Epidemiology, clinical and prognostic factors in Spanish patients with heart failure: The RICA-2 registry

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Abstract

Introduction: Heart failure (HF) is a syndrome of epidemic proportions and one of the main reasons for hospitalization worldwide. Different scientific societies have risen interest in the creation of their own registries to study the characteristics and prognosis of these patients. Each registry covers a part of the spectrum of this heterogeneous syndrome and is useful to address questions that are difficult to answer in clinical trials. The RICA-2 is a national registry created by the Heart Failure Working Group of the Spanish Society of Internal Medicine and offers an Internal Medicine perspective of this pathology. **Objectives:** The main objective is to assess clinical and epidemiological characteristics and prognostic factors among patients with HF. Secondary objectives include: (1) To determine clinical/epidemiological/phenotypic characteristics and prognosis specifically in patients with HF and preserved left-ventricle ejection fraction (LVEF); (2) To examine how functional status, cognition, frailty, and nutrition influence the prognosis of patients with HF; (3) To assess congestion and strategies to achieve decongestion during the acute decompensation phase. **Methods:** A multicentre, prospective, observational cohort study including patients with HF attended in Spanish Internal Medicine Departments. Patients will be recruited in the acute decompensation phase or in the stable phase in the outpatient setting, including *de novo* and chronically decompensated patients. Patients will be included regardless of HF aetiology, LVEF values and comorbidities. **Conclusions:** Our work is a prospective study that aims to improve knowledge regarding epidemiology and prognosis in patients with HF, with focus on functionality, cognition, frailty, nutrition, and congestion phase.

Key words: Heart failure. Congestive heart failure. Epidemiology. Frailty. Nutrition. Registries.

Visual abstract available at https://spanishjmed.com/frame_esp.php?id=56

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Date of reception: 12-11-2021

Date of acceptance: 01-12-2021

DOI: 10.24875/SJMED.21000024

Available online: 24-12-2021

Span J Med. 2021;1(4):177-182

www.spanishjmed.com

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Introduction

Heart failure (HF) is a clinical syndrome of epidemic proportions in developed countries and is a major health problem due to its incidence, prevalence, mortality, and consumption of resources^{1,2}. HF registries have become powerful tools that provide valuable epidemiological data and contribute decisively to the understanding of this syndrome³. The information collected in most of these registries include demographic data, patients' comorbidities, diagnosis and classification of the disease, mortality and hospitalization rates, prescribed medication, among others⁴. To the best of our knowledge, there are three large HF registries in Spain, one developed from the perspective of Cardiology (REDINSCOR registry)⁵, another one from the Emergency Medicine and Emergencies (EAHFE registry)⁶ and finally a registry from the perspective of Internal Medicine (RICA registry)⁷. A large number of publications from these registries have contributed to improve the understanding of HF mainly on its clinical, epidemiological, and prognostic aspects. They have also shown the different points of view of the three main specialties that care for these patients in hospital clinical practice (Cardiology, Internal Medicine, and Emergency Medicine) on a syndrome defined by its heterogeneous and complex nature^{8,9}.

Over the past 13 years, the RICA registry has included more than 7,000 patients and a lot of scientific work has been carried out based on its data that has been communicated through almost 50 scientific publications (in national and international indexed journals), or in more than 50 scientific national and international communications in medical meetings. On the other hand, HF has undergone notable changes in the last decade, in clinical and epidemiological aspects, diagnostic criteria, and therapeutic targets, which require updating the initial research questions and modifying the necessary variables to be able to answer these questions. For these reasons, the Research Committee of the RICA registry belonging to the Heart Failure and Atrial Fibrillation Working Group of the Spanish Society of Internal Medicine decided to update the RICA registry by creating a new one named RICA-2. The main objective of this registry is to continue investigating the clinical and epidemiological characteristics of HF but (unlike the RICA) it aims to provide more knowledge in some areas that are highly prevalent in Internal Medicine such as HF with preserved ejection fraction (HFpEF), the geriatric evaluation (including functionality, cognition, and frailty), the nutritional status and finally the

