ORIGINAL ARTICLE

Prognostic Value of Clinical Presentation in Acute Heart Failure Syndromes

Valor pronóstico de la presentación clínica en los síndromes de insuficiencia cardíaca aguda

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ABSTRACT

Background: Heart failure is a highly prevalent disease with elevated morbidity and mortality. It is a very heterogeneous condition and there is no consensus in its classification.
Objective: The aim of this study was to compare the incidence of in-hospital and annual mortality as well as rehospitalizations due to heart failure, during the first follow-up year, according to the clinical presentation.
Methods: A retrospective descriptive and survival analysis was carried out in a cohort of 758 consecutive patients from the health plan of our hospital who were admitted to the cardiology intensive care unit for acute heart failure, evaluating the association between clinical presentation and annual mortality.
Results: Treatment and use of resources were different in the diverse presentations. Overall in-hospital mortality was 6.3%; 5.4% corresponded to acute pulmonary edema, 4.9% to volume overload and 40.7% to cardiogenic shock (p <0.001). The incidence of mortality per 100 patient-years was 40 (95% CI: 31-51), 45 (95% CI: 39-52) and 100 (95% CI: 60-100), respectively, with an incidence of 34.3% overall annual mortality. In the multivariate analysis, the annual mortality associated with cardiogenic shock had a HR of 3.39 (95% CI: 1.79-6.44) compared with that associated with acute pulmonary edema. There were no statistically significant differences in the rate of readmissions.
Conclusions: In patients with acute heart failure, clinical presentation was associated with mortality at one-year follow-up. Patients with cardiogenic shock on admission had a worse prognosis compared with the rest of the groups.

Key words: Heart Failure – Shock, Cardiogenic - Hospital Mortality

RESUMEN

Introducción: La insuficiencia cardíaca es una patología con una elevada prevalencia y morbimortalidad. Es un cuadro muy heterogéneo y no existe unanimidad en su clasificación.
Objetivo: Comparar la incidencia de mortalidad hospitalaria y anual así como de reinternaciones durante el primer año de seguimiento, según la forma de presentación clínica.
Materiales y métodos: Se evaluó una cohorte retrospectiva de 758 pacientes consecutivos del plan de salud de nuestro hospital que estuvieron internados en la unidad de cuidados intensivos cardiológicos por insuficiencia cardíaca aguda. Se realizó un análisis descriptivo y de sobrevida, y se evaluó la asociación entre la forma de presentación clínica y la mortalidad anual.
Resultados: La terapéutica y el uso de recursos fueron diferentes en las distintas presentaciones. La mortalidad hospitalaria global fue del 6,3%; el 5,4% correspondió al edema agudo de pulmón, el 4,9% a la sobrecarga de volumen y el 40,7% al shock cardiogénico (p<0,001). La tasa de incidencia de mortalidad cada 100 pacientes-año seguidos fue de 40 (IC95%: 31-51), 45 (IC95%: 39-52) y 100 (IC95%: 60-100), respectivamente, con una incidencia de mortalidad anual global del 34,3%. En el análisis multivariado, la mortalidad anual asociada al shock cardiogénico tuvo un HR de 3,39 (IC95%: 1,79-6,44) con respecto a aquella vinculada al edema agudo de pulmón. No hubo diferencias estadísticamente significativas en la tasa de reinternaciones.
Conclusiones: En pacientes con insuficiencia cardíaca aguda, la presentación clínica se asoció con la mortalidad al año de seguimiento. Los pacientes con shock cardiogénico al ingreso tuvieron peor pronóstico en comparación con el resto de los grupos.

Palabras claves: Insuficiencia cardíaca- Choque cardiogénico - Mortalidad hospitalaria

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INTRODUCTION

Acute heart failure is a growing problem with an impact on health, the health system and the economy of the population. (1-4) Despite the unanimous acceptance of the problem, there is still no agreement on its definition. The difficulty lies in the fact that this entity includes a broad spectrum of different clinical conditions, such as decompensated chronic heart failure or de novo failure, which presents with preserved or depressed systolic function, signs of hypoperfusion or congestion, and other forms of the disease. (5-8)

Following previous studies, we consider it appropriate to refer to acute heart failure as acute heart failure syndromes of (AHFS), because there can be different types of presentation, with different prognoses and treatment requirements. (9)

A comprehensive definition of AHFS would be the change of the heart failure signs and symptoms that require urgent therapy.

