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Original Contributions

ACUTE HEART FAILURE IN THE EMERGENCY DEPARTMENT: THE SAFE-SIMEU EPIDEMIOLOGICAL STUDY

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☐ **Abstract—Background: Patients with acute heart failure (AHF) have high rates of attendance to emergency departments (EDs), with significant health care costs. Objectives: We aimed to describe the clinical characteristics of patients attending Italian EDs for AHF and their diagnostic and therapeutic work-up. Methods: We carried out a retrospective analysis on 2683 cases observed in six Italian EDs for AHF (January 2011 to June 2012). Results: The median age of patients was 84 years (interquartile range 12), with females accounting for 55.8% of cases (95% confidence interval [CI] 53.5–57.6%). A first episode of AHF was recorded in 55.3% (95% CI 55.4–57.2%). Respiratory disease was the main precipitating factor (approximately 30% of cases), and multiple comorbidities were recorded in > 50% of cases (history of acute coronary syndrome, chronic obstructive pulmonary disease, diabetes, chronic kidney disease, valvular heart disease). The treatment was based on oxygen (69.7%; 67.9–71.5%), diuretics (69.2%; 67.9–71.5%), nitroglycerin (19.7%; 18.3–21.4%), and noninvasive ventilation (15.2%; 13.8–16.6%). Death occurred within 6 h in 2.5% of cases (2.0–3.1%), 6.4% (5.5–7.3%) were referred to the care of their general practitioners within a few hours from ED attendance or after short-term (< 24 h) observation 13.9% (12.6–15.2%); 60.4% (58.5–62.2%) were admitted to the hospital, and 16.8% (15.4–18.3%) were cared for in intensive care units according to disease severity. Conclusions: Our study reporting the "real-world" clinical activity indicates that subjects attending the Italian EDs for AHF are rather different from those reported in international registries. Subjects are older, with a higher proportion of females, and high prevalence of cardiac and noncardiac comorbidities.**

☐ **Keywords—acute heart failure; emergency department; clinical characteristics; epidemiology**

INTRODUCTION

Acute heart failure (AHF) is a global public health issue characterized by high mortality and high rates of hospital admissions and re-hospitalizations, with a massive economic burden for national health systems (1). A recent state-of-the-art review reported that the number of patients with AHF exceeds 20 million in Europe and the United States, with an incidence of over 1.5 million cases/year (2–4). Patients with AHF are a very heterogeneous group in terms of etiology, precipitating

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factors, comorbidities, and the extent and severity of signs and symptoms at presentation (2).

The majority of studies are derived from inpatient settings; only a few have been obtained in the setting of emergency departments (EDs) (1,4–6). Compared with inpatient settings, the ED represents a high-yield area to identify symptomatic patients eligible for enrollment in large AHF trials testing the early treatment phase (7). Exclusion of the ED phase of patient management has been suggested as a possible reason for the lack of success of AHF studies (4).

In clinical practice, AHF mainly affects old subjects, whose management and outcome are dictated by acute and chronic comorbidities (8,9). Differences are reported in the clinical characteristics at presentation, in the clinical course, treatment, and prognosis (8,10). In addition, specific health care system configurations are likely to have an impact on the measured incidence rate, due to different methods of data retrieval (9).

Our primary outcome was to investigate the demographic and clinical characteristics at ED presentation, as well as the treatment of subjects with a final diagnosis of AHF treated in a few EDs of Italian general hospitals. The secondary outcome was to analyze the contribution of different comorbidities to recurrent vs. new-onset AHF.

METHODS

Data Collection

In 2012, the Study and Research Centre of the Italian Society of Emergency Medicine (SIMEU) launched a study on patients seen in the EDs for acute heart failure (Screening of Acute Heart Failure Emergency Department – SAFE). According to a predefined case report form, chart data from six Italian EDs (approximately 350,000 visits/year, covering an area of approximately 1.5 million inhabitants) were extracted from the local databases for the period between January 2011 and June 2012. Expert emergency physicians (local investigators) retrieved the electronic ED records with primary or secondary diagnosis of AHF in all centers. The diagnosis was based on the definition of the working group of the European Society of Cardiology (International Classification of Diseases, Ninth Revision, Clinical Modification codes: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0); data retrieval followed a standardized training and validation program organized by the coordinating center (11). During the study period the principal investigator actively monitored abstractors on chart reviews. Quality control was performed by an independent physician for all cases to ensure the accuracy and validity of the data entered in the case report form, by random checking of the original records in approximately 30% of cases.

