. During hospitalization, the severity of functional regurgitation may decrease as a result of decongestive therapies.

In-hospital management

The type and proportions of vasoactive medications, stratified by clinical profile, are similar to those reported by other contemporary registries,^{5–10,18} except for i.v. inotropes. The ESC-HF-LT

Registry shows a lower use of i.v. inotropes in non-CS patients compared to previous registries.

Although ischaemic heart disease is by far the most common aetiology of AHF, coronary angiography and PCI/CABG were performed only in 21% and 10% of patients. Furthermore, even in patients classified as ACS-HF, coronary angiography and PCI/CABG were performed in 45.9% and 33.9% of patients, suggesting large variations in available facilities,²² as well as variations in guideline adherence across the participating centres.

The proportion of patients with cardiac resynchronization therapy/cardioverter-defibrillator implants is similar to other studies.²² Although guidelines do not recommend to implant devices during acute decompensation, several patients may derive benefit from in-hospital screening targeting device implantation during hospitalization. Further research is necessary to clarify the optimal timing of device implantation during hospitalization or soon after discharge among AHF patients.

In-hospital outcomes

The highest mortality rates were observed in patients with CS, in those with SBP <85 mmHg, and in patients presenting with both congestion and hypoperfusion signs. Notably, in-hospital and 1-year mortality in CS were higher than in the group with SBP <85 mmHg

Table 4 One-year outcome rate by different classifications of acute heart failure

A. Clinical profile classification	Overall (n = 6629)	PO (n = 875)	CS (n = 195)	DHF (n = 4052)	HT-HF (n = 320)	RHF (n = 233)	ACS-HF (n = 954)	P-value
In-hospital mortality, %	5.5	6.4	36.1	4.2	1.8	9.4	4.2	<0.0001
One-year all-cause death, %	26.7	28.1	54.0	27.2	12.8	33.9	20.6	<0.0001
Cardiac	53.4	48.9	78.0	50.6	51.3	50.7	62.8	<0.0001
Vascular	3.8	6.5	6.0	3.0	2.5	1.3	4.7	0.0970
Non-cardiovascular	12.4	14.3	4.0	13.5	17.9	13.7	6.8	0.0098
Unknown	30.4	30.3	12.0	32.9	28.2	34.2	25.6	
One-year all-cause hospitalization, %	44.4	39.7	43.4	48.1	34.4	48.3	35.7	<0.0001
One-year HF hospitalization, %	25.9	20.8	20.8	29.91	14.34	31.2	17.6	<0.0001
One-year all-cause death and/or HF hospitalization, %	42.3	40.6	61.6	45.4	22.9	50.7	32.3	<0.0001
B. Systolic blood pressure classification	Overall (n = 6629)	SBP <85 mmHg (n = 128)	SBP 85–110 mmHg (n = 1653)	SBP 110–140 mmHg (n = 2845)	SBP >140 mmHg (n = 2003)	P-value		
In-hospital mortality, %	5.5	26.5	8.71	4.7	2.6	<0.0001		
One-year all-cause death, %	26.7	34.8	29.0	21.2	17.4	<0.0001		
Cardiac	53.4	61.3	47.7	44.3	44.5	0.2294		
Vascular	3.8	0.0	2.7	4.1	3.1	0.4588		
Non-cardiovascular	12.4	19.3	11.1	13.1	14.3	0.4141		
Unknown	30.4	19.3	38.3	38.5	38.0			
One-year all-cause hospitalization, %	44.4	53.6	48.1	45.2	40.0	<0.0001		
One-year HF hospitalization, %	25.9	33.7	31.7	25.7	21.6	<0.0001		
One-year all-cause death and/or HF hospitalization, %	42.3	55.0	47.7	38.0	32.1	<0.0001		
C. Congestion/hypoperfusion classification	Overall (n = 6502)	No congestion no hypoperfusion (n = 983)	Congestion without hypoperfusion (n = 4562)	Hypoperfusion without congestion (n = 66)	Hypoperfusion and congestion (n = 891)	P-value		
In-hospital mortality, %	5.5	1.7	4.1	13.6	16.5	<0.001		
One-year all-cause death, %	26.7	12.9	23.	18.5	29.8	<0.001		
Cardiac	53.4	43.7	41.5	70.0	63.4	<0.001		
Vascular	3.8	4.2	3.1	10.0	3.8	0.571		
Non-cardiovascular	12.4	10.1	14.2	10.0	9.1	0.175		
Unknown	30.4	42.0	41.1	10.0	23.5			
One-year all-cause hospitalization, %	44.4	38.7	44.3	51.9	49.2	0.004		
One-year HF hospitalization, %	25.9	16.4	26.9	25.0	32.2	<0.001		
One-year all-cause death and/or HF hospitalization, %	42.3	24.8	40.3	37.0	49.4	<0.001		

ACS-HF, acute heart failure and associated acute coronary syndromes; CS, cardiogenic shock; DHF, decompensated heart failure; HF, heart failure; HT-HF, hypertensive heart failure; PO, pulmonary oedema; RHF, right heart failure; SBP, systolic blood pressure.

or in the group with both congestion and hypoperfusion signs, suggesting that general metabolic compromise and multi-organ failure, characteristic of CS, have distinct pathways beyond SBP and hypoperfusion, and may be responsible for the excess mortality.