Regarding the forms of presentation, there are also several classifications. Some authors classify it into three types: a) de novo heart failure, b) due to progression of a chronic heart failure pattern, and c) advanced heart failure. (10) The European Society of Cardiology initially considered six groups according to clinical and hemodynamic characteristics. (9) In the 2016 guidelines, the use of the classic classification of Stevenson is postulated, which considers four groups based on the presence of hypoperfusion and congestion: "wet and cold", "wet and warm", "dry and cold" and "dry and warm". (6, 11)

These classifications do not allow guiding the treatment in all patients and are not unanimously accepted. Therefore, we decided to classify AHFS according to their clinical presentation in the following categories: 1. Acute pulmonary edema (APE), 2. Volume overload (VO) and 3. Cardiogenic shock (CS). Each of these presentations have different initial therapeutic requirements. (12) The aim of this study was to know whether the clinical presentation of AHFS has a prognostic value in in-hospital mortality, annual mortality and rehospitalizations.

METHODS

This was an observational, retrospective cohort study consecutively including patients with a primary diagnosis of AHFS admitted to the cardiology intensive care unit of a university hospital. Follow-up was carried out through review of the electronic medical records of each patient and the administrative databases. It consisted of patients with health insurance coverage who were hospitalized between January 1, 2013 and December 31, 2016. It included patients older than 18 years who were hospitalized for any AHFS. Patients presenting with acute coronary syndromes, symptomatic valve diseases without surgical contraindication, heart transplantation, Takotsubo syndrome and acute myocarditis were excluded from the study. The exclusion was based on the underlying condition and the different therapeutic management of these entities. Primary endpoints were the incidence of mortality during index hospitalization and during the first follow-up year according to the clinical presentation of AHFS. The secondary endpoint was the incidence of readmissions during the first follow-up year according to the clinical presentation of AHFS.

Operational definition of variables

Types of clinical presentation of AHFS. They were defined according to the following criteria:

- Acute pulmonary edema: Sudden dyspnea, saturation on admission below 92% and congestive chest x-ray in the 4 quadrants. This form of clinical presentation exhibits a clear respiratory involvement.
- Volume overload: Signs and symptoms compatible with splanchnic congestion and little respiratory repercussion: lower limb edema, hepatomegaly, jugular engorgement, etc.
- Cardiogenic shock: Hypotension on admission (blood pressure below 90 mmHg and/or average blood pressure below 60 mmHg), requirement of inotropic drugs, presence of signs and symptoms of peripheral hypoperfusion (lividities, oliguria, sensory deterioration) and/or pulmonary capillary pressure above 18 mmHg.

The data was collected by a cardiologist appointed for this purpose, through review of the electronic medical record, which included clinical data, and hemodynamic and complementary studies.

Mortality: It was defined as all-cause death within 365 days following hospital admission for AHFS. The information was obtained through clinical records and the administrative health insurance databases.

Readmission: the first re-admission for AHFS was defined as the unplanned hospitalization that required a hospital stay >24 h and was caused by a substantial worsening of the signs and/or symptoms of heart failure, with need for new administration of intravenous pharmacological treatments.

Statistical considerations

Because a new AHFS classification was applied and since bibliographic data was not available on the differences in mortality rates at one year between the various clinical types, all cases admitted to the center were consecutively included during the study period. Continuous variables were expressed as mean and standard deviation or median and interquartile range, according to their distribution. Categorical variables were expressed as absolute and relative frequency. Demographic, clinical and treatment characteristics of the patients in the different clinical presentation groups were compared using the chi-square test in the case of categorical variables, or ANOVA or the Kruskal-Wallis test in the case of numerical variables, according to their distribution.

The annual incidence of mortality density in each AHFS clinical presentation was estimated and represented by Kaplan-Meier curves.