Table 1. Inclusion and exclusion criteria

Inclusion criteria
<ol style="list-style-type: none"> 1. Age equal to or greater than 18 years 2. Patients diagnosed with HF following the recommendations of the European HF Guidelines^{a,b,10} 3. Patients will be included in the decompensation phase (defined as the need to administer parenteral loop diuretic, either in hospitalization or in the HF Units) or in the stable phase in the outpatient setting 4. Both <i>de novo</i> and chronically decompensated patients will be included 5. Patients will be included regardless of the HF etiology, LVEF values, and comorbidities 6. Patients must sign an informed consent for inclusion in the study
Exclusion criteria
There are no specific exclusion criteria and only those patients who do not strictly comply with the inclusion criteria, those who do not give their informed consent to participate and / or those patients who cannot be followed up will be excluded.

^aDiagnostic criteria: 1) Symptoms ± Signs; 2) LVEF value (to be classified as HFrEF, HFmrEF or HFpEF) and in case of HFpEF; 3) Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides.

^bNatriuretic peptide cut offs: in the non-acute setting 35 pg/mL for BNP and 125 pg/mL for NT-proBNP. In the acute setting 100 pg/mL for BNP and NT-proBNP values depend on age: > 450 pg/mL if aged < 55 years, > 900 pg/mL if aged between 55 and 75 years and >1800 pg/mL if aged > 75 years.

HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF: left-ventricle ejection fraction.

assessment and treatment of congestion during the decompensation phase.

Methods

Design and study population

This is a nationwide, prospective, multicentre, observational cohort study. Patients will be recruited from the Internal Medicine Departments of Spanish hospitals whose researchers are members of the Heart Failure and Atrial Fibrillation Working Group of the Spanish Society of Internal Medicine.

Patient selection and inclusion/exclusion criteria

The inclusion of patients will be done prospectively and consecutively. Each center will be assigned a minimum number of patients to include each year tailored to the size of the hospital. Only those patients who strictly meet the diagnostic criteria for HF of the European Guidelines will be included¹⁰. The rest of the inclusion and exclusion criteria are detailed in Table 1.

Objectives

The main objective of the study is to know the clinical and epidemiological characteristics and the prognostic factors of patients with HF treated in the Spanish Internal Medicine Departments. Secondary objectives include: (1) To determine the clinical, epidemiological, phenotypic, and prognostic characteristics of patients with HFpEF; (2) To examine how functional status, cognition, and frailty influence the prognosis of patients with HF; (3) To analyze the nutritional status of patients with HF and to know how malnutrition influences the prognosis of these patients; and (4) To determine which are the best tools to assess congestion, as well as the best strategies to achieve decongestion in patients with HF during the acute decompensation phase.

Study variables and data collection

Study visits consist of an inclusion visit at baseline, a 30-day follow-up visit (only for patients included after an acute HF decompensation), and two follow-up visits at one year and two years after inclusion. Additional visits, whenever necessary and according to clinical judgment are allowed. Most of the study variables will be collected during the inclusion visit and are detailed in Table 2. Briefly, the following parameters will be collected: demographic data, HF-related variables, comorbidities, social, functional, and cognitive status, variables related to frailty and nutrition, variables related to the acute HF decompensation episode and its management, analytical parameters, and treatments (at baseline and during the acute decompensation phase). Data will be collected through an electronic medical record, which contains the database, accessed with a personal password. Confidentiality will be preserved since no personal data will be stored.

Sample size

A sample size calculation has not been performed as the RICA-2 will be an “open” HF registry with five different objectives. Based on the experience of the researchers in the development of the RICA registry, we estimate the inclusion of 1,000 patients per year with the objective of including at least 5,000 patients in a period of 5 years. In order to achieve this inclusion rate, the same recruitment strategy used in other studies of our working group will be followed and consists

