Original Article

Predictors of In-hospital Lethality in Patients with Advanced Heart Failure

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Objectives

Describe the clinical characteristics and identify potential risk factors for in-hospital lethality in patients with decompensated heart failure admitted to an intensive care unit.

Methods

Decompensated heart failure patients consecutively admitted to an intensive care unit between June 2001 and December 2003 were selected and followed during hospitalization until discharge or death. Clinical characteristics at admission were recorded and evaluated as independent risk predictors for in-hospital mortality by multiple logistic regression analysis.

Results

A total of 299 patients (69±13 years of age and 54% men) were enrolled. Coronary artery disease was the main cause of heart failure in 49% of the cases. Diabetes mellitus and systemic arterial hypertension occurred in 37.5% and 78% of the patients, respectively. At admission, 22% of them had atrial fibrillation, 21.5% had renal dysfunction, and 48% anemia (16.5% with severe anemia). Severe systolic dysfunction (left ventricular ejection fraction <30%) affected 44% of the patients. In-hospital mortality was 17.4%. After the multivariate analysis had been performed, previous history of stroke, atrial fibrillation, renal failure, age > 70 years, and hyponatremia were independently associated with in-hospital mortality.

Conclusion

Patients admitted to an intensive care unit due to decompensated heart failure have high in-hospital lethality. In this study, variables recorded at admission, such as previous stroke, atrial fibrillation, hyponatremia, renal failure, and age > 70 years were predictors of in-hospital lethality.

Key words

Heart failure, epidemiology, in-hospital lethality, predictors.

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Heart failure is a disease of high prevalence that has a great impact on morbidity and mortality worldwide, particularly among elderly people[1]. Long-term prognosis is still poor, with a five-year survival rate below 50%[1,2]. According to DATASUS, 340,000 people were hospitalized due to heart failure in Brazil during 2004, accounting for 28% of all hospital admissions due to cardiovascular diseases and 3% of all-cause hospitalizations[3].

Most observational studies that evaluate patients admitted for heart failure are restricted to single centers or based on small samples. Distinct clinical manifestations and different prognostic markers have been described for those patients with severe heart failure compared to those who have milder forms of the disease. For instance, the left ventricular ejection fraction does not seem to affect the prognosis of patients with advanced heart failure, contrary to what happens with individuals with mild-to-moderate forms of the disease[4,5].

It is possible that advances in clinical and surgical therapy for heart failure[6], as well as aging of the population, may contribute to increase the rate of hospital admissions of more advanced cases of the disease, which can be further aggravated by other concurrent chronic diseases. The evaluation of patients with severe heart failure, such as those who are admitted to intensive care units, is necessary and consistent with today's needs.

The objectives of this study are to describe clinical characteristics and identify predictors of in-hospital lethality among patients with decompensated heart failure admitted to an intensive care unit in the city of Salvador, state of Bahia.

Methods

Study design and sample - Ours is a prospective cohort study consisting of decompensated heart failure patients consecutively admitted to the intensive care unit of a tertiary hospital in Salvador, Bahia, between June 2001 and December 2003. The diagnosis of heart failure was made based on a suggestive clinical history (worsening dyspnea or resting dyspnea) and signs of pulmonary congestion or peripheral edema, as per established criteria[7]. When deemed necessary, results of ancillary tests (chest X-ray, echocardiogram) were also used to establish the diagnosis of the syndrome. Patients needed to have been hospitalized at least once during the previous year due to decompensated heart failure to be considered as chronic patients. Follow-up corresponded to the total number of days of hospital stay, since patients were followed from ICU discharge through hospital discharge. Patients with a definitive diagnosis of acute myocardial infarction with ST-segment elevation were excluded from the study.