The association between the clinical presentation type and annual mortality was evaluated applying a Cox proportional hazards model, which was adjusted for covariates of clinical interest.

A two-tailed $p<0.05$ was considered statistically significant. In cases where multiple comparisons are mentioned, the Bonferroni correction was applied. STATA 13.1 (Stata Corp, Texas, USA) software package was used for the analysis.

Ethical considerations

The study was performed according to current regulations for human research. The study protocol was approved by an institutional review committee.

RESULTS

The study included 758 consecutive patients who were admitted to the cardiac intensive care unit diagnosed with AHFS. The clinical types of presentation were distributed as follows: APE, 26.7%, VO, 69.6% and CS, 3.5%. Median age was 85 years (IQR 80-89 years), mean age was 83±8 years and 40.8% of the population were men. According to the protocol, each patient was followed-up for a 12-month period. A total of 2.2% of cases was lost to follow-up. The population characteristics are presented in Table 1.

Overall in-hospital mortality was 6.3%; 5.4% was associated to the group with APE; 4.9% to the group with VO and 40.7% to the group presenting CS ($p<0.001$). The cumulative incidence of annual global mortality was 34.3%. According to the AHFS clinical presentation, the mortality rate per 100 patient years followed-up was 40 (95% CI: 31-51) for APE, 45 (95% CI: 39-52) for VO and 100 (95% CI 60-100) for CS (See Figure 1).

The multivariate analysis showed that annual mortality, after adjusting for covariates of clinical interest (sex, age, history of chronic kidney failure, ejection fraction category, readmission for AHFS and number of cardiological consultations at follow-up), had a HR of 3.39 (95% CI: 1.79-6.44) for CS (See Table 2). Readmission at follow-up had an annual incidence of 29.2% and an incidence rate of 46 per 100 patient years (95% CI: 41-53), without statistically significant differences between the different types of AHFS clinical presentation. .

In the time-to-event multivariate model in which readmission was considered as an event of interest and death as a competitive event, after adjusting for covariates of clinical interest (sex, age, history of chronic kidney failure, ejection fraction category and cardiological consultations during follow-up), no statistically significant differences were observed between the clinical presentation and the probability of rehospitalization due to heart failure.

DISCUSSION

In the last 30 years, a great progress has been made in the understanding of the physiopathological mechanisms of chronic heart failure. This has allowed the incorporation of new treatments that have improved survival, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers and, lately, neprilysin receptor antagonists, all drugs that act on the neurohumoral axis. (13)

On the other hand, there is less knowledge of AHFS, both of their pathophysiology and their management and prognosis. We have witnessed the failure of many drugs, probably due to the pleomorphic nature of this entity and the difficulty of performing an adequate classification of patients included in research studies. (14-16)

The population of this study presents differences with respect to other registries. These are consecutive patients admitted to a cardiac intensive care unit, while in other registers they could be hospitalized in other areas. This inclusion criterion was adopted because it has been demonstrated that patients admitted to the cardiac intensive care unit have higher mortality than those admitted to other areas. (17)

In all cases, heart failure was the primary diagnosis for hospitalization, unlike other records that included patients with other primary causes of admission and

