Original Article

Survival and Prognostic Factors in Systolic Heart Failure with Recent Symptom Onset

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Objective

To study survival and prognostic factors associated with mortality in patients with systolic heart failure followed up since symptom onset.

Methods

We carried out a study with a cohort of 204 consecutive patients with systolic heart failure, whose symptom onset occurred within the 6 weeks preceding the first medical visit. They were followed up for 46 months. The prognostic variables analyzed were collected when the patients were included in the study and were correlated with cardiovascular mortality. An EF ≤40% on echocardiography characterized systolic ventricular dysfunction.

Results

The overall survival rates according to the Kaplan-Meier technique were 98.0%, 90.6%, and 70.2% at 3, 12, and 48 months of follow-up, respectively. The multivariate analysis identified the independent effect of 6 variables on the risk of cardiovascular death. Functional classes III and IV increased risk 2.7 times as compared with class II; 10-mmHg increments in systolic blood pressure reduced the risk of death by 25%; each 10-bpm increase in heart rate increased the risk of death 1.6 times; and each 0.25-mg/dL increment in serum creatinine caused a 60% increase in risk. The presence of the third cardiac sound caused a 3-fold increase in the risk of death, and chagasic etiology was also associated with cardiovascular mortality (P<0.0001).

Conclusion

Evidence shows that mortality in the initial phase is not elevated, and that etiology, advanced functional class, arterial hypotension, tachycardia, presence of the third cardiac sound, and elevated serum creatinine lead to a worse prognosis.

Key words

heart failure, epidemiology, prognosis, analysis of survival

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Most of the knowledge regarding prognosis in heart failure originates from studies in patients with chronic heart failure [1-3]. Thus, prognosis at an initial stage, ie, an early phase of the disease, has been the object of little study inside and outside Brazil. The follow-up of patients with heart failure of recent symptom onset is the better approach to evaluate the prognosis of the condition, as time has not yet selected the most resistant individuals.

In Brazil, neither prospective population-based nor hospital-based studies have been carried out in patients with heart failure of recent symptom onset, whose clinical diagnosis was confirmed on echocardiography due to a predominance of left ventricular systolic dysfunction, leading to a reduction in cardiac output (systolic heart failure), a consensual criterion in defining that condition.

Methods

In an inclusion period of 24 months, 504 patients with a presumed diagnosis of heart failure of recent symptom onset were assessed. Most patients (90.9%) originated from outpatient clinics, 232 being referred from 8 municipal health centers and 206 from the cardiology outpatient clinic of our institution, whose assisting physicians had agreed on referring all patients suspected of having heart failure of recent symptom onset. The remaining patients (n=66) were identified during the daily visits to the cardiology ward by one of the members of the specialized clinic. After undergoing reanalysis of the clinical history and physical examination, electrocardiography, chest X-ray, and echocardiography, 224 patients had their diagnosis confirmed. Twenty patients were excluded from the study due to the following reasons: heart failure in the presence of acute coronary syndrome; serum creatinine elevation beyond 2.3 mg/dL; significant obstructive pulmonary disease; diagnosed neoplasia and neoplasia under treatment; the presence of an implanted pacemaker; and planned change of municipal dwelling.

Heart failure of recent symptom onset was characterized as that whose symptoms started within the 6 weeks preceding the medical visit, and the patient should be using neither digitalis nor loop diuretics. To meet the criteria of heart failure, the patient had to have characteristic symptoms of the syndrome (dyspnea or fatigue, or both) with clinical signs of fluid retention (pulmonary or peripheral) in the presence of an underlying abnormality in cardiac structure or function. If doubt persisted, the beneficial clinical response, with symptom improvement after the use of diuretics, would be considered to confirm the diagnosis [4].

Thus, only the patients with left ventricular systolic dysfunction

and ejection fraction equal to or below 40%, on echocardiography, measured according to the Teichholz method, were included [5,6].

After identifying a new case of heart failure, the patient was medicated according to the specific protocol, which was not followed in the presence of contraindications or side effects that justified withdrawal or replacement of the medications [4,7].