Table 2. Study variables at inclusion and follow-up visits

Inclusion visit	
Demographic variables	Age Gender
Body composition estimate	Body mass index
HF-related variables	HF etiology NYHA scale Previous admissions for AHF Previous ED visits for AHF
Comorbidities ⁷	Charlson Comorbidity Index
Social variables	Place of living and caregiver needs
Functional status ¹⁶	Barthel Index
Cognitive status ¹⁵	Delirium Pfeiffer test
Frailty ¹⁴	FRAIL scale Clinical Frailty Scale
Advanced HF and palliative care ²³	EPICTER score
Nutritional status ^{18,19}	Nutritional Risk Screening 2002 Mini Nutritional Assessment CONUT score
Acute HF decompensation variables ^{*22}	EVEREST score Precipitating factors Pharmacological treatment Non-pharmacological measures Outcomes
Analytical parameters ¹⁰	Blood cell count Biochemical parameters** Natriuretic peptides Cardiac Troponin Carbohydrate antigen 125 ²¹ Iron metabolism parameters Vitamin D Urine analysis**
Complementary procedures	Electrocardiogram Echocardiogram parameters Chest X-ray Lung and inferior vena cava ultrasound Other cardiologic procedures***
Cardiac amyloidosis diagnostic criteria	ESC working group on myocardial and pericardial diseases criteria ²⁴
Baseline treatment	HF-related medications Other medications
Follow-up visits	
Outcomes	Vital status and causes of death Hospitalizations for AHF and other causes ED visits for AHF Outpatient clinic visits

(Continue)

Table 2. Study variables at inclusion and follow-up visits (*Continued*)

Follow-up visits	
Analytical parameters	Blood cell count Kidney function Electrolytes Natriuretic peptides
Treatment	Optimization of prognostic-modifying treatment for HF

*Only in patients included during and acute decompensation but not for those included in a stable phase.

**Including glucose, kidney function (urea, creatinine, and glomerular filtration rate estimates using CKD-EPI formula), uric acid, electrolytes (sodium, potassium, chloride, magnesium), blood gasometry parameters, c-reactive protein, liver enzymes, lipids (total cholesterol, LDL, HDL, triglycerides), albumin. Urine analysis includes sodium, potassium, chloride, and albumin-to-creatinine ratio).

***Including: coronary angiography, myocardial perfusion SPECT, cardiac scintigraphy with 99mTc-DPD.

AHF: acute heart failure; CONUT: Controlling Nutritional Status; ED: Emergency Department; ESC: European Society of Cardiology; HF: heart failure; NYHA: New York Heart Association.

of assigning to each center a minimum number of patients to be included each year which is proportional to the centers' number of beds.

Statistical analysis

There is no single statistical methodology for the different studies that will be carried out with the RICA-2 registry. Every study will have its own methodology depending on the research question to be answered (and it will be detailed in a timely manner when it is necessary to present results). We can foresee that most studies will be descriptive, univariate, and multivariate comparative studies (using regression analysis) as well as survival analysis using Kaplan Meier curves and Cox regression analysis.

Ethical aspects

The patients included in this study will be treated following usual medical care, since being an observational study does not modify the usual clinical practice. The study will be carried out in accordance with the Declaration of Helsinki. The study has been approved by the Clinical Research Ethics Committee of the Dr. Josep Trueta University Hospital in Girona and an informed consent will be obtained from all participating subjects.

Discussion

Despite advances in the knowledge of HF and the development of new treatments that improve its prognosis, this syndrome, with a high prevalence and

incidence, continues to be a determinant of poor prognosis and presents high morbidity and mortality¹¹. The need to keep promoting knowledge to continue improving our patients has served as a stimulus to work in this direction and is what has led the Heart Failure and Atrial Fibrillation working group to propose this new RICA-2 registry. In this new version, apart from revisiting epidemiological aspects, the authors have decided to focus on answering more specific questions about which there is currently less evidence and which can help to enhance awareness, especially in those patients with HFpEF.

Clinical, epidemiological, phenotypic characteristics, and prognosis in heart failure with preserved ejection fraction

HFpEF is not even present a clear clinical entity. It is a mixture of cardiovascular, metabolic, renal, and geriatric conditions¹². A rational focus on the improvement of the outcomes of patients with HFpEF may be to tackle the patients according to the conditions that led them to seek medical counseling. In this regard, a phenotype-oriented approach to HF and, in particular, to HFpEF could be interesting mainly if these presumable phenotypes lead to new therapeutic approaches¹³.

