

# Mortality markers in outpatients diagnosed with heart failure

## Marcadores de mortalidad en pacientes ambulatorios con diagnóstico de insuficiencia cardíaca

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### Abstract

**Introduction:** Heart failure is a global health problem. In Ecuador it is estimated that between 1% and 2% of the population suffers this disease. **Objective:** To determine mortality markers in outpatients with a diagnosis of heart failure in the Ecuadorian Andean population. **Methods:** A cross-sectional and monocentric study was carried out in 230 mestizo, indigenous and Afro-descendant patients diagnosed with heart failure. The differences between the three ethnic groups were statistically analyzed by one-way ANOVA and Crammer's V test. Additionally, a logistic regression analysis was performed. **Results:** The predominant ethnic group was mestizo (73.5%), followed by indigenous people (15.5%) and afro-descendants (10.5%). The logistic regression analysis showed that age (OR: 1.046; 95% CI: 1.014-1.078;  $p = 0.04$ ), ethnicity (OR: 1.713; 95% CI: 1.053-2.78;  $p = 0.030$ ), the presence of atrial fibrillation (OR: 2.711; 95% CI: 1.03-7.12;  $p = 0.042$ ) and the number of hospitalizations (OR: 3.026; 95% CI: 1.85-4.94;  $p = 0.000$ ), were markers of poor prognosis. On the other hand, mean arterial pressure (OR: 0.969; 95% CI: 0.94-0.99;  $p = 0.010$ ), absence of ischemic cerebrovascular event (OR: 0.15; 95% CI: 0.48-0.527;  $p = 0.03$ ) and total cholesterol levels (OR: 0.991; 95% CI: 0.987-0.996;  $p = 0.000$ ) were protection markers. **Conclusions:** In this population, ethnicity, atrial fibrillation, mean arterial pressure, ischemic cerebrovascular event, total cholesterol levels and the number of hospitalizations were established as mortality markers in outpatients diagnosed with heart failure.

**Keywords:** Heart failure. Ethnicity. Mortality. Prognosis.

### Resumen

**Introducción:** La insuficiencia cardíaca es un problema de salud global. En Ecuador se estima que entre el 1 y el 2% de la población padece esta enfermedad. **Objetivo:** determinar los marcadores de mortalidad en los pacientes ambulatorios con diagnóstico de insuficiencia cardíaca en población andina ecuatoriana. **Métodos:** Se llevó a cabo un estudio transversal y monocéntrico en 230 pacientes mestizos, indígenas y afrodescendientes diagnosticados con insuficiencia cardíaca. Las diferencias entre los tres grupos étnicos fueron analizadas estadísticamente por ANOVA unidireccional y el test V de Crammer. Adicionalmente, se realizó un análisis de regresión logística. **Resultados:** El grupo étnico predominante fue el mestizo

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(73,5%), seguido por el indígena (15,5%) y por el afrodescendiente (10,5%). El análisis de regresión logística mostró que la edad (OR: 1,046; IC 95%: 1,014-1,078;  $p = 0,04$ ), la etnia (OR: 1,713; IC 95%: 1,053-2,78;  $p = 0,030$ ), la presencia de fibrilación auricular (OR: 2,711; IC 95%: 1,03-7,12;  $p = 0,042$ ) y el número de hospitalizaciones (OR: 3,026; IC 95%: 1,85-4,94;  $p = 0,000$ ), fueron marcadores de mal pronóstico. Por otro lado, la presión arterial media (OR: 0,969; IC 95%: 0,94-0,99;  $p = 0,010$ ), la ausencia de evento cerebrovascular isquémico (OR: 0,15; IC 95%: 0,48-0,527;  $p = 0,03$ ) y los niveles de colesterol total (OR 0,991; IC 95%: 0,987-0,996;  $p = 0,000$ ) fueron marcadores de protección. **Conclusiones:** En esta población, la etnia, la fibrilación auricular, la presión arterial media, el evento cerebrovascular isquémico, el colesterol total y el número de hospitalizaciones se configuraron como marcadores de mortalidad en pacientes ambulatorios con diagnóstico de insuficiencia cardíaca.