The case report form included demographic characteristics (age, gender, race), medical history, and clinical presentation (comorbidities, precipitating factors, and time between first occurrence of symptoms and ED arrival and registration). The main precipitating causes of the AHF episode were grouped into the following categories: noncompliance with therapy, uncontrolled hypertension, sudden dysrhythmia, worsening renal failure, ischemic heart disease, fever, acute respiratory disease, pneumonia, anemia, other causes, and undefined causes.

Cardiovascular comorbidities included dysrhythmias (atrial fibrillation, atrial flutter), valvular heart disease, any diagnosis of coronary artery disease, and the presence of a pacemaker or implantable cardiac defibrillator. In particular, the abstractors checked patients' history of previous AHF episodes. Noncardiac comorbidities included chronic kidney disease (CKD; any type), chronic obstructive pulmonary disease, diabetes mellitus, cerebrovascular disease, cognitive deficit, and poor nutritional status.

The chronic use of drugs for the cardiovascular system prior to ED admission was also registered and grouped as angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs), furosemide, mineral-corticoid receptor antagonists, anticoagulants, or antiplatelet drugs. All medications that were administered in the ED were also recorded (oxygen, noninvasive ventilation, furosemide, nitroglycerine and opiates).

The following biochemical data were registered: plasma sodium concentration (high-risk cut-off value: < 135 mEq/L); N-terminal pro brain natriuretic peptide (NT-proBNP) concentration (high-risk cut-off: > 5000 ng/L), troponin T or I concentration soon after ED arrival – predefined cut-off values: ≥ 10 μg/L for troponin T and ≥ 0.5 ng/L for troponin I, and systolic blood pressure (high risk cut-off: < 110 mm/Hg) (1,12–15). The mean glomerular filtration rate at baseline was estimated by Chronic Kidney Disease Epidemiology Collaboration equation (16).

The left ventricular ejection fraction was measured by transthoracic echocardiography either during prolonged ED stay or during hospital admission, and was always interpreted by a cardiologist.

Disposition was categorized as: 1) rapid referral to general practitioners (GPs) for continuous care, after 3–6 h of ED treatment; 2) short-term (12–24 h) intensive observation prior to discharge from ED to follow-up with their GPs; 3) admission to in-hospital ordinary wards; 4) admission to intensive coronary care unit.

Exclusion criteria were: 1) renal failure needing hemodialysis, due to different AHF pathophysiology and treatment (55 cases); 2) noncardiac pulmonary edema, including suspected sepsis (23 cases); 3) "do

not resuscitate" status, that is, death expected within weeks from chronic, noncardiac diseases (78 cases).

The ethical committee of the coordinating center of Forlì CEAV-AVR Romagna approved the study (1112/2014/O/OssN, February 19, 2014).

Data Analysis

The study population was described as number of cases and percentages (categorical variables) with 95% confidence intervals, or as means and standard deviation, or as median and interquartile range (IQR) (continuous variables). We then stratified data based on the main comorbidities in relation to new-onset vs. recurrent AHF. Differences between groups were analyzed by χ^2 test as crude odds ratios and corresponding 95% confidence intervals (CI). The contribution of different comorbidities to recurrent vs. new-onset AHF was tested by predefined univariate analysis.

Analyses were performed using SPSS software, version 17 (SPSS Inc., Chicago, IL).

RESULTS

Clinical Characteristics

During the enrollment period, 2683 AHF events were included in the database; 1485 patients were classified as first-episode AHF (55.3%; 95% CI 53.5–57.3%). Demographics, precipitating factors, and comorbidities are reported in Table 1. The median age was 84 years (IQR 12; range 21–98), with 1691 subjects (63.0%, 95% CI 61.3–64.8%) aged ≥ 80 years and females accounting for 55.8% of cases (95% CI 53.9–57.6%). Acute respiratory disease, uncontrolled hypertension, ischemic cardiopathy, and new-onset dysrhythmia were registered as the main precipitating factors (over 60% of cases) (Table 1).