Data source - Information was obtained through consultation of medical records. Data were also obtained by directly interviewing the patient or a family member. When necessary, the ICU cardiologist or the patient's physician were also consulted. Data were collected by means of a questionnaire specifically developed for this study, including variables on demographics, clinical aspects, ancillary tests, and therapy employed, besides information about the patient's clinical progression in the hospital up until discharge or death. This research project is in accordance with the Declaration of Helsinki guidelines[8] and was approved by the Research Ethics Committee of the institution. Before patients were enrolled in the study, they were asked to sign the informed consent form.

Ancillary tests - The twelve-lead electrocardiogram (ECG) and laboratory test results used for analysis were those obtained at admission. Laboratory tests included serum electrolytes, urea, creatinine, and glucose, as well as a complete blood count. Two hundred and ninety-six patients (99%) underwent echocardiograms during hospitalization in order to evaluate heart chambers and left ventricular systolic and diastolic functions. Coronary angiography was performed according to the hospital's standard procedures, as were the other ancillary tests.

Definition of variables - Heart failure etiologies were defined as follows[9,10]**:** a) ischemic cardiopathy due to previous myocardial infarction, angina pectoris, previous coronary revascularization by percutaneous angioplasty or surgery, or critical artery block in epicardial branches detected by coronoriography; b) hypertensive cardiopathy, defined as a long-term history of systemic arterial hypertension with poor blood pressure control or long-term use of antihypertensive drugs, associated with myocardial hypertrophy identified by electrocardiogram or echocardiogram; c) valvular cardiopathy defined as a history of previous valvular disease or based on echocardiogram results; d) Chagas' disease, defined by positive serum tests; e) idiopathic myocarditis, with ventricular dilation and dysfunction in the absence of any other evident cause; f) viral myocarditis detected by the presence of left ventricular dysfunction and transient inflammatory abnormalities detected by myocardial scintigraphy with gallium-67 or endomyocardial biopsies. Comorbidities were defined as per clinical history, use of specific medications, or results of ancillary tests.

Acute renal failure during hospitalization was defined as a serum level of creatinine ≥1.4 mg/dL in patients with normal baseline values, or an increase of at least 0.5 mg/dL in patients with serum creatinine greater than 1.4 mg/dL at admission.

Left ventricular ejection fraction was measured by M-mode echocardiography using Teichholz's formula or Simpson's modified formula for end left ventricular systolic and diastolic diameters, at the apical two-chamber view. Values of the left ventricular ejection fraction were recorded at the following intervals: >55% or normal systolic function, 45-55% or mild systolic dysfunction, 30-44% or moderate systolic dysfunction,

and <30% or severe systolic dysfunction. Left ventricular diameters were measured in the parasternal views, and left ventricular dilation was considered present when the final diastolic diameter was >56mm. Heart failure with preserved left ventricular systolic function was defined as left ventricular ejection fraction ≥45%. The diastolic function was evaluated by measurements of the early transmitral velocity (E wave) and late (A wave), the E/A ratio, and by the E wave desacceleration time, and classified according to the following standards: normal, altered ventricular relaxation, pseudonormalization, and restrictive filling pattern[11].

Continuous variables were converted into categorical variables for statistical analysis and stratified as follows: age (>70 and ≤70 years), serum creatinine (<1.8 and ≥1.8 mg/dL), and serum sodium (Na) (<136 and ≥136 mEq/L). The presence of anemia was defined by criterion established by the World Health Organization (WHO)[12]: hemoglobin (Hb) <13.0 g/dL for men and Hb <12.0 g/dL for women. For bivariate and multivariate analysis purposes, patients were a part of the "at risk" subgroup when they had lower levels of Hb, corresponding to the 20th percentile of the sample (Hb <11.0 g/dL for men and Hb <10.0 g/dL for women), and were called "severe anemia" patients. This resulted from the fact that, as the sample consisted of critically ill patients, prevalence of anemia was expected to be very high (according to the WHO criterion), making it difficult to detect possible differences between the groups of anemic and nonanemic patients, if any.