**Palabras clave:** Insuficiencia cardíaca. Etnia. Mortalidad. Pronóstico.

## Introduction

Heart failure is a worldwide health problem that affects approximately 60 million people<sup>1</sup>. According to data recorded in Europe and the United States of America, the prevalence of this disease varies between 1% and 12% of the population and the costs associated with its treatment are equivalent to the per capita consumption of 17.9% of the world's gross domestic product<sup>2,3</sup>.

In Ecuador, there is no precise data on the prevalence of this disease. However, it is estimated that it could be found in between 1% and 2% of the total population<sup>4</sup>: (i) arterial hypertension, (ii) rheumatic fever, (iii) coronary heart disease, (iv) valvular heart disease, (v) primary cardiomyopathies, (vi) cardiopulmonary diseases, (vii) congenital heart disease, (viii) being of African descent, and (ix) advanced age has been described as predisposing to the development of this pathology<sup>5,6,7</sup>.

Given that most of this information comes from studies carried out in "first world" countries, with different socio-demographic and ethnic characteristics with respect to the Latin American population and the Andean population in particular, it was decided to carry out this study to determine the mortality markers in outpatients diagnosed with heart failure in the Ecuadorian Andean population.

## Method

### Study design

A single-center, cross-sectional study was conducted in patients diagnosed with heart failure at the "Hospital General San Vicente de Paúl" in the city of Ibarra, Ecuador.

### Population

Patient records were analyzed based on medical records registered between the years 2015 to 2018.

Cases were identified based on the coding defined by the International Classification of Diseases (ICD-10) with codes I-50, I-51, I-52, I-52, I-23 and I-42 corresponding to: complications of heart failure and ill-defined descriptions of heart disease, other cardiac disorders in diseases classified elsewhere, current frequent complications of acute myocardial infarction and cardiomyopathy, respectively.

The inclusion criteria were: the clinical manifestations reported by the patients during the first consultation, the presence of at least one echocardiographic study in which the left ventricular ejection fraction and a baseline electrocardiographic study were recorded, and the presence of at least one echocardiographic study in which the left ventricular ejection fraction was recorded.

Based on these criteria, a total of 270 patients were identified, of whom 40 were excluded because they did not meet the inclusion criteria, had incomplete records, or had a history of heart failure secondary to congenital heart disease.

### Demographic parameters

As demographic variables, age in years completed, sex of the patients and ethnic self-definition were evaluated.

### Clinical, laboratory, and echocardiographic parameters.

Among the clinical variables, the etiology of heart failure, functional class and comorbidities were evaluated.

Regarding laboratory and echocardiographic parameters, glomerular filtration rate, sodium levels, total cholesterol levels, NT-Pro-BNP levels, mean arterial pressure values and left ventricular ejection fraction were considered.

All the cases of atrial fibrillation belonged to patients classified as permanent atrial fibrillation, based on the electrocardiographic records obtained from the clinical history.

The median blood pressure values were obtained from the average of all the ambulatory blood pressure controls. Regarding laboratory data, the results obtained after the patient's first outpatient control were taken into account.

Functional class was systematized according to the NYHA classification, glomerular filtration rate was calculated by the CKD-EPI formula, and ejection fraction was measured by the Simpson method. Finally, cases were classified according to ejection fraction, as proposed by the European Society of Cardiology.

### Statistical analysis

Descriptive statistics were used for quantitative and qualitative variables. The comparison of the different subgroups was performed using the one-way ANOVA test and Cramer's V test.

Bivariate analysis was performed using the Chi-square test with Yates correction and Fisher's exact test. Multivariate analysis was performed by binary logistic regression.

p-values < 0.05 were considered significant with 95% confidence intervals.

Data processing was performed using the SPSS v22 statistical package (IBM Corp).

## Results

### Baseline characteristics

According to the last population census of Ecuador, in 2010, 26% of the inhabitants of the province of Imbabura defined themselves as indigenous, 6% as Afro-descendants and 68% as mestizos, making this province the most ethnically diverse region in Ecuador<sup>8</sup>.

In total, 230 patients with a diagnosis of heart failure were analyzed. The mean age was 75.88 years, with a similar distribution between men and women, and the most important etiology was hypertensive (57.9%) (Table 1).