Among the other comorbidities, a history of acute coronary syndrome or coronary heart disease, diabetes, chronic obstructive pulmonary disease, CKD, and valvular heart disease were the conditions most commonly reported. In 1536 events, the subjects (57.4%; 95% CI 55.4–59.1%) had three or more comorbidities, and in 548 (20.4%; 95% CI 18.8–21.8%) subjects had five or more comorbidities (Table 1).

The time from symptom onset to ED presentation (recorded in 75% of cases) was < 12 h in 700 cases (26.1%; 95% CI 24.5–27.8%) and 12–24 h in 1113 (41.5%; 95% CI 39.7–43.4%); no relationship was observed between time from the occurrence of symptoms and age, sex, or comorbidity.

Acute respiratory disease and pneumonia were recorded as the most frequent precipitant factor, registered in over 30% of cases (Table 1). A high number of comorbidities was more common in subjects with recurrent episodes than in subjects attending EDs for a first episode of AHF (Table 2).

Table 1. Demographic and Clinical Characteristics of Patients Visited in the Emergency Department for Acute Heart Failure (N = 2683)

	Number of Cases (%; 95% CI)
Demographics	
Female	1497 (55.8%; 53.5–57.6)
Age, years*	84.0 [12.0]
Time from symptom onset, hours*	34 [26]
Precipitating factors	
Acute respiratory diseases	759 (28.3%; 26.6–30.0)
New-onset dysrhythmias	370 (13.8%; 12.5–15.1)
Fever	205 (7.6%; 6.7–8.7)
Non-adherence to therapy	201 (7.5%; 6.4–8.4)
Worsening renal failure	129 (4.8%; 4.0–5.6)
Ischemic cardiopathy	126 (4.7%; 3.9–5.6)
Anemia	90 (3.4%; 2.7–4.0)
Pneumonia	72 (2.7%; 2.1–3.3)
Other specific causes	32 (1.2%; 0.8–1.6)
Undefined	358 (13.3%; 12.1–14.6)
Comorbidities	
Chronic dysrhythmias	1265 (47.1%; 45.2–49.0)
History of acute heart failure	1198 (44.7%; 42.7–46.4)
Diabetes mellitus	834 (31.1%; 29.3–32.8)
Heart valvular diseases	820 (30.6%; 28.7–32.4)
COPD	799 (29.8%; 28.1–31.4)
Chronic kidney disease	715 (26.6%; 24.8–28.4)
Impaired cognitive status	702 (26.2%; 24.4–27.9)
History of coronary artery disease	639 (23.8%; 22.1–25.6)
Cerebral-vascular disease	598 (22.3%; 20.7–23.8)
Intracardiac devices (PM/ICD)	243 (9.1%; 7.9–10.2)
Nutritional deficit	201 (7.5%; 6.5–8.5)
Number of comorbidities	
n = 0	192 (7.2%; 6.1–8.1)
n = 1	405 (15.1%; 13.9–16.5)
n = 2	547 (20.1%; 18.9–21.9)
n = 3	527 (19.7%; 18.2–21.2)
n = 4	464 (17.1%; 15.9–18.8)
n ≥ 5	548 (20.4%; 18.8–21.8)

COPD = chronic obstructive pulmonary disease; PM = pacemaker; ICD = implantable cardioverted defibrillator.
* Variables described as median [interquartile range].