All patients were followed up with regular visits to the heart failure clinic.

When a patient died at home or at a hospital, the death certificate was accessed, to provide data and the circumstances of death.

The following were considered death of a cardiovascular cause: death due to progressive worsening of heart failure and sudden death due to acute myocardial ischemia or stroke. All deaths were presumed to be of a cardiac cause, unless a definitive non-cardiac cause was determined.

All 204 patients of this cohort were followed up regarding the outcome death.

The accumulated probabilities of survival, both overall survival and the prognostic factors studied, were calculated by using the Kaplan-Meier method, also known as the product-limit method [8]. For those estimates, 95% confidence intervals were used.

For constructing the multivariate predictive model, the Cox proportional hazards model was used [9].

For adjusting the multivariate model to the prognostic factors studied, estimates of the risks of cardiovascular death were initially obtained through the univariate Cox proportional hazards model. All variables showing an association with $P<0.15$ were initially placed in the multivariate model, in a progressive form, and were ruled out only if they did not significantly improve the adjustment of the model.

Results

The initial characteristics of the patients studied are summarized in table I.

Of the 204 patients studied, 70 died before the end of the follow-up period, whose median duration was 46.0 months (interquartile variation: 35.0 to 51.0). Most deaths (n=62, 88.6%) were related to cardiovascular diseases. Figure 1 shows the overall survival curve of that population.

The accumulated probabilities of overall survival, according to the Kaplan-Meier method, were 98.0%, 90.6%, 82.3%, 73.3%, and 70.2% after 3 months, 1, 2, 3, and 4 years of follow-up, respectively (tab. II).

The univariate analysis by use of the Cox proportional hazards model revealed that age, functional class, etiology, diabetes, systolic blood pressure, heart rate, third cardiac sound, jugular stasis, and lower limb edema were significantly associated with cardiovascular death, some in a positive and others in a negative way ($P<0.05$). The presence of divisional heart block on the electrocardiogram and cardiothoracic index, as well as the left ventricular end-systolic diameter (LVESD) and left ventricular ejection fraction, was significantly associated with cardiovascular death. Ejection fraction, even being a restrictive variable in the process of mounting the cohort, was associated with cardiovascular death, as well as the serum concentrations of sodium and creatinine.

Considering the built-up knowledge and not overlooking the strong risk factors consistently associated with the prognosis of heart failure, a multivariate model was constructed to better adjust the independent contribution of each variable in the prognostic assessment of the patients.

The independent effects of functional class, etiology, systolic blood pressure, heart rate, third cardiac sound, and serum creatinine on cardiovascular mortality are shown in table III, as well as the univariate estimates.

Discussion

The accumulated probability of overall survival in patients with heart failure of recent symptom onset (incident) identified in our study does not seem discouraging. The risk of cardiovascular death was only 9.4% (95% CI: 5.5 - 13.3) in the first year after establishing the diagnosis of heart failure.

This mortality is similar to that observed in a series of clinical trials of medicamentous interventions in patients with mild to moderate heart failure, such as the one predominating in our study [10-12]. In the SOLVD study [12] (FC II and III), a 10.2% mortality rate (95% CI: 6.2 - 26.0) was reported in one year in the active

Table I - Demographic, clinical, and laboratory characteristics at the time of inclusion in the study