Functional status, cognition and frailty on patients with heart failure

Persons with HF are more likely to be frail and suffer cognitive impairment than their age-matched equivalents without HF¹⁴. The reasons for this are not well known and may be linked to hemodynamic, vascular, and inflammatory changes that take place as heart failure progresses. Frailty, denoted by an increased physiologic vulnerability to stressors, may induce sickly persons with HF to exacerbation and worsening of this entity due to greater liability to the harmful pathophysiologic responses in HF, such as inflammation and autonomic dysfunction. Deepening the knowledge of the role of frailty in patients with HF can be useful to find mechanisms that attenuate the poor prognosis that its presence imposes on the patients. In addition, cognitive impairment many times associated to frailty, and highly prevalent in older people with HF adds a worse prognosis to these patients as was reported in our previous registry RICA¹⁵. The understanding of this association will be also a new reason for studying it in the new RICA-2. Finally, functional status was already studied previously¹⁶. Previous data from the RICA registry

showed that severe functional disability existed in more than half of older patients admitted because of a HF decompensation. For this population, preadmission Barthel index was a robust predictor of short-term mortality. It would be worthy to analyze again this aspect in the sample of this new registry.

Nutrition and heart failure

Cachexia and malnutrition are significant complications of numerous diseases such as chronic kidney disease and severe HF. Malnutrition in HF is associated with loss of muscles, fat, and bone mass. Its causes can be due to decreased intake, increased metabolic rate, and cytokine dysfunction involving several molecules such as tumor necrosis factor- α , cortisol, epinephrine, renin as well as aldosterone. Drugs used in the treatment of HF such as diuretics or beta-blockers may suppose the loss of micronutrients and water-soluble vitamins. On the other hand, it is not clear what method is the best to assess nutritional status in patients whose weight and body mass index may be overestimated as a consequence of a congestive situation and biochemical tests such as albumin has also limitations because its variation with several non-nutritional factors such as status of hydration (states of overhydration lead to overestimation and dehydration leads to underestimation of serum albumin)¹⁷. The question is not trivial, since the state of malnutrition has prognostic repercussions both in outpatients¹⁸ where it will be evaluated and in patients with acute decompensation¹⁹ where we will also evaluate it.

Assessment of congestion and strategies to achieve decongestion

Congestion is defined as the signs and symptoms of extracellular fluid accumulation, established by an increase in left-sided cardiac filling pressure²⁰. The mechanisms that produce this status beyond a progressive accumulation of sodium and water deserve a thorough study of their causes, development, or markers. In this regard, we included the study of the role to detect congestion and its prognosis of the carbohydrate antigen 125 (CA 125)²¹. CA 125 is synthesized by serous epithelial cells as reaction to congestion and/or inflammatory stimulus. In recent years, increasing evidence has raised indicating that plasma levels of this glycoprotein could be useful as a biomarker in HF.

On the other hand, congestion is directly related to acute decompensation of HF. This aspect, crucial in the

timeline progression of HF, will be also evaluated in the new RICA-2. The underlying cardiac disease, the clinical presentation and precipitating factors may be very variable. Therefore, the pathophysiology of acute HF is highly heterogeneous. In addition, current management of acute HF is mostly symptomatic, led on decongestive drugs, at best tailored according to the initial hemodynamic status but with little regard to the underlying pathophysiological particularities. As a consequence, acute HF is linked to high mortality and hospital readmissions. As there is an unmet need for increased individualization of in-hospital tackle, including treatments targeting the causative factors, and continuation of treatment after hospital discharge to improve long-term outcomes²², we decided to include these aspects to widely research it.

Finally, other relevant aspects of HF are going to be included in the registry. It is of interest the approach of patients with advanced HF. A previous study of this working group showed a high prevalence of advanced disease and a low use of palliative care along with new criteria for defining it²³. In this new registry, we will prove its validity in that new population. Furthermore, we will also aim to study the characteristics of an emerging entity as cardiac amyloidosis²⁴ in the setting of internal medicine wards.

Conclusions

RICA-2 is a prospective study that aims to improve knowledge regarding epidemiology and prognosis in patients with HF, with special attention to relevant aspects such as functionality, cognition, frailty, nutrition, and congestion phase without forgetting other emergent topics such as advanced HF and cardiac amyloidosis.

Funding

This research is funded by Sociedad Española de Medicina Interna.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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