ORIGINAL ARTICLE

Argentine Registry of Acute Heart Failure (ARGEN-IC) in the COVID Era. "Reality in pandemic times"

Registro ARGEN-IC en la era COVID. Realidad en tiempos de pandemia

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ABSTRACT

Background: The ARGEN-IC registry allowed knowing the clinical and epidemiological characteristics of acute heart failure (AHF) in our country; however, there are no available national data of the consequences on AHF of social, preventive and mandatory distancing due to the SARS-CoV-2 pandemic.
Objective: The aim of this study was to evaluate the clinical and epidemiological characteristics of patients admitted to the ARGEN-IC registry during confinement and social distancing due to the SARS-CoV-2 pandemic.
Methods: Patients included in the ARGEN-IC registry during March-June 2019 (group A: Non-COVID era) were compared with those admitted in the same period of 2020 (group B: COVID era). Affiliation data, clinical, biochemical, imaging and therapeutic characteristics during hospitalization and the associated complications (cardiovascular and non-cardiovascular mortality) were recorded.
Results: A total of 361 patients were included in the study: 222 in group A and 139 in group B. Significant differences were observed between both populations in terms of age (group A: 70.9±14.8 years vs. group B: 75±13.3, p=0.008), history of hypertension (group A: 70.2 % vs. group B: 87.7 %, p <0.001), history of ischemic stroke (group A: 4.5% vs. group B: 10.07%, p=0.039), and left ventricular hypertrophy (group A: 4.9 % vs. group B: 1.5 %, p=0.021). No significant differences were found between the two populations regarding other variables such as etiology, triggering factors, and forms of clinical presentation, although there was a trend towards greater history of depression in group B. There was no difference in the length of hospital stay or mortality.
Conclusions: During compulsory social distancing in our country, we observed a decrease in hospitalizations for AHF in 2020 compared with those registered in the same period of 2019, but the population requiring hospitalization was older and with more comorbidities. No differences were observed in overall and cardiovascular mortality, or in the length of hospital stay.

Keywords: Heart failure - SARS-CoV-2 - COVID-19/complications

RESUMEN

Introducción: El registro ARGEN-IC permitió conocer las características clínicas y epidemiológicas de la insuficiencia cardíaca aguda (ICA) en nuestro país; sin embargo, no contamos con datos nacionales de las consecuencias sobre la ICA de la implementación del distanciamiento social, preventivo y obligatorio a causa de la pandemia por SARS-CoV-2.
Objetivo: Evaluar las características clínicas y epidemiológicas de los pacientes ingresados al registro ARGEN-IC durante el confinamiento y distanciamiento social debido a la pandemia por SARS-CoV-2.
Materiales y métodos: Se compararon pacientes (p) incorporados al registro ARGEN-IC durante marzo-junio de 2019 (grupo A: Era No COVID) con los ingresados en igual período de 2020 (grupo B: Era COVID). Se registraron los datos de filiación, las características clínicas, bioquímicas, imagenológicas y terapéuticas durante la hospitalización y las respectivas complicaciones (mortalidad cardiovascular y no cardiovascular).
Resultados: Se incluyeron 361 p, 222 en el grupo A y 139 en el grupo B. Se observaron diferencias significativas entre ambas poblaciones en cuanto a edad, grupo A 70,9 ± 14,8 años vs. grupo B 75 ± 13,3 (p 0.008); antecedente de hipertensión arterial, grupo A 70,2% vs. grupo B 87,7% (p <0,001); antecedente de accidente cerebrovascular isquémico, grupo A 4,5% vs. grupo B 10,07% (p = 0,039); e hipertrofia ventricular izquierda, grupo A 4,9 % vs. grupo B 1,5 % (p = 0,021). En relación con otras variables como etiología, factores desencadenantes y forma de presentación clínica, no se hallaron diferencias significativas entre ambas poblaciones, aunque hubo una tendencia a mayor antecedente de depresión en el grupo B. No hubo diferencia en la duración de la estadía hospitalaria ni en la mortalidad.
Conclusiones: Durante el distanciamiento social y obligatorio en nuestro país, observamos una disminución de las internaciones por ICA en 2020 respecto de las registradas en el mismo período de 2019. Entre aquellos que requirieron internación, hallamos un perfil de paciente más añoso, con más comorbilidades. No se observaron diferencias en la mortalidad total y cardiovascular, ni en la estadía hospitalaria.