At the time of evaluation, most patients were diagnosed in functional class III (36.5%), and the most common comorbidities were arterial hypertension (76%), atrial fibrillation (32.5%) and type 2 diabetes mellitus (18.5%) (Table 1).

**Table 1.** Baseline characteristics of patients

Age (years)	75.88 ± 13
Ethnicity %	
Mestizo	170 (73.5)
Indigenous	36 (15.5)
Afro-descendant	24 (10.5)
Sex %	
Female	115 (50)
Etiology %	
Hypertensive	114 (57.9)
Ischemic	38 (19)
Valvular	7 (3.5)
Alcoholic	15 (7.5)
Other	5 (2.5)
Unknown	21 (10.5)
Functional class %	
Class 1	4 (2)
Class 2	66 (33)
Class 3	73 (36.5)
Class 4	57 (28.5)
Comorbidities	
Hypertension	152 (76)
Diabetes mellitus type 2	37 (18.5)
Stroke	23 (11.5)
Atrial fibrillation	65 (32.5)
Mean number of hospitalizations for heart failure	1.15 ± 0.97
Mean number of outpatient consultations (IQR)	3.2 (1.1-5)
Laboratory results	
Glomerular filtration rate (ml/kg)	53.57 ± 28.7
Sodium (mEq/l)	128.3 ± 38.3
Total cholesterol (mg/dl)	113.28 ± 159
NT-Pro-BNP (pg/ml) (interquartile range)	2165 (377.7-3357.5)
Treatment (%)	
Beta-blockers	89 (44.5)
Angiotensin-converting enzyme inhibitors	81 (40.5)
Angiotensin type II receptor antagonists	39 (19.5)
Aldosterone antagonists	86 (43)
Loop diuretics	140 (70)
Digoxin	39 (19.5)
Hemodynamic and echocardiographic parameters	
Mean arterial pressure (mmHg)	90 ± 15.8
Patients with preserved left ventricular ejection fraction %	34 (23.6)
Patients with partially reduced left ventricular ejection fraction %	39 (27.1)
Patients with reduced left ventricular ejection fraction %	71 (49.3)

IQR: interquartile range.

Of the patients, 49.3% corresponded to the heart failure group with reduced ejection fraction, and treatment was mainly based on the use of loop diuretics, followed by aldosterone receptor antagonists, ACE inhibitors/ARAI and beta-blockers (Table 1).

Among the hematometric values, the presence of moderate hyponatremia (128.3 mEq/l) and a mean glomerular filtration rate corresponding to grade IIIA of the KDIGO classification stood out (Table 1). Other findings were the presence of hypocholesterolemia (113.28mg/dl) and elevated NT-proBNP levels (2165pg/ml) (Table 1).

### Comparison between ethnic groups

Of the patients, 73.5% defined themselves as mestizo, 15.5% as indigenous and 10.5% as Afro-descendant. When comparing the ethnic groups, the three were homogeneous, finding differences only in the history of stroke ( $p = 0.0206$ ). (Appendix 1)

### Bivariate analysis

Bivariate analysis showed that the absence of stroke (OR 0.28 CI95% 0.12-0.67  $p = 0.005$ ), mean arterial pressure (OR 0.22 CI95% 0.06-0.75,  $p = 0.01$ ), total cholesterol (OR 0.24 CI95% 0.08-0.72,  $p = 0.012$ ), diuretic use (OR 0.35 CI95% 0.18-0.65,  $p = 0.001$ ) and HDL cholesterol (OR 0.18 CI95% 0.06-0.54,  $p = 0.001$ ) were protective factors. Meanwhile, creatinine (OR 2.35 CI95% 1.36-4.07,  $p = 0.003$ ), absence of aldosterone receptor type 2 antagonists (OR 2.78 CI95% 1.30-5.93,  $p = 0.010$ ), and beta-blockers (OR 2.92 CI95% 1.68-5.09  $p = 0.0001$ ) were identified as factors associated with worse prognosis.

### Multivariate analysis

Binary logistic regression analysis identified age, ethnicity, presence of atrial fibrillation, and number of hospitalizations as markers of poor prognosis. On the other hand, mean arterial pressure, the absence of a history of stroke, and total cholesterol were associated as markers of better vital prognosis. (Table 2).