Characteristic	Value
Mean age, years (SD)	61.5 (13.5)
Color	
White, n (%)	115 (56.4)
Mixed, n (%)	66 (32.4)
Black, n (%)	23 (11.3)
Female sex, n (%)	78 (38.2)
Diabetes, n (%)	39 (19.1)
Current tobacco smoking, n (%)	52 (25.5)
Mean systolic blood pressure, mmHg (SD)	124.7 (23.5)
Mean heart rate, bpm (SD)	88.5 (13.9)
Etiology of heart failure	
Chagas´ disease, n (%)	57 (27.9)
Coronary heart disease, n (%)	65 (31.9)
Arterial hypertension, n (%)	37 (18.1)
Dilated cardiomyopathy and others, n (%)	45 (22.1)
Characteristics of the physical examination	
Jugular stasis, n (%)	88 (43.1)
Pulmonary rales, n (%)	134 (65.7)
Third cardiac sound, n (%)	47 (23.0)
Lower limb edema, n (%)	79 (38.7)
NYHA functional class	
II, n (%)	118 (57.8)
III, n (%)	72 (35.3)
IV, n (%)	14 (6.9)
Mean cardiothoracic index (SD)	0.62 (0.05)
Electrocardiographic alterations	
Atrial fibrillation, n (%)	42 (20.6)
Divisional heart block, n (%)	74 (36.3)
"Q" wave, n (%)	50 (24.5)
Echocardiography	
Mean LVEDD, mm/m^2 (SD)	63.4 (5.5)
Mean LVESD, mm/m^2 (SD)	54.0 (5.8)
Mean ejection fraction (SD)	0.33 (0.07)
Serum sodium, mEq/L (SD)	138.5 (3.7)
Mean serum potassium, mEq/L (SD)	4.1 (0.3)
Mean serum creatinine, mg/dL (SD)	1.2 (0.40)

bpm: beats per minute; mg/dL: milligram per deciliter; LVEDD: left ventricular end-diastolic diameter; mm: millimeter; SD: standard deviation; mmHg: millimeter of mercury; LVESD: left ventricular end-systolic diameter; n: number; mEq/L: milliequivalent per liter; NYHA: New York Heart Association.

arm of treatment, ie, patients receiving enalapril. On the other hand, in the MERIT-HF study [11], which assessed the use of the beta-blocker metoprolol for treating heart failure (FC II and III), the one-year mortality rates in the group that did not receive metoprolol and in the active group were 11.0% and 7.2%, respectively (RR: 0.66; 95% CI: 0.54 – 0.81). In the latter group, as well as in the control group, the patients were already on appropriate clinical treatment, which included ACEI.

It is worth emphasizing that the good prognosis obtained in clinical trials is partially due to the selection of the patients included. Patients are recruited based on numerous criteria of exclusion, which reduces patients to a group with a better prognosis than that of most patients with heart failure.

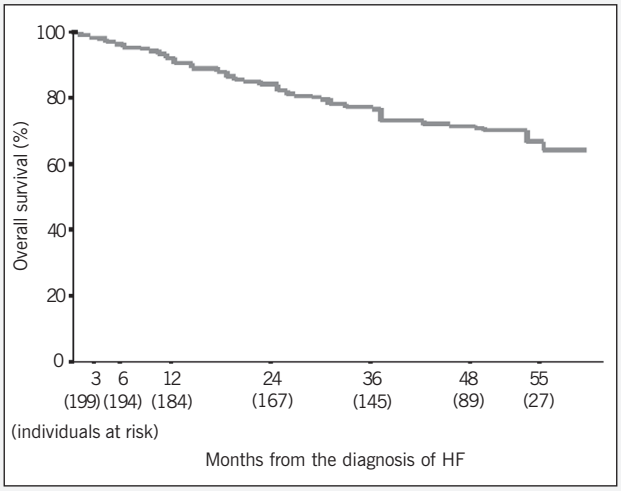

Fig. 1 - Curve of accumulated probabilities of overall survival (n=204).

Table II - Accumulated probabilities of overall survival according to the Kaplan-Meier method

Time elapsed in months	Nº of patients at risk	Accumulated probabilities of overall survival in % (95% CI)
3	199	98.0 (96.0 - 99.9)
6	194	95.6 (92.9 - 98.3)
12	184	90.6 (86.7 - 94.5)
24	167	82.3 (77.0 - 87.6)
36	145	73.3 (67.2 - 79.4)
48	89	70.2 (63.8 - 76.7)
55	27	64.4 (55.8 - 73.0)

CI - confidence interval.

Most clinical trials require that the patients have stable heart failure for months before recruitment. The mean duration of the condition in several patients taking part in clinical trials is 2 to 3 years [13].

On the other hand, regarding observational studies, such as ours, ie, those based on specific populations that assessed heart failure with recent symptom onset, our results seem better [14-17].