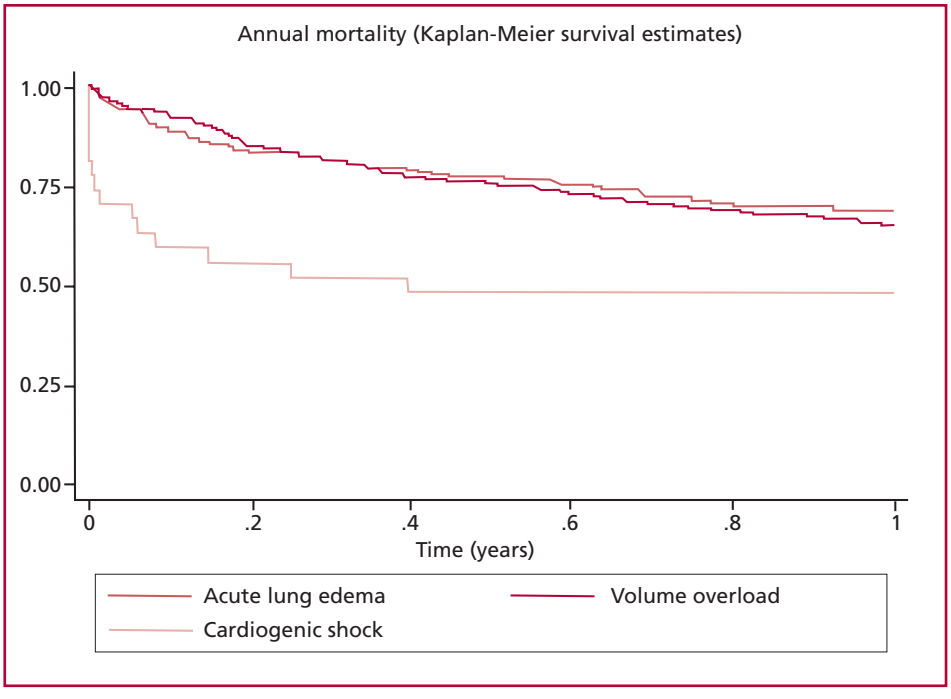

Fig. 1. Annual mortality according to the type of clinical presentation

Table 1. Characteristics of the population hospitalized for acute heart failure syndromes (AHFS)

	Total n (%)	Acute pulmonary edema n (%)	Volume overload n (%)	Cariogenic shock n (%)	p
	758 (100%)	203 (26.5%)	528 (70%)	27 (3,5%)	
Age (years), median (IQR 25-75)	85 (80-89)	86 (81-90)	85 (80-89)	81 (74-85)	0.009*
Male gender	309 (40.8%)	62 (30.5%)	232 (43.9%)	15 (55.6%)	0.001**
Hypertension	670 (88.4%)	185 (91.1%)	465 (88.1 %)	20 (74.1%)	0.031**
Dyslipidemia	390 (51.5%)	100 (49.3%)	273 (51.7%)	17 (63%)	0.40**
Diabetes	151 (19.9%)	38 (18.7%)	106 (20.1%)	7 (25.9%)	0.67**
Smoking	158 (20.8%)	27 (13.3%)	123 (23.3%)	8 (29.6%)	0.006**
Prior heart failure	261 (34.4%)	64 (31.5%)	187 (35.4%)	10 (37%)	0.59**
Chronic kidney failure	164 (21.6%)	31 (15.3%)	124 (23.5%)	9 (33.3%)	0.017**
Prior stroke	79 (10.4%)	9 (4.4%)	68 (12.9%)	2 (7.4%)	0.003**
Peripheral vascular disease	60 (7.9%)	17 (8.4%)	39 (7.4%)	4 (14.8%)	0.36**
History of coronary heart disease1	144 (18.9%)	43 (21.1%)	93 (17.6%)	8 (29.6%)	0.19**
History of coronary revascularization2	104 (13.7%)	27 (13.2%)	73 (13.8%)	4 (14.8%)	0.97**
Clinical presentation					
Systolic blood pressure (mmHg), median (IQR 25-75)	136 (120-160)	170 (150-190)	130 (117-140)	96 (90-120)	<0.001*
Oxygen saturation (%), median (IQR 25-75)	92 (88-96)	88 (85-90)	94 (90-96)	87 (83-94)	<0.001*
Atrial fibrillation	287 (37.9%)	59 (29.1%)	219 (41.5%)	9 (33.3%)	0.007**
Complementary studies					
EF >49%	429 (58.5%)	112 (57.4%)	309 (60.1%)	8 (33.3%)	0.048**
EF 40-49%	124 (16.9%)	40 (20.5%)	78 (15.2%)	6 (25%)	
EF <40%	180 (24.6%)	43 (22.1%)	127 (24.7%)	10 (41.7%)	
Moderate-severe pulmonary hypertension	129 (17%)	22 (10.8%)	105 (19.9%)	2 (7.4%)	0.006**
Pro BNP (pg/ml), median (IQR 25-75)	4,787 (2,377-9,053)	4,589 (2,467-7,883)	4,757.5 (2,365.5-9,885.5)	8,994 (5,370.5-14,455)	0.030***
High-sensitivity cardiac troponin T (ng/l), median (IQR 25-75)	41.8 (24.1-75.1)	39.25 (25.7-60.85)	41.05 (22.5-80.6)	106.65 (51.6-676.7)	0.0016***
Treatment					
Non-invasive ventilation	220 (32.3%)	132 (66.3%)	83 (18%)	5 (22.7%)	<0.001**
Mechanical respiratory assistance	50 (7.6%)	23 (12.4%)	11 (2.5%)	16 (66.7%)	<0.001**
Counterpulsation balloon	5 (0.8%)	1 (0.5%)	1 (0.2%)	3 (12.5%)	<0.001**
Ultrafiltration	14 (2.1%)	4 (2.2%)	7 (1.6%)	3 (13%)	<0.001**
Dobutamine	35 (4.6%)	9 (4.4%)	21 (4%)	5 (18.5%)	0.002**
Dopamine	30 (4%)	7 (3.4%)	10 (1.9%)	13 (48.1%)	<0.001**
Nitroglycerin	227 (29.9%)	129 (63.5%)	94 (17.8%)	4 (14.8%)	<0.001**