Palabras claves: Insuficiencia cardíaca - SARS-CoV-2 - COVID-19 / complicaciones

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INTRODUCTION

Acute heart failure (AHF) is the leading cause of hospitalization in elderly patients and is responsible for approximately one million hospitalizations per year, with a very important economic and social burden for the health system. Thus, this condition requires urgent management, both from a diagnostic and therapeutic point of view. (1)

In December 2019, the first case of the disease caused by the SARS-CoV-2 virus (coronavirus type 2 causing severe acute respiratory syndrome) was reported in Wuhan, China. Since then, this disease has had a global expansion, with more than 200 countries affected, generating a true global pandemic, with devastating socio-economic consequences. (2)

Currently, COVID-19 is responsible for a substantial increase in morbidity and mortality throughout the world, with multisystemic manifestations and frequent cardiovascular (CV) involvement. In patients with COVID-19, CV disease and its risk factors are common comorbidities associated with worse outcomes. (3)

SARS-CoV-2 infection ranges from asymptomatic cases to severe pneumonias; it also triggers a systemic inflammatory response with overproduction of cytokines and chemokines, such as tumor necrosis factor-α, IL-1β and IL-6, leading to multi-organ damage. (4, 5)

In the CV system, this infection can produce disorders such as myocarditis, acute coronary syndrome, arrhythmias and thromboembolic complications, and it has been shown that CV involvement is an independent factor of high mortality. (6)

A Chinese report of 80 cases showed a significant increase in morbidity and mortality with age; this was approximately 8% in patients between 70 and 79 years and 14.8% in patients older than 80 years. (7)

The aim of this substudy of the Argentine Registry of Acute Heart Failure (ARGEN-IC) was to evaluate and compare the clinical and epidemiological characteristics of patients hospitalized for AHF in our country from March to June 2019 (Non-COVID era) with those hospitalized for the same reason and during the same period, but in 2020 (COVID era), as so far there are no national data about the impact of the pandemic on patients with AHF.

METHODS

The data used were obtained from the prospective, multicenter, national and descriptive ARGEN-IC registry. The centers voluntarily participated in the survey generated by the SAC Research area and Heart Failure and Pulmonary Hypertension Council and approved by the institutional Ethics Committee. Two cross-sections were made to compare between groups: one that included patients hospitalized for AHF from March to June 2019 (group A: Non-COVID era) and another that included patients hospitalized for AHF from March to June 2020 (group B: COVID era), representing the period of preventive and compulsory social confinement. After signing the informed consent, patients' affiliation data and clinical, biochemical, imaging and treatment characteristics were recorded during hospitalization, and overall and cardiovascular mortality were determined.

Statistical analysis

Qualitative variables were defined as percentages and the risk ratio as odds ratio (OR), with its 95% confidence interval (95% CI). Quantitative variables were expressed as mean and standard deviation or median and interquartile range (IQR), according to their normal or non-normal distribution. Student's t test, the chi-square test, or Wilcoxon or Mann Whitney tests were used to compare groups, according to variable quality and distribution. STATA 14 software package was used for statistical analyses. Event adjudication was carried out by central monitoring of the Argentine Society of Cardiology. Statistical significance was defined with a p value <0.05.

Ethical considerations

The protocol for this registry was approved by the Ethics Committee of the Argentine Society of Cardiology.