In those population-based studies, no preoccupation in optimizing and standardizing the treatment used was observed. The patients were followed up neither in specialized heart failure clinics, nor necessarily by cardiologists experienced in treating that condition.

In our consecutive series of patients, the treatment of heart failure was optimized with the systematic use of appropriate doses of ACEI, beta-blockers, and aldosterone antagonists, in addition to symptom control with digitalis and loop diuretics. The treatment was initiated as soon as the diagnosis of heart failure was established at the beginning of clinical decompensation, perhaps explaining the low mortality of that group in a period reported as being of high risk for death [15-17].

This fact also allowed us to control the possible factor of confusion caused by different heart failure treatments, enabling a better identification of the natural prognostic factors of that syndrome.

This study identified the following 6 factors independently associated with cardiovascular mortality: functional class; systolic blood pressure; etiology; third cardiac sound; heart rate; and serum creatinine level.

We demonstrated by use of multivariate analysis that the patients in functional classes III and IV had their adjusted risk of cardiovascular death 2.66 times greater (95% CI: 1.36 - 5.19) than those in class II. The loss of tolerance to physical exercise is one of the characteristics of heart failure, and studies have shown that the intensity of the symptoms is an important prognostic marker [18,19].

Systolic blood pressure was associated with prognosis in a statistically significant and inverse way, ie, at every 10-mm Hg increment in blood pressure, a 25% reduction in mortality was observed (RR: 0.75; 95% CI: 0.60 - 0.93). Systolic blood pressure may be a surrogate marker for cardiac reserve, and, therefore, have a predictive value. Several small studies [20,21] have suggested that systolic blood pressure is a predictor of events in patients with advanced heart failure, showing that the greater the systolic blood pressure level, the better the survival in heart failure.

Patients whose cause of heart failure was Chagas' disease had an adjusted risk of death 10.62 times greater (95% CI: 3.46

Table III - Independent effects of functional class, etiology, systolic blood pressure, heart rate, third cardiac sound, and serum creatinine level on cardiovascular mortality through the Cox proportional hazards regression model

	Univariate analysis RR (95% CI)	P Value	Multivariate analysis RR (95% CI)	P Value
Functional class III and IV vs II (86 vs 118)	5.51 (3.11 - 9.76)	< 0.001	2.66 (1.36 - 5.19)	0.004
Etiology				
CCHD (57)	4.12 (1.56 - 10.89)	0.008	10.62 (3.46 - 32.60)	< 0.001
CAD (65)	4.35 (1.67 - 11.31)		1.81 (0.67 - 4.91)	
SAH (37)	2.08 (0.68 - 6.37)		4.84 (0.86 - 27.25)	
DCM (45)	1.00	< 0.001	1.00	
Systolic blood pressure (each 10-mmHg increase)	0.75 (0.66 - 0.86)	<0.001	0.75 (0.60 - 0.93)	0.005
Third cardiac sound (yes X no)	9.32 (5.54 - 15.70)	<0.001	3.02 (1.55 - 5.90)	0.002
Heart rate (each 10-bpm increase)	1.61 (1.31 - 1.99)	<0.001	1.58 (1.23 - 2.04)	< 0.001
Serum creatinine (each 0.25-mg/dL increase)	1.64 (1.44 - 1.87)	<0.001	1.60 (1.33 - 1.92)	< 0.001

CCHD - chronic chagasic heart disease; DCM - dilated cardiomyopathy; CAD - coronary artery disease; SAH - systemic arterial hypertension; RR - relative risk.

- 32.60) than those with dilated cardiomyopathy. However, considering the wide confidence interval, this estimate should be classified as relatively unstable. The 95% confidence intervals are superimposed on the 3 etiological categories, when compared with the dilated cardiomyopathy group.

In our study of patients with heart failure of recent symptom onset, heart rate was also associated in a statistically significant manner with cardiovascular death (RR: 1.58; 95% CI: 1.23 - 2.04) for each 10-bpm increment. The analysis of heart rate allows the assessment of one of the earliest pathophysiological alterations in heart failure, which is sympathetic activation. Elevated heart rates seem to be associated with a worse prognosis, although this piece of information from physical examinations has been reported only in a few publications [21,22].