Statistical analysis - Continuous variables were described as means ± standard deviations and compared by the Student's t-test for independent samples. Categorical variables were described as ratios and compared by the chi-square or Fisher's exact tests. Bivariate analyses between clinical/laboratorial variables and in-hospital deaths were made for gross estimates (relative risk) and their respective 95% confidence intervals (CI). Exploratory multivariate analysis by the logistic regression models was used to determine potential independent risk factors for in-hospital lethality. Hospital admission variables were selected for the exploratory logistic model provided they were associated with in-hospital death, at a <10% significance level in the bivariate analysis. The significance level (p value) for all other associations was defined as 5% for two-tailed hypotheses. SPSS software, version 10, was used for the analyses.

Results

Clinical and electrocardiographic characteristics - Two hundred and ninety-nine patients were evaluated. Table 1 shows the main clinical and demographic characteristics. Patients were elderly (mean age 69±13 years), and ischemic cardiopathy was the leading cause of heart failure in nearly half of the cases. Systemic arterial hypertension was observed in 78% of the patients, previous stroke in 15%, atrial fibrillation in 22% and diabetes in 37% of the patients. Most patients had resting dyspnea at admission, and 9% of them had low cardiac output syndrome.

Diabetes mellitus was most common among patients with ischemic etiology. In patients under 60 years of age, this association was stronger, with a prevalence ratio for diabetes equal to 3.6 (CI 95% 1.9-6.9) when comparing ischemic and nonischemic patients. Individuals with left ventricular ejection fraction <30% had broader QRS complexes (60% versus 37%; p <0.001), and higher frequency of total left bundle branch block (32% versus 19%), when compared to patients with ejection fraction ≥30%.

Echocardiographic results - Two hundred and ninety-six patients underwent echocardiogram. Table 1 displays main results. Severe left ventricular systolic dysfunction affected 44% of the patients, whereas 34% of them had heart failure with preserved systolic function. Of the individuals with valvular dysfunction, 80% had moderate-to-severe mitral regurgitation.

Laboratory findings - Abnormal laboratory results at admission were frequent. Forty-eight percent of the patients in the total sample had anemia, 43% males and

Table 1- Overall Characteristics

	N	%
Age (years)		
Mean ± SD	69±13	
>70	144	48.5
Male	163	54.5
Etiology		
Ischemic	147	49.2
Systemic arterial hypertension	77	25.8
Valvular	35	11.7
Chagas' disease	29	9.7
Idiopathic	9	3.0
Viral	3	0.7
Coronary artery disease	175	58.5
Hypertension	233	77.9
Diabetes mellitus	112	37.5
Previous stroke	46	15.4
Renal dysfunction at admission	137	45.9
Previous venous thromboembolism	24	8.0
Functional class IV (NYHA) at admission	229	76.5
Atrial fibrillation*	65	22.0
QRS ≥ 120 msec*	135	47.4
Anemia at admission (WHO)	144	48.0
Severe anemia	49	16.5
Total left bundle branch block*	62	22.0
Systolic dysfunction		
Moderate	64	21.6
Severe	131	44.2
Heart failure with systolic function preserved	101	34.1
Left ventricle dilation	223	76.4

*NYHA - New York Heart Association; * Electrocardiogram at admission; WHO - World Health Organization; # Hemoglobin <10.0 g/dL for women and <11.0 g/dL for men*

53% females (p=0.09). Severe anemia affected 16.5% of the cases. Abnormal serum potassium levels were found in 13%, and hyponatremia was present in 21% of the cases, with 34% of them showing levels below 130mEq/L. Increased levels of creatinine were found in 21.5% (65 cases).

In-hospital events - Pulmonary embolism was detected in 15% of the patients, sepsis in 5.7%, and acute stroke in 4% of the cases during hospitalization. Acute renal failure developed in 42% of the patients.