RESULTS

A total of 361 patients were included for the analysis: 222 patients in group A and 139 in group B. Population characteristics (Table 1) showed that patients in group B were older and with a tendency to higher prevalence of women, as well as more frequent history of hypertension (87.7% vs. 70.2%), but not of dyslipidemia, smoking, diabetes and chronic kidney failure. Mean left ventricular ejection fraction (LVEF) was 43.1±15.3% in group A and 40.8±15.6% in group B. Cardiovascular history indicated differences in stroke (4.5% in group A vs. 10.0% in group B, p=0.039) and left ventricular hypertrophy (4.9% in group A vs. 11.5% group B, p = 0.021). No differences were observed in hemorrhagic stroke, acute myocardial infarction (AMI), chronic atrial fibrillation (CAF), stable chronic angina, coronary percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and previous heart valve surgery. There was also no difference in N-terminal pro-brain natriuretic peptide (NT-proBNP) values on admission. Similarly, no differences were found in terms of prior pharmacological treatment for heart failure (HF) with angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), beta-blockers, aldosterone antagonists, sacubitril/valsartan, furosemide or ivabradine. No differences between the groups were encountered in the percentage of previous vaccination, both for pneumococcal as for influenza vaccine. There were no differences in the etiological distribution of HF or between the most common triggers of AHF. Neither were differences found in the form of clinical presentation, when considering mixed congestion (p=0.19), peripheral congestion (p=0.86), simple pulmonary congestion (p=0.83), acute pulmonary edema (p=0.31) and cardiogenic shock (p=0.81). No significant differences were obtained in total length

Table 1. ECG and Clinical Characteristics According to patients' Age

Clinical Characteristics	Group A Non COVID era (n=222) (%)	Group B COVID era (n=139) (%)	P Value
Age (years)	70.9 ± 14.8	75.0 ± 13.3	0.008
Male Sex	139 (62.6)	73 (52)	0.058
Hypertension	156 (70.27)	122 (87.76)	<0.001
Dyslipidemia	98 (44.1)	54 (38.8)	0.321
Smoking	59 (26.5)	48 (34.5)	0.107
Diabetes	64 (28.8)	46 (33)	0.392
COPD	32 (14.4)	23 (16.5)	0.583
Chronic kidney failure	40 (20.1)	28 (18.8)	0.615
Prior LVEF (%)	43.1 ±15.3	40.8 ± 15.6	0.403
Prior AMI	33(14.8)	23 (16.5)	0.668
Prior ischemic stroke	10 (4.5)	14 (10.0)	0.039
Prior hemorrhagic stroke	1 (0.4)	2 (1.4)	0.314
Chronic AF	72 (32.4)	42 (30.2)	0.659
Depression	5 (2.2)	8 (5.7)	0.082
Alcohol consumption	8 (3.6)	6 (4.3)	0.733
Obesity	42 (18.9)	34 (24.4)	0.209
Left ventricular hypertrophy	11 (4.9)	16 (11.5)	0.021
Prior CABG	17 (7.6)	12 (8.6)	0.740
Prior PCI	23 (10.3)	14 (10.0)	0.930
Prior heart valve surgery	30 (13.5)	18 (12.9)	0.387
Influenza vaccine	57 (25.6)	35 (25.1)	0.916
Pneumococcal vaccine	47 (21.1)	26 (18.7)	0.570
Pacemaker	17 (7.6)	15 (10.7)	0.308
Implantable cardioverter defibrillator	11 (4.9)	2 (1.4)	0.081
Admission hematocrit (%)	38.5%	37%	0.07
Admission creatinine (mg/dl)	1.6 ±1.6	2.49 ± 12.2	0.31
Admission proBNP (pg/ml)	8. 392	6.143	0.096
MRA	12 (5.4)	9 (6.4)	0.45
Complete treatment	68(30.6)	47 (33.8)	0.528
- ACEI	57 (25.6)	33 (23.7)	0.679
- ARBs	122 (54.9)	75 (53.9)	0.853
- Betablockers	58 (26.1)	29 (20.8)	0.255
- Antialdosterone agents	71 (32.1)	49 (35.4)	0.510
- Sacubitril/Valsartan	4 (1.8)	0 (0)	0.112
- Ivabradine	19 (8.5)	12 (8.6)	0.980
- Amiodarone	96 (43.2)	58 (41.7)	0.777
- Furosemide	3 (1.3)	2 (1.3)	0.945
- Hydralazine	5 (2.2)	2 (1.4)	0.585
- Nitrates	64 (28.8)	33 (23.7)	0.289
- Aspirin	6 (2.7)	11 (7.9)	0.023
- Clopidogrel	31 (13.9)	23 (16.5)	0.503
- Oral hypoglycemic drugs	14 (6.3)	11 (7.9	0.503
- Insulin	60 (27.0)	40 (28.7)	0.718
Etiology			
- Unknown	54 (24.3)	26 (18.7)	0.210
- Ischemic-necrotic	66 (29.7)	24 (17.2)	0.419
- Idiopathic	10 (4.5)	12 (8.6)	0.965
- Hypertensive	25 (11.2)	24 (17.2)	0.105
- Valvular	43 (19.3)	23 (16.5)	0.499
- Restrictive	6 (2.7)	3 (2.1)	0.746
- Myocarditis	3 (1.3)	0 (0)	0.571
- Chagas	7 (3.1)	2 (1.4)	0.309