### Discussion

The present study demonstrated that age, ethnicity, presence of atrial fibrillation, mean arterial blood pressure levels, history of stroke, number of hospitalizations, and total cholesterol levels independently influenced the vital prognosis of patients with heart failure.

With respect to comorbidities, our study identified arterial hypertension, coronary artery disease, type 2 diabetes mellitus and atrial fibrillation as the most

**Table 2.** Multivariate analysis of prognostic markers in outpatients diagnosed with heart failure

Variable	OR	CI 95%	Wald	p
Age	1.046	1.014-1.078	8.187	0.04
Ethnicity	1.713	1.053-2.78	4.708	0.030
Atrial fibrillation	2.711	1.03-7.12	4.117	0.042
Mean arterial pressure	0.969	0.94-0.99	6.667	0.010
Stroke	0.15	0.048-0.527	9.046	0.003
Number of hospitalizations	3.026	1.85-4.94	19.520	0.000
Total cholesterol	0.991	0.987-0.996	13.455	0.000
Constant	-7.102			0.048

CI: confidence interval; OR: odds ratio.

important, as has been described in previous research in the Latin American population, where arterial hypertension and atrial fibrillation were the most commonly found pathological antecedents<sup>2,9</sup>.

Regarding the etiology of heart failure, our study showed that the main cause was hypertension. This finding is in agreement with previous studies carried out in populations of middle and low-income countries - in Latin America, Europe and Africa - but contrasts with studies conducted in first world countries, where ischemic coronary disease is the leading cause of heart failure<sup>3,5,10</sup>.

Likewise, it is important to highlight that in our study, one of the most prevalent groups was that of patients with heart failure of alcoholic etiology (7.5%). This result is similar to that reported in previous studies such as the one published by Bocchi E et al. which identified a prevalence of this etiology between 1% and 8% of cases<sup>3</sup>.

Regarding ejection fraction, and similar to that reported by Dewan et al. and Ciapponi et al. the highest percentage of patients was categorized in the group with reduced ejection fraction, followed by those with partially reduced ejection fraction and finally by the group with preserved fraction<sup>10,11</sup>.

When comparing this distribution with respect to the ethnicity of the patients, no statistically significant differences were found between the groups.

When analyzing functional class and treatment, most patients were diagnosed in class 3 and 4, and management was based on the use of loop diuretics, ACEI/ARAI, aldosterone antagonists and beta-blockers. These

findings are similar to those reported in previous studies; however, with respect to the use of beta-blockers and ACEI/ARII, our prescription percentage was lower than that described in previous studies<sup>3,10,11</sup>.

With regard to age, it is known that 10% of the population over 70 years of age can present heart failure, and that at least 20% of people between 40 and 80 years of age are at risk of developing it<sup>12</sup>. In our study, the mean age was 75 years, similar to that reported in Europe and some Latin American countries such as Argentina and Chile, although compared to studies carried out in Africa and Brazil, our mean age was higher<sup>2,3,5</sup>.

With respect to ethnicity, we found that people of African descent tended to develop heart failure at younger ages, whereas mestizos presented a greater number of comorbidities, with no significant differences between the groups<sup>6,7,13,14</sup>.

On the other hand, when multivariate analysis was performed, ethnicity behaved as a marker of poor vital prognosis. This finding is similar to that described by Vivo et al. who found higher mortality in blacks and people of Hispanic descent compared to non-Hispanic<sup>14</sup>.

Regarding the behavior of this disease in the indigenous population, the evidence is much scarcer. A systematic review in indigenous Australians showed a prevalence of 5.3% and a mortality rate 2 times higher compared to the general population, especially in patients aged between 45 and 65 years<sup>15</sup>.

As for Atrial Fibrillation, it is known to be the most commonly diagnosed arrhythmia, however, its relationship with mortality in patients with heart failure is contradictory<sup>2</sup>. For example, Slee A et al. demonstrated a 27% increase in mortality in patients with heart failure and Atrial Fibrillation<sup>16</sup>. Along the same lines, a meta-analysis published by Cheng M et al. identified an increase in all-cause mortality between 13% to 27% (OR 1.17 CI 95% 1.11-1.23)<sup>17</sup>.