In-hospital lethality was 17.4%. Patients who died were, on average, older than those who survived their hospital stay (73±12 years versus 69±13 years; p=0.03). In the bivariate analysis, some variables (p<0.05) were associated with higher risks of death and included a prior stroke; atrial fibrillation, increased levels of creatinine (≥1.8mg/dL), and severe anemia at admission; left ventricular dilation; moderate-to-severe valvular dysfunction (80% corresponded to mitral insufficiency); acute renal failure and stroke during current hospitalization. The analysis of age as a categorical variable (>70 and ≤ 70 years) identified a statistically significant correlation between advanced age and death (RR=2.0; CI 95% 1.2-3.5). Severe hyponatremia at admission increased the risk of in-hospital death, although at a marginal significance level (RR=2.0; CI 95% 1.1-3.9; p=0.07). The use of vasoactive amines during hospitalization showed a strong association with lethality (RR=20.3; CI 95% 9.0-45.7). Left ventricular ejection fraction, gender, and ischemic etiology did not have a statistically significant association with in-hospital lethality in this cohort of advanced heart failure patients.

Multivariate analysis - Table 2 displays the results of the multiple logistic regression analysis. Among variables recorded at admission, the potential independent predictors of in-hospital lethality were**:** previous history of stroke (RR=2.55; CI 95% 1.17-5.55), serum creatinine ≥1.8mg/dL (RR=2.27; CI 95% 1.13-4.54), atrial fibrillation (RR=2.18; CI 95%1.09-4.36), age >70 years (RR=1.92; CI 95%1.00-3.70), and hyponatremia (RR=3.06; CI 95%1.08-8.67). The presence of severe anemia, although associated with a higher risk for in-hospital death (RR=2.02) after the adjustment, was not confirmed as an independent predictor of lethality at a statistical significance level of 5%.

Discussion

This study involving severe heart failure patients admitted to an intensive care unit showed that previous history of stroke, renal failure and hyponatremia at admission, age >70 years, and atrial fibrillation on the initial ECG are potential independent predictors of in-hospital lethality. A high prevalence of women, elderly patients, and comorbidities such as *diabetes mellitus*, systemic arterial hypertension, and renal failure was observed. It is worth mentioning that advanced heart failure was defined primarily according to clinical criteria, associated with the need for admittance to the intensive care unit.

Studies involving patients with severe heart failure are scarce, and are generally retrospective and based on samples of individuals included in programs for heart transplantation[5,13]. Patients selected for transplantation, although almost always in terminal stages of heart failure, are younger and meet very strict inclusion criteria. Consequently, it is possible that the results in this study may give a more appropriate representation of the patients with advanced heart failure seen in clinical settings.

Patient characteristics - As previously mentioned, the average age of patients in this study was high, with a large percentage of females. Previous trials have shown that women with heart failure are older than men, and have a greater frequency of preserved left ventricular systolic function[14-18]. This study also found a high proportion (1/3 of all cases) of heart failure cases with preserved systolic function, that probably is a result of the profile of our sample. In this aspect, some studies have shown conflicting results, generally due to different inclusion criteria employed in selecting heart failure patients. For instance, the EPICAL study[9] evaluated a sample of patients with advanced heart failure that was primarily defined by the presence of severe left ventricular systolic dysfunction (ejection fraction <30%). This resulted in a selection of younger patients, most of whom (75%) were men. Randomized clinical assays about heart failure, on the other hand, also tend to select samples with small numbers of female patients (usually below 20%)[18], which is not consistent with the reality in clinical practice. Generalization of its results is, therefore, restricted to the subgroup of women. The findings in this observational study seem to portray a better picture of the population of patients with heart failure seen and admitted to hospitals due to their cardiopathies.