IQR: Interquartile range; EF: Ejection fraction
1Includes history of acute myocardial infarction, unstable angina or stable chronic angina.
2Includes endovascular or surgical coronary artery revascularization.
Statistical test used:
* Kruskal – Wallis
** Pearson's chi-square test
*** ANOVA
The Bonferroni correction was applied for multiple comparisons.

Table 2. Multivariate analysis of annual mortality according to the acute heart failure syndrome type of clinical presentation

	Hazard ratio	p	CI (95%)
Clinical presentation*			
Volume overload	1.17	0.287	0.87 -1.58
Cardiogenic shock	3.39	>0.001	1.78 -6.44
Ejection fraction			
40 - 49%	0.78	0.202	0.54 -1.13
<40 %	1.21	0.222	0.88 – 1.65
Male gender	1.22	0.155	0.92 -1.61
Age	1	0.449	0.98 -1.02
Chronic kidney failure	1.19	0.229	0.89 – 1.60
Ambulatory consultations	0.74	>0.001	0.69 – 0.78
Rehospitalizations	1.5	0.002	1.15 – 1.95

*Taking as reference the subgroup with acute lung edema

intercurrent development of heart failure

Compared with other AHFS registries, such as the ADHERE (18), OPTIMIZE-HF (19), EHFS I (20), EHFS II (21), EFICA (22) and Italian AHF (23) studies and five registries from Argentina (24) , our population was older, with an average age >10 years with respect to other reports and with 50% of patients over 85 years of age. Prevalence of females (59.2%) and history of hypertension (88%) were also higher. Patient age resembles that recorded in a large Italian population database, but in our study, female sex, renal failure and history of heart failure were more frequent. (25) These differences are even greater when compared with randomized AHFS studies, such as the VMAC (26) and OPTIME (27) studies.

History of myocardial infarction, coronary revascularization and moderate/severe left ventricular ejection fraction deterioration was lower than in the aforementioned registries. This is probably due to the decision of having a "pure" population of heart failure, excluding acute ischemic syndromes, which have a specific treatment and a different evolution.

In-hospital mortality was 6% and the cumulative annual mortality incidence was 34%. It is difficult to establish comparisons with other registries due to different inclusion criteria and population characteristics. For example, in the ADHERE study, in-hospital mortality was 4%, but in patients in intensive care it was 11%. In the OPTIMIZE-HF study, which also included patients with secondary diagnosis of heart failure, in-hospital mortality was 3.85%, but if the triggering factor for heart failure was ischemic, the mortality rate was 4.2%, if it was a pulmonary infection, 5.8%, and in the case of renal dysfunction, 8%.

In the EHFS II study, with more than 3,500 patients, in-hospital mortality was 6.7%, but unlike our registry, part of the patients were hospitalized in non-intensive care areas. In contrast, in a national registry of the United Kingdom, in-hospital mortality was 10% and 30% at one year. (28)

The population with the highest mortality rate belongs to the French EFICA registry, with 27.4% 4-week mortality. This registry only included patients from intensive care areas with a prevalence of CS of 29%, which was much higher than that of all the other registries.