Contrary to these findings, the study published by Mogensen UM et al. evidenced increased mortality only in patients with Paroxysmal Atrial Fibrillation (HR: 1.20 95% CI: 1.09-1.32;  $p < 0.001$ ), compared to those with persistent or permanent Atrial Fibrillation (HR: 1.09 95% CI 0.97-1.24,  $p = 0.156$ ; HR: 1.12 95% CI 0.98-1.28,  $p = 0.088$ ), respectively<sup>18</sup>.

In our case, all patients belonged to the permanent atrial fibrillation group, which was a limitation, since it was not possible to explore the behavior of the other types of atrial fibrillation with respect to vital prognosis.

From the pathophysiological point of view, the increase in mortality in atrial fibrillation carriers would be related to electrical instability, the generation of arrhythmias and the occurrence of fatal cardio embolic events<sup>18</sup>.

In relation to a history of stroke, Son MK et al. demonstrated a 38.7% increase in mortality in patients with heart failure and a recently diagnosed stroke<sup>19</sup>. Also, Lip GY et al. showed that the increase in mortality was not only greater at the time of the event, but was maintained even six months after diagnosis<sup>20</sup>.

In this same line, Witt BJ et al. identified in patients with dilated cardiomyopathy, an increase in mortality in those cases with a history of stroke OR 2.31 (95% CI 1.84-2.89)<sup>21</sup>.

In our study, the prevalence of stroke was 11.5%, and its absence became a protective factor.

With respect to mean arterial pressure values, it is known from previous studies that for every 10mmHg reduction in mean arterial pressure, there was an 11% increase in mortality (OR 0.86 CI 95% 0.82-0.91, ( $p = 0.0001$ ))<sup>22</sup>. The pathophysiological basis of this relationship would be conditioned to greater proarrhythmic activity and the appearance of malignant ventricular arrhythmias<sup>23</sup>.

In relation to the number of hospitalizations, it is known from previous evidence that it is a direct marker of disease progression and is associated with a worse vital prognosis and increased hospital costs<sup>24</sup>.

According to data published by Butler J et al. 50% of patients requiring hospitalization were readmitted during the first 6 months, and of these 30% died within the first year<sup>1</sup>. Also, Dokainish H et al. higher mortality associated with the need for rehospitalization during the last year after the first hospitalization (OR 1-6 CI 95% 1-3-1-9)<sup>9</sup>.

These antecedents are in agreement with the findings of our study, which showed an increase in mortality of up to three times in those patients with a greater need for hospitalization.

Regarding total cholesterol levels, Rauchhaus M et al. identified a 36% increase in mortality in those patients with total cholesterol concentrations below 200mg/dl, regardless of age, etiology of heart failure or nutritional status of the patient<sup>25</sup>.

On the other hand, Sakatani T et al. showed that in the case of patients with heart failure and without a history of coronary heart disease, total cholesterol levels less than or equal to 185mg/dL were associated with a worse prognosis for life<sup>26</sup>.



Our work, as previously described, showed an association between total cholesterol levels and increased mortality; however, we were unable to demonstrate that other lipid fractions are related to the vital prognosis of patients.

Finally, this study had some limitations with respect to the design and selection of cases.

The inclusion of patients was based on the diagnosis recorded in the clinical history using ICD-10 coding, which could have excluded cases that had not been properly classified.

On the other hand, being a single-center study, many cases of greater clinical complexity would not be adequately represented, and the lack of more specialized diagnostic means may have influenced the etiological under-diagnosis of the disease.

## Conclusions

The factors associated with increased mortality in outpatients with heart failure were similar to those described previously.

However, it is important to emphasize that this study, unlike others, included ethnicities such as mestizo, Afro-descendant, and indigenous, which have not been adequately represented, and therefore ethnicity should be considered as a marker to be taken into account when determining the prognosis of patients with heart failure.

## supplementary data

Supplementary data are available at *Revista Colombiana de Cardiología* online (<https://10.24875/RC-CAR.20000002>). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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## 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 they have followed the protocols of their work center on the publication of patient data.

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

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