Table 2 – Exploratory Multivariate Analysis for In-hospital Lethality

Characteristics at admission	*Odds Ratio*	Confidence Interval (95%)	p value
Previous stroke	2.40	1.09 - 5.29	0.03
Atrial fibrillation	2.35	1.17 - 4.72	0.02
Hyponatremia (Na<130 mEq/L)	2.88	1.01 - 8.22	0.05
Renal failure (C‡≥1.8 mg/dL)	2.27	1.13 - 4.54	0.02
Age > 70 years	1.92	1.00 - 3.70	0.05
Severe anemia*	2.02	0.96 - 4.25	0.06

C=creatinine; # Hemoglobin <10.0 g/dL for women and <11.0 g/dL for men.

Similar to previous studies[14,16], coronary artery disease was the leading cause of heart failure in this sample, followed by hypertensive cardiopathy. Chagas' disease, although reported as the primary etiology of heart failure in 1/3 of all cases in Brazil[19], accounted for just 10% of the cases in this study. On the other hand, this is in agreement with the findings of Barreto et al[20], who conducted a cross-section study with heart failure patients admitted to the *Instituto do Coração (INCOR)*, in São Paulo. The prevalence of chagasic miocardiopathy was just 6%. It is interesting to note that currently, in two of the largest cities in Brazil (São Paulo and Salvador), Chagas' disease does not seem do play an important role in the etiology of heart failure, probably as a reflection of epidemiological changes that took place in our country during the past decades, particularly the control of the vectorial transmission of the infection.

Comorbidities were frequently observed in this sample. Systemic arterial hypertension was present in almost 80% of all cases. *Diabetes mellitus* was detected in 38%, and 15% of the patients had a previous history of stroke. Chronic diseases are more frequently seen in older patients[21,22], as in this sample. Likewise, hypertension and diabetes are part of heart failure etiologies with preservation of systolic function, mainly among older women[17,23,14], characteristics that also match the profile of the population we analyzed. The prevalence of diabetes is higher among patients with ischemic heart failure than in those with nonischemic etiology[9]. In this study, there was a positive association between *diabetes mellitus* and ischemic etiology. This association was stronger among patients <60 years of age, which may partially explain the presence of such severe heart disease in a group of younger patients. The prevalence of atrial fibrillation, higher in the male group, was compatible with the findings in other studies[14,20] and probably reflects the presence of older patients and the greater severity of the cardiopathy in this sample. QRS widening (>120m/sec) was quite frequent, affecting almost half of all patients. Similar results have already been described[25], probably associated with a smaller left ventricular ejection fraction. In this study, 44% of the patients had an ejection fraction <30%, which justifies the prolonged duration of the QRS complex, since the more severe the myocardial dysfunction, the slower the ventricular activation.

Changes in the diastolic function were found in 90% of the 248 patients who were evaluated for this purpose. Of these, 21% had a normal systolic function. This is an interesting finding that differs from the results in previous studies that almost always associate advanced heart failure with severe systolic dysfunction[26,27]. The primarily clinical definition for advanced heart failure adopted in this study, as well as the high frequency among women in this sample, may explain this finding. Indeed, there is evidence that the severity of the clinical manifestation of heart failure is not necessarily related to the degree of systolic dysfunction[28].

Anemia, hyponatremia, and increased urea and creatinine serum levels were frequent findings at admission. These factors are currently recognized as predictors of long-term poor prognosis in patients with severe heart failure[29-31]. However, the short-term prognostic role of these variables has not yet been established.

Incidence of hospital outcomes - In-hospital lethality was 17.4%. This concurs with the results of other studies involving patients admitted to hospital due to heart failure[20,32-35] in whom lethality rates vary from 6.4%[32] to 23.4%[33]. In Brazilian public institutions, in-hospital lethality due to heart failure is 7.5%[3]. Although the current sample comes from a reference hospital belonging to the network of private institutions in which all cardiac patients receive specific treatment and care, probably according to updated and adequate disease management strategies, these patients had severe heart failure and needed to be initially admitted to an intensive care unit. This may well explain the higher in-hospital lethality in this study. On the other hand, since heart failure is a disease that is clinically diagnosed, classification errors in both directions (diagnosing people who do not have the disease or giving another diagnosis to those who do have heart failure) may happen more frequently in general and public network hospitals, which is not the case of this institution. It is possible that in this study the frequency of diagnostic errors may be lower, thus increasing the reliability of the values found.