For patients admitted with CS, 49% of in-hospital deaths occurred in the first 24 hours from presentation, suggesting that early identification of hypoperfusion signs, as well as

appropriateness of initial therapies, may be potentially life-saving in this setting.

NYHA class and residual congestive signs and symptoms at discharge varied across clinical profiles, indicating different entities with different responses to AHF therapies,²³ and suggesting that future clinical trials in hospitalized HF patients should take into account phenotypic diversity.²⁴

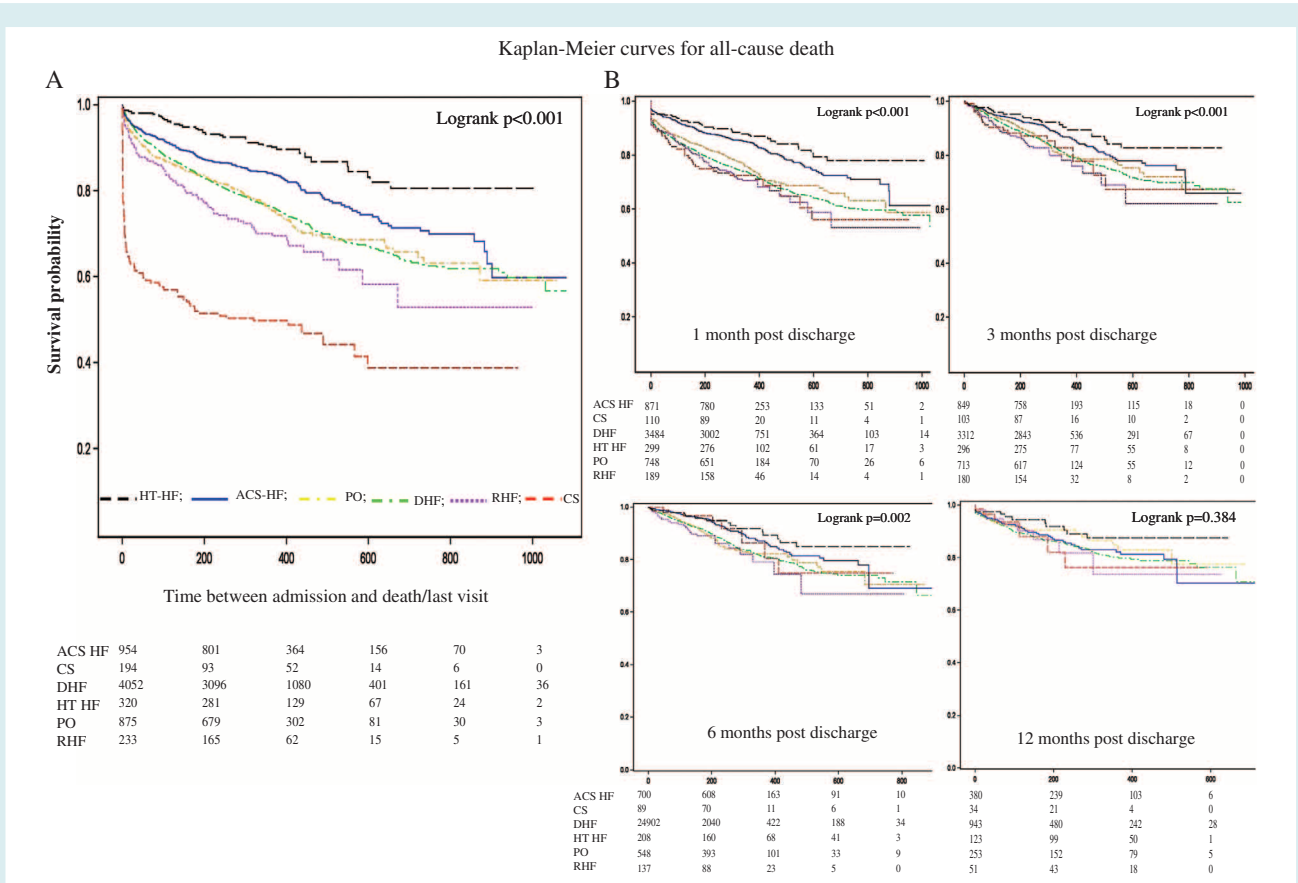


Figure 3 Kaplan–Meier curves for all-cause death at different time points: at admission (A), and at 1, 3, 6, and 12 months post-discharge (B). ACS-HF, acute heart failure and associated acute coronary syndromes; CS, cardiogenic shock; DHF, decompensated heart failure; HT-HF, hypertensive heart failure; PO, pulmonary oedema; RHF, right heart failure.