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(continuation)

Clinical Characteristics	Group A Non COVID era (n=222) (%)	Group B COVID era (n=139) (%)	P Value
- Alcoholic	2 (0.9)	1 (0.7)	0.853
- Other	17 (7.6)	19 (13.6)	0.636
Triggering factor			
- Unknown	59 (26.57)	25 (18.0)	0.601
- Food Transgression	26 (11.7)	23 (16.5)	0.191
- Treatment suspension	28 (12.6)	13 (9.35)	0.342
- Supraventricular arrhythmia	26 (11.7)	15 (10.8)	0.788
- Infection	38 (17.0)	22 (15.8)	0.748
- Hypertensive crisis	24 (10.8)	18 (12.9)	0.537
- ACS	3 (1.3)	2 (1.4)	0.959
Types of Presentation			
Mixed Congestion	14 (17.1)	14 (10.8)	0.193
Simple Peripheral Congestion	40 (40.4)	26 (25.5)	0.869
Simple Pulmonary Congestion	127 (57.5)	78 (79.3)	0.838
Acute Pulmonary Edema	32 (28.8)	15 (18.2)	0.319
Cardiogenic Shock	7 (7.3)	5 (4.6)	0.818

*Association of the renin angiotensin system inhibitors/antagonists or sacubitril/valsartan with beta-blockers and anti-aldosterone agents. COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, AMI: Acute myocardial infarction, AF: Atrial fibrillation, CABG: Coronary artery bypass grafting, PCI: Percutaneous coronary intervention, MRA: Mechanical respiratory assistance, ACEI: Angiotensin converting enzyme inhibitors, ARBs: Angiotensin II receptor blockers, ACS: Acute coronary syndrome

of hospital stay (group A, 7 days IQR 4-10 vs. group B, 8 days IQR 5-13, p=ns) and neither in its distribution by areas [length of stay in the coronary care unit: 5 days (IQR 3-8) in group A vs. 6 days (IQR 3-9) in group B, p=ns, and in the general ward: 5 days (IQR 3-8) in group A vs. 5 days (IQR 2-10) in group B, p=ns] (Table 2). Finally, no differences were observed in total mortality: 6.3% in group A and 6.4% in group B (p=0.93), or in cardiovascular and non-cardiovascular mortality [4.5% in group A and 4.3% in group B (p=0.93) and 1.8% group A and 2.1% in group B (p=0.81), respectively].

DISCUSSION

The pandemic has generated an emerging reorganization of the healthcare system with a focus on the epidemiological control of COVID-19; however, this has been detrimental to the care of cardiovascular diseases with high morbidity and mortality, such as HF.