Among the other hospital outcomes observed, the high incidence of acute renal failure (42%) and of pulmonary embolism (15%) stands out. The severity of cardiopathy and the large proportion of elderly patients in this study may explain these findings.

Multivariate analysis of risk factors for in-hospital lethality - In this study, the independent predictors for in-hospital lethality recorded at admission were: previous history of stroke, atrial fibrillation, age >70 years, hyponatremia, and high levels of serum creatinine. Although the prognostic role of all these characteristics has already been recognized for long-term outcomes in heart failure[9,29-31,36,37], the description of their potential risk in increasing early lethality during hospitalization is a novel result.

Previous history of stroke and atrial fibrillation at admission were associated with the reduction of late survival in patients who were discharged after their first hospitalization due to heart failure[37]. Other studies have shown controversial results as to the role of atrial fibrillation in patients with heart failure. In some of them, the presence of atrial fibrillation at admission was not independently associated with higher risk of mortality[38-40] or morbidity[38-41] after hospital discharge in patients with advanced heart failure. On the other hand, in the retrospective analysis of the SOLVD study[42] involving symptomatic and asymptomatic patients with severe left ventricular systolic dysfunction, the authors described a

significant and independent increase in the risk of death by progression of heart failure and of total death in the subgroup with atrial fibrillation at admission.

Severe hyponatremia and renal dysfunction have been recognized as some of the most important prognostic markers of long-term survival in patients with heart failure[43]. These two metabolic changes may result from the seriousness of the cardiopathy, as well as they may aggravate heart failure manifestations in critically ill patients. In any case, this study raises the possibility that these laboratory characteristics may help identify, at the very time of hospital admission, a subgroup of patients with an even higher risk of early lethality.

The role of age in the prognosis of heart failure has already been evaluated in several studies. In the EPICAL study[9], individuals between 70 and 80 years of age had an independent risk of death 50% higher than those <70 years of age. In this study, older patients also maintained a higher risk of in-hospital lethality after multivariate analysis with a borderline statistical significance level, since the 95% confidence interval of this association included the unit. This may be a problem related to the size of the sample, however there are other studies conducted with severe heart failure patients who did not show that advanced age was an independent risk factor for mortality[4,5,44-46].

In previous studies, anemia has been associated with lower late survival rates in patients with severe left ventricular systolic dysfunction (ejection fraction <35%) and New York Heart Association functional class I to IV[29-31]. In the same way, the presence of even relatively mild degrees of anemia was associated with a worsening of symptoms and higher readmission rates in patients with moderate-to-severe heart failure[29]. From a statistical point of view, this study was not able to demonstrate anemia, even at a more significant level, as an independent risk factor for reducing in-hospital survival of patients with advanced cardiac failure. It is possible that our study did not have the sufficient power to detect this association. The fact that we included patients with milder anemia in the group of nonanemic patients (taking in consideration the WHO criterion) may have contributed to this. Important clinical factors generally associated with the worst prognosis in heart failure, such as reduced left ventricular ejection fraction and ischemic etiology, were not significantly associated with death in this study, even in the bivariate analysis. The fact that we are measuring such an early outcome in a sample of patients with severe disease may justify the absence of these associations. Differences in the prognostic role of variables in heart failure have already been recognized. Left ventricular ejection fraction, for instance, is associated with lower late survival rates in patients with mild-to-moderate forms of heart failure, but not in the subgroup with the severe form of the disease[4,5]. Concerning the ischemic etiology, information available is still contradictory. Patients with ischemic heart failure have been associated with a worse prognosis[9,47-50], comparable[51] or even better[14] than patients with nonischemic heart failure.

Conclusion

In this sample of patients with heart failure