One-year outcomes

Similar to previous registries,^{25–28} 1-year outcome rates of each clinical profile considered by the ESC-HF-LT Registry remain unacceptably high, confirming that hospitalization for AHF represents a change in the trajectory of the disease process. This finding can be explained by the fact that in-hospital therapeutic approaches to these patients have remained practically unchanged during the last few decades.

In the ESC-HF-LT Registry, the proportion of cardiovascular deaths (57.5%) is lower than in the ESC-HF Pilot study (66%) and lower than in the Italian IN-HF Outcome registry (71%).

Present data reveal that 20% of patients are discharged despite persistent signs and symptoms of HF. A negligible decrease or an increase in body weight suggest a possible failure to relieve clinical congestion during index hospitalization, which may potentially contribute to the high post-discharge event rate in the registry. Furthermore, for some AHF patients, natriuretic peptide levels do not decrease, or decrease insufficiently during hospitalization. Although the complete mechanisms are unknown, an insufficient decrease or re-elevation of natriuretic peptides during hospitalization suggests residual haemodynamic congestion as a result of suboptimal treatment.²⁹

The highest rate of 1-year death was observed in patients admitted with CS, and the highest rate of 1-year HF re-hospitalization was noted in patients with RHF. Patients with HT-HF and ACS-HF had the best survival during hospitalization and throughout the follow-up. These patients presented with high or normal SBP, had a lower index of non-cardiac co-morbidities, and were discharged with minimal residual congestion, better NYHA class and better renal function when compared to other clinical profiles. Furthermore, identification of aetiological factors and precipitants, as well as aetiological treatment (coronary interventions or hypertension treatment) is easier in these two clinical profiles.

Differences in 1-year outcome among clinical profiles and SBP categories depend on the time of the analysis. In particular, when performed later after discharge, differences in outcome rates among clinical profiles tend to disappear, and all clinical profiles have comparable 1-year outcomes between 6 and 12 months post-discharge. ACS-HF and HT-HF patients tend to equalize 1-year mortality rate of CS patients after 6 months post-discharge. A similar finding was found when 1-year outcomes were compared among SBP categories, and after 6 months post-discharge, no differences in 1-year outcome were noted.

This finding can be relevant for future clinical trials enrolling patients hospitalized for AHF at different time intervals