The findings of the ARGEN-IC registry are consistent with several registries published internationally, such as the one from Charlotte Andersson et al., developed at Boston University, using the Danish government database, which describes a 30% drop in AHF hospitalizations, and the North Bristol NHS Trust single-center registry from the UK, reporting a 27% drop for the same disease. In our registry, the percent reduction was 37%, with no significant differences in in-hospital mortality. (8, 9)

In agreement with these results, the Department of Cardiology at King's College Hospital and the National Heart Failure Audit Institute of England and Wales reported that during the pandemic there was a drop in the rate of hospitalization for AHF, and that those patients requiring hospitalization showed greater functional impairment (NYHA FC III-IV) and level of congestion. (10)

A retrospective registry by König et al. including 67 hospitals in Germany comparing two 2020 periods, one without confinement and the other during confinement, and this with the same period in 2019, reported a decrease in hospitalizations for HF. In patients requiring hospitalization, there was a higher proportion of men with more severe comorbidities and forms of clinical presentation. Although this did not lead to longer length of hospital stay (mean 7.7±5.8 days), it increased in-hospital mortality. (11)

This COVID-19 impact on hospitalizations for AHF could be associated with several factors, including the lower number of outpatient and emergent consultations, the possible decrease in non-COVID-19 respiratory infections (frequent HF decompensating factor) and the appearance of virtual medical consultations, which could be detrimental to the early detection of decompensation signs. (12-15)

When we analyze the most common triggers for HF, no differences between the two periods were found; however, less access to drugs, both for the control of risk factors as for HF treatment, added to the decrease in medical routine controls may have possibly generated clear problems of adherence and therapeutic non-compliance.

On the other hand, our data reveal that elderly patients with comorbidities, a particularly vulner-

	COVID Era	Non-COVID era	p
Days of hospital stay	8 (IQR 5-13)	7 (IQR 4-10)	ns
Days of ICU stay	6 (IQR 3-9)	5 (IQR 3-8)	ns
Days of general ward stay	5 (IQR 2-10)	5 (IQR 3-8)	ns
CV mortality, n(%)	10 (4.5)	6 (4.3)	ns
Non-CV mortality, n(%)	4 (1.8)	3 (2.2)	ns
Overall mortality, n (%)	14 (6.3)	9 (6.4)	ns

ICU; Intensive care unit, CV: Cardiovascular

Table 2. Length of hospital stay and mortality

able population, led the number of hospitalizations for AHF during the confinement stage. Regarding this latter aspect, a univariate analysis of the aforementioned UK registry found a direct relationship between advanced age, confinement and mortality. Nevertheless, we did not find significant differences in cardiovascular and non-cardiovascular mortality.

The association of COVID-19 and HF has generated the need for adapting the medical care system, with an increase in the use of telemedicine as a practical resource for the management of patients during confinement. Consequently, the Chinese Heart Failure Association and the European Society of Cardiology created a consensus document for the management of HF in COVID-19 patients. (16-18)

Unfortunately, we do not have sufficient data on the percentage of patients hospitalized for AHF who tested positive for COVID-19.

Limitations

The ARGEN-IC represents a heterogeneous, non-randomized population, so selection biases cannot be excluded. This substudy performed a cross-section of the registry comparing two populations in different periods of time, not allowing the collection of follow-up data and, hence, of the long-term consequences of COVID-19 in this population.

We understand that there is under-registration of AHF hospitalizations and their consequences and, on the other hand, we consider that it would have been useful, in the current era, where tests are more widespread, to obtain data on the direct impact of SARS-CoV-2 infection in patients admitted for AHF.

Finally, although the ARGEN-IC is a multicenter registry and represents, to a certain extent, the reality of AHF care in Argentina, we realize that it is necessary to include more hospitals from different regions throughout our country to obtain greater wealth of data.

CONCLUSIONS

The COVID-19 pandemic proved to generate clear social, cultural and economic consequences worldwide. Mandatory population confinement has impacted on overall cardiovascular disease and on HF in particular, exposing a vulnerable population with high morbidity and mortality.

The ARGEN-IC multicenter registry allows us to understand the reality of AHF in our country and analyze the consequences of the COVID-19 pandemic in this patient population.

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