Clinical, Laboratory Data, and Pharmacological Interventions

At first evaluation, the median systolic blood pressure was 138 (40) mm Hg, with 18.7% of cases (95% CI 17.3–20.2%) with values < 110 mm Hg. The estimated mean glomerular filtration rate – Chronic Kidney Disease Epidemiology Collaboration equation method – was 49.7 (22.4) mL/min/1.73 m^2 (16). Severe renal dysfunction (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) was present in 624 subjects (24.3%; 95% CI 22.6–26.0%), mainly in cases with a history of recurrent AHF. When measured at first evaluation in the ED,

Table 2. Contribution of Different Comorbidities to Recurrent vs. New-Onset Acute Heart Failure in Patients Attending the ED (N = 2683)

	Recurrent AHF* 1198 (44.7%)	New-Onset AHF* 1485 (55.3%)	Odds Ratio (95% CI)	*p*-Value
Comorbidities				
Heart valvular diseases	478 (58.3)	342 (41.7)	2.2 (1.9–2.6)	< 0.001
Chronic dysrhythmias	651 (51.5)	614 (48.5)	1.7 (1.4–2.0)	< 0.001
History of coronary artery disease	328 (51.3)	311 (48.7)	1.4 (1.2–1.7)	< 0.001
Intracardiac devices (PM or ICD)	130 (53.5)	113 (46.5)	1.5 (1.1–1.9)	0.002
Chronic obstructive pulmonary disease	440 (55.1)	359 (44.9)	1.8 (1.5–2.1)	< 0.001
Chronic kidney disease	447 (62.5)	268 (37.5)	2.7 (2.3–3.2)	< 0.001
Diabetes mellitus	443 (53.1)	391 (46.9)	1.6 (1.4–1.9)	< 0.001
Cerebral-vascular disease	293 (49.0)	305 (51.0)	0.9 (0.8–1.0)	0.015
Impaired cognitive status	367 (52.3)	335 (47.7)	1.5 (1.3–1.8)	< 0.001
Nutritional deficit	113 (56.2)	88 (43.8)	1.6 (1.2–2.2)	< 0.001

ED = emergency department; AHF = acute heart failure; PM = pacemaker; ICD = implantable cardioverted defibrillator; CI = confidence interval.
* Data reported as number of cases and percentage; p for significance < 0.05.

troponin T or I values, registered in 2208 cases (82.3%), were above the cut-off levels in 1573 cases (71.2%; 95% CI 69.3–73.1%). The median values of NT-proBNP or BNP were elevated, and were > 5000 pg/mL in 784 cases (36.4%; 95% CI 34.5–38.1%). Left ventricular ejection fraction was measured in the ED in 1839 subjects (68.6% of enrolled), and was < 40% in 658 cases (35.8%; 95% CI 33.7–38.1%).

Prior to ED arrival, over 50% of subjects were being treated at home (chronic therapy) with furosemide (63.6%; 95% CI 61.8–65.2%), and with ACE-Is or ARBs (51.8%; 95% CI 49.8–55.4%) (Table 3). Higher rates of chronic treatment were recorded in cases occurring in older patients (>75 years) than in younger subjects. In particular, treatment with furosemide (65% vs. 57%; $p < 0.001$) and antithrombotic agents (47.5% vs. 37.2%; $p < 0.001$) was significantly more prevalent in older patients. Conversely, the rate of treatment with β-blockers was lower in older subjects (42.5% vs. 47.3%; $p = 0.046$). After arrival in the ED, a pharmacological intervention was immediately instituted in 2355/2683 cases (87.8%). In 655 subjects (24.4%), three or more treatments were administered, with oxygen, furosemide, and i.v. nitroglycerine being the more represented treatments. Noninvasive ventilation with oxygen was needed in only 408 cases (15.2%; 95% CI 13.8–16.6) (Table 3).

Disposition

Disposition was recorded in 2683 cases (100% of cases). Of these, 67 subjects (2.5%; 95% CI 1.9–3.1%) died within 6 h from cardiogenic shock. After visit and treatment in the ED, 451 subjects (16.8%; 95% CI 15.4–18.2%) were admitted to the coronary care unit, and 1621 patients (60.4%; 95% CI 58.6–62.3%) to different medical wards, according to specific conditions or local hospital configuration. Only 171 patients (6.4%; 95% CI 5.5–7.4%) were discharged from the ED within a few hours after ED arrival, whereas 373 patients (13.9%; 95% CI 12.6–15.3%) were discharged from the ED to follow-up with their GPs after a short-term (12–24 h) observation.

DISCUSSION

The study shows that subjects admitted to Italian EDs with a final diagnosis of AHF are different from subjects included in most international registries (1). Our patients were older, the proportion of females was higher, patients arrived in EDs later than commonly reported, and the majority of subjects had a high number of cardiac and noncardiac comorbidities.