In the EPICAL study [22], which aimed at elaborating a classification for prognostic assessment of severe heart failure, heart rate was identified by use of multivariate analysis as an independent predictor of death in both ischemic heart disease ($P=0.015$) and dilated cardiomyopathy ($P<10^{-4}$).

On univariate analysis, both jugular stasis and the third cardiac sound were associated with an increase in cardiovascular mortality. However, on multivariate analysis, jugular stasis looses statistical power, the third cardiac sound remaining as the only independent predictor of mortality (RR: 3.02; 95% CI: 1.55 - 5.90). A decline has been evidenced in the ability and interest of physicians at residency programs to improve their cardiac semiologic capacity, which is partially due to the increasing availability of technologies, mainly echocardiography. The fact that physical examination findings provide useful information about the prognosis of patients with heart failure may motivate physicians to refine their diagnostic abilities.

Serum creatinine level was also an independent predictor of mortality, being associated 1.6 times more frequently with cardiovascular mortality (95% CI: 1.33 - 1.92) at every 0.25mg/dL-increment. This finding is in accordance with that reported in the study by Cowie et al [15], performed in patients with heart failure of recent symptom onset. Those authors reported that elevated serum levels of creatinine were independently related to an increase in cardiovascular mortality (RR: 2.64; 95% CI: 1.87 - 3.74). In heart failure of recent symptom onset, the contribution of the decrease in cardiac output and subsequent renal damage due to chronic hypoperfusion should be smaller than that in heart failure of longer duration, which makes us believe that, after clinical compensation, serum creatinine levels may become almost normal, and its persistence in elevated levels would indicate the existence of baseline renal disease.

Metabolic and neurohumoral abnormalities in heart failure have been extensively studied [2,23]. In our study, no relation was found between serum sodium levels and prognosis on multivariate analysis, although that marker of activation of the renin-angiotensin system had been validated as an important prognostic predictor in previous studies of heart failure [24,25]. The lack of an independent relation between serum sodium and prognosis in our study may perhaps be due to the fact that, in heart failure of recent symptom onset, the kidney is normal because it is undergoing hypoperfusion for a shorter period than that in chronic forms, and it is able to maintain the sodium balance and prevent volume expansion.

The variables identified in our study as independently associated with survival may reflect the degree of dysfunction of the baseline cardiac disease. On multivariate analysis, no association was found between left ventricular ejection fraction, assessed on echocardiography, and survival, probably because the spectrum of measurements was limited: maximum EF of 40%. In reality, that condition was part of the inclusion criteria of patients for follow-up. In our study, left ventricular dimensions were measured in 204 patients, and, as occurred with ejection fraction, on univariate analysis they seemed to be associated with survival. That association, however, was not maintained in the multivariate model. It is worth emphasizing that our study assessed only patients with heart failure of recent symptom onset, and that the chronic process of dilation and ventricular remodeling may not have happened.

This fact may also reflect lack of statistical power, because of the reduced size of our sample.

The addition of the variables treatment with ACEI and treatment with beta-blockers in the multivariate model did not significantly change the magnitude of the association between survival and the prognostic factors (tab. III). However, it is unlikely that the associations described are caused by the confounding effect of the prescription of ACEI or beta-blockers.

The results found allow concluding that, in patients with heart failure of recent symptom onset, no increase in mortality was evidenced in the initial phase of clinical decompensation. Of the prognostic factors studied, those that were significantly and independently associated with the increase in cardiovascular mortality were as follows: functional class, third cardiac sound, heart rate, systolic blood pressure, serum creatinine, and cause of heart failure. In the present cohort, the chagasic etiology seems to signal a worse prognosis as compared with ischemic, hypertensive, and dilated heart disease. A specific study to test the hypothesis regarding etiology and mortality should be carried out.

Knowledge and assessment of those findings are clinically useful for the management of patients in the initial phase of heart failure decompensation.

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