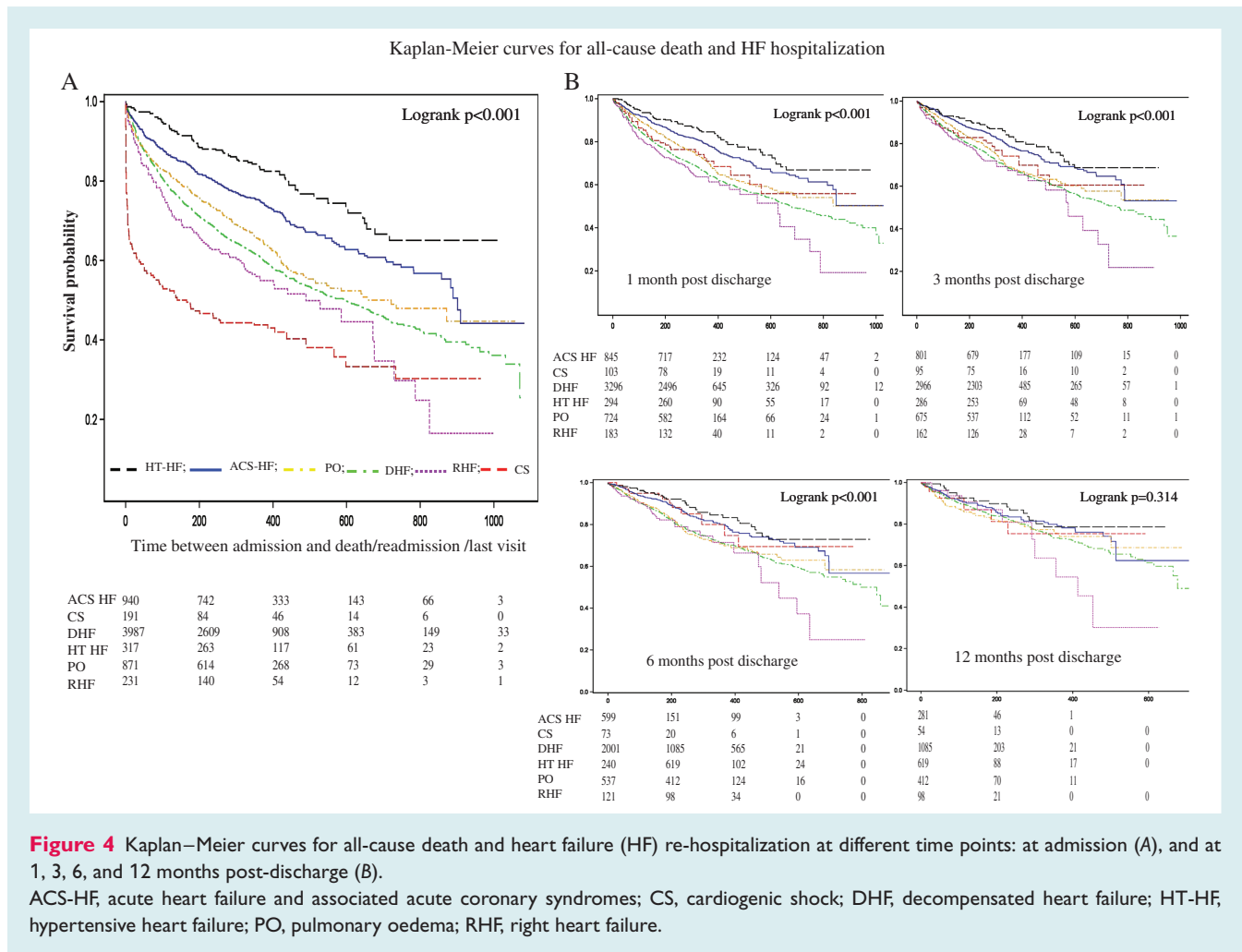


Figure 4 Kaplan–Meier curves for all-cause death and heart failure (HF) re-hospitalization at different time points: at admission (A), and at 1, 3, 6, and 12 months post-discharge (B). ACS-HF, acute heart failure and associated acute coronary syndromes; CS, cardiogenic shock; DHF, decompensated heart failure; HT-HF, hypertensive heart failure; PO, pulmonary oedema; RHF, right heart failure.

post-discharge. When testing a novel therapy during HF hospitalization or in the first months post-discharge, the investigators should be aware of the differences in outcome rates among AHF clinical profiles or SBP categories.³⁰ Patients who have survived 6 months post-discharge represent a more uniform group, and their subsequent 1-year outcome rate is less influenced by clinical profile or SBP classification at admission.

Limitations

Although AHF criteria and classification are well established in the ESC guidelines and provided to the investigators, the AHF diagnosis and clinical profile assignment were made at the point of care by each clinician-investigator, without central confirmation, potentially resulting in incomplete or inaccurate classification. The reliability of classification (i.e. agreement between two or more study investigators) was not assessed in this study and needs further investigation. Absence of the restricting criteria to grade severity of pulmonary congestion may have resulted in inconsistent classification and overlap between PO and HT-HF patients.

There was no central committee to adjudicate the causes of death and type of re-hospitalization.

The registry included only patients from cardiology departments or specialized HF units, and the extent to which the findings from this study can be generalized to other populations is unclear.

Conclusions

The ESC-HF-LT Registry demonstrates the importance of systematic characterization of AHF patients during their in-hospital course. Classifying AHF patients on the basis of clinical relevant data may mediate improvements in quality of care and outcomes.

Rates of adverse outcomes in patients admitted for AHF remain very high, both in-hospital and during the follow-up period, and substantial differences were found when patients were stratified by clinical profile, SBP, or congestion/hypoperfusion phenotypes. However, differences in 1-year outcome rates tend to diminish in the first few months post-discharge, and 1-year outcome rates of patients following 6 months after discharge did not vary significantly by clinical profile or SBP at admission, suggesting extinction of the initial acute process leading to decompensation and homogeneity in the long-term course.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Committee and Investigators.

Appendix S2. Clinical profiles at presentation according to the 2008 ESC guidelines.

Table S1. Pairwise comparison by Tukey's adjustment for each outcome at each time point.

Table S2. Adjusted Cox regression analysis for each outcome; 1-year all-cause death, 1-year HF hospitalizations, 1-year all-cause death or HF hospitalizations.

Figure S1. Kaplan–Meier survival curves for all-cause death (excluding patients with ACS-HF and HT-HF) at admission, and at 1, 3, 6 and 12 months post-discharge.

Figure S2. Kaplan–Meier survival curves for all-cause death for SBP categories at admission, and at 1, 3, 6 and 12 months post-discharge.

Figure S3. Kaplan–Meier curves for all-cause death and HF hospitalization for SBP categories at admission, and at 1, 3, 6 and 12 months post-discharge.

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Overall activities were coordinated and supervised by Dr Aldo P. Maggioni (EORP Scientific Coordinator). All investigators are listed in the Supplementary material online, *Appendix S1*.

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