Table 3. Pharmacology Intervention Prior to and Following the Admission to the ED for Acute Heart Failure (N = 2683)

	Number of Cases (%; 95% CI)
Drug prescriptions prior to ED admission	
Furosemide	1705 (63.6%; 61.8–65.2)
ACE Inhibitors/ARBs	1389 (51.8%; 49.8–55.4)
Antithrombotic agents	1188 (44.2%; 43.6–47.3)
β-blockers	1166 (43.5%; 41.5–45.2)
Oral anticoagulants	737 (27.5%; 25.7–29.0)
MRA	451 (16.8%; 15.4–18.1)
Pharmacological intervention in ED	
Oxygen therapy	1870 (69.7%; 67.9–71.5)
Furosemide	1857 (69.2%; 67.4–71.0)
Nitroglycerin	528 (19.7%; 18.3–21.4)
Non-invasive ventilation	408 (15.2%; 13.8–16.6)
Opiates	227 (8.5%; 7.5–9.5)

ED = emergency department; CI = confidence interval; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; MRA = mineral-corticoid receptor antagonists.

Age (median, 84 years) was the most striking difference. In most large international registries, the mean age of patients ranges from 69 to 79 years (1,10,17–20). Regional variations in age are likely to be explained by the different prevalence of the underlying risk factors as well as by the mean age of the population. In particular, patients included in North American registries tend to be older than patients enrolled in countries with developing economies, with a different standard of living, as calculated by the human development index (a composite measure including life expectancy, adult literacy, educational level, and standard of living) (1,21). Both age and the standard of living contribute to the prevalence of the main risk factors associated with outcome (21). Our population comprised a large number of elderly subjects, possibly at higher risk of unfavorable outcomes due to comorbidities, with women over 75 years of age being more represented than men (84.8% vs. 73.3%; $p < 0.001$).

Over 55% of patients in our series were women, a proportion similar to that observed in the U.S. and European observational surveys, but different from most clinical trials carried out in hospitalized subjects, which included only 40–50% of females (5,8,22,23). This is a noteworthy observation, as female patients tend to be older at the time of initial diagnosis and are more likely to have AHF with preserved ejection fraction (24).

The time interval between the onset of symptoms and the arrival in the ED is another important aspect. Large international trials included subjects hospitalized after a median time of 6.6 h (IQR 9.4) from symptom onset and 2.5 h from arrival in the ED (25,26). In our study we included all consecutive subjects, and the median time from the onset of symptoms to ED admission (reported in 90% of cases) was 34 h, with a large variability (IQR, 84 h). However, the time from symptom onset did not differ in relation to final disposition after ED diagnostic work-up.

Inclusion rate is another important source of difference, because large-scale retrospective registries only included hospitalized patients, not all cases seen in the ED (5,8,18). This selection bias produces a different clinical profile of enrolled subjects and different event rates, which also depend on different health care configurations (27). In a recent study on a large sample of patients enrolled in 26 Spanish EDs, admission rate was again driven by age, and had a significant impact on outcome following hospitalization (19). This further underlines the importance of age on the management of patients with AHF, which must be carefully considered by health care planners.

Cardiac and noncardiac comorbidities are both highly prevalent among hospitalized patients in most large studies, and dictate the management of acute AHF patients across Europe, according to the guidelines on the diagnosis and treatment of AHF published by the European Society of Cardiology (1,8,11). In our series, a history of coronary artery disease was recorded in more than 50% of patients, and acute myocardial infarction was reported in 20–30% of cases, frequently resulting in systolic dysfunction. Similarly, noncardiac comorbidities including diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disease are reported in approximately 30% of patients (1). Our database is in keeping with the main large clinical registries: both cardiac and noncardiac comorbidities were extremely prevalent, but noncardiac diseases were of particular importance, with over 20% of subjects having two or more comorbidities (Table 1). Comorbidities were more represented in subjects with recurrent AHF than in subjects with new-onset AHF, supporting a specific role of the number and severity of comorbidities in the recurrence of AHF (Table 2).