There is no agreement in the cardiology community regarding the classification of AHFS. For this reason, we chose to consider patients according to their clinical presentation, because that is what determines the initial treatment. As expected, the three groups presented diverse clinical characteristics and the treatments adopted were different.

Patients with APE compared with those in the CS group were older, with a higher prevalence of women and history of hypertension, and had higher blood pressure on admission. In them, the correction of arterial hypertension and hemoglobin O2 desaturation was privileged, and proof of this was the greater use of nitroglycerin and non-invasive ventilation.

Patients with VO compared with those in the APE group had greater prevalence of atrial fibrillation, pulmonary hypertension, and history of stroke.

The group with CS had greater prevalence of men and higher troponin levels than the other two groups, which may suggest the presence of underlying coronary heart disease, despite the exclusion of acute coronary syndromes. It was also the group with the highest pro-BNP values. As expected, inotropic drugs and aortic counterpulsation balloon were used more frequently in this group.

Regarding the prognosis according to the clinical presentation, patients with CS were clearly differentiated from the other groups; they presented high in-hospital mortality (40.7%), in agreement with data from other registries. Effectively, in-hospital mortality was 39.6% in the EHFS II study and 57.8% in the EFICA study at 4 weeks. In contrast, patients with APE or VO had a lower mortality rate, which was similar between these two groups.

At one year, patients with CS had more than two-fold risk of dying than those with the other two forms of clinical presentation, and after adjustment for age, sex, ejection fraction, chronic kidney failure, readmissions and number of ambulatory consultations during follow-up, the risk of death was more than three-

fold (adjusted HR: 3.39). Unlike what is observed in chronic HF, it is significant that in patients who were hospitalized for AHFS, the degree of EF deterioration had no independent prognostic value when the type of clinical presentation was considered.

The EFICA study authors postulate the classification of AHFS into three groups: CS, APE with hypertension and without CS, and a third group without hypertension and without CS. This classification is similar, though not identical to that of our group.

In our study we excluded acute ischemic syndromes, which were very prevalent in the French study mentioned above (42%). Patients with APE were more frequent in our study, 27% vs. 15% in the EFICA study, probably because we did not require them to be hypertensive at admission. Patients with APE had the lowest in-hospital mortality in both studies: 5.4% in ours, 7% in the EFICA study.

In our classification, patients with VO, which could resemble patients without CS and without APE of the EFICA study, were the most numerous (56% in the EFICA study and 69% in ours). However, in our study, mortality in the VO group was not different from that in the APE group (4.9%), unlike the EFICA study, where mortality in this group was more than twofold that of the APE group (17%). Probably, different populations are responsible for this difference.

In our analysis, the prevalence of CS was much lower than in the EFICA study (3.6% vs. 29%), but mortality was very high (40.7%).

The high mortality of patients with CS has been attributed to the presence of acute ischemic syndrome. In our registry, these patients were excluded; however, there was also high mortality, probably because it was a very old population group with many comorbidities. These results support the prognostic value of the clinical presentation.

As widely reported, readmissions represent a serious problem in this pathology. (25, 29, 30) They were also frequent in our study (with an incidence of 29.2% at 1 year), although in this aspect there was no difference between the three types of clinical presentation considered.

The population with heart failure without a reversible cause, as the one in our study, will be increasingly prevalent due to population aging, the greater survival of pathologies such as myocardial infarction and the better prognosis of heart failure due to the use of drugs and more efficient devices. Thus, we consider it is important to have prognostic information from the moment of hospitalization.

Limitations

Since it is a single-center registry of patients admitted to a cardiac intensive care unit, it is not advisable to extrapolate the results to other contexts; however, as it is a homogeneous population with slight loss to follow-up, the quality of the results is strengthened.

Another limitation is not having evaluated the adherence of patients to medication during outpatient follow-up.

CONCLUSION

The type of clinical presentation of AHFS guides the initial treatment and also determines the prognosis of mortality during the first year.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

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