However, a history of AHF was recorded in only 55% of subjects, a lower percentage in comparison with most published studies, where prevalence rates of recurrent AHF were reported in 57–75% of cases (6,8,20,28). An unselected older population and different hospital configuration services may explain the lower percentage of cases with history of AHF.

The analysis of chronic therapy prior to the AHF episode in our cohort deserves a few comments, because treatment adherence may be a relevant problem. In a recent study, over 75% of cases were treated with furosemide, 54% with β-blockers, 39% with ACE-Is, and 13% with mineral-corticoid receptor antagonists (18). In other studies, only 50.7% of subjects studied were treated with furosemide, 50.7% with ACE-Is or ARB, and 44.7% with β-blockers (3). Compared with most series, the chronic treatment of our patients was characterized by a much lower use of ACE-Is and ARBs.

Also, the immediate treatment after ED admission deserves comments. In a recent study in 29 Spanish EDs, the most frequently used therapy was based on bolus loop diuretics (85.1%), conventional oxygen therapy (78.5%), and i.v. nitroglycerine (20.7%), with noninvasive ventilation in only 6.6% of cases (19,20). In our series we recorded similar treatment rates with oxygen therapy, furosemide, and i.v. nitroglycerine (70.2%), but a much higher use of noninvasive ventilation (15.6% vs. 6.6%); these differences can only be explained by a different case mix.

In most clinical registries, admission to the hospital is explained by worsening of chronic heart failure, with one or more acute precipitating factors, and about 50% of patients being hypertensive at presentation. Only 2% of patients are recorded with an initial systolic blood pressure < 90 mm Hg, suggestive of cardiogenic shock and systemic hypoperfusion, and 15% with acute pneumonia

(22). In our series, uncontrolled hypertension was reported in only 12.7% of cases, whereas acute pneumonia was registered as the main precipitating factor in only 2.7% of cases. Only the number of cases admitted with an initial systolic blood pressure < 90 mm Hg was in keeping with the literature (55 cases, 2.1%).

Limitations

Firstly, an interrater reliability within abstractors was not calculated during the retrieval process and chart review. In our series, the diagnoses were made by the emergency physicians according to their clinical judgment and were not validated centrally. However, the selection criteria, based on the diagnosis after medical evaluation in EDs, were discussed during an investigator meeting, and all centers were invited to follow current guidelines. Secondly, the representativeness of the sample is often recognized as a limitation in retrospective studies. To make up for this issue, the participating centers were selected in proportion to the size of the reference population, taking into account the different technological levels of the selected units. Thirdly, the patients were enrolled after arrival in EDs, and the database also included cases visited for mild symptoms and then referred to their GPs within a few hours. Accordingly, the present population differs from the population of the large international registries that enrolled patients hospitalized in cardiology settings.

CONCLUSIONS

Our study shows that the subjects admitted to a group of Italian EDs with a diagnosis of AHF have peculiar characteristics when compared with subjects included in most international registries. The attendance of these elderly and frail patients produces a considerable impact on National Health Systems. Although this study is limited to Italian patients, the results demonstrate that the demographic picture of this disease may have changed in recent years. Repeating the study in other countries can help researchers gain more detailed and updated information. This will also offer health care authorities solid evidence to plan resource use to reduce the burden of disease on this old and frail population.

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ARTICLE SUMMARY

1. Why is this topic important?

Acute heart failure (AHF) is a global public health issue characterized by high hospital admission rate, high re-hospitalization, and mortality, with a massive economic burden for the national health systems.

2. What does this study attempt to show?

The study aims to show work-up of AHF patients prior to admission, their clinical patterns, the biological characteristics, and the treatment of subjects attending the emergency departments of a few Italian general hospitals.

3. What are the key findings?

The patients considered in the analysis are rather different from those included in most international registries: they are older, the proportion of females is higher, they arrived in emergency departments later than commonly reported, and the majority of cases had several cardiac and noncardiac comorbidities.

4. How is patient care impacted?

The attendance of elderly and frail patients in the emergency department produces a considerable impact on National Health Systems. Our data mark the importance of AHF management to reduce the burden of disease on resource use by this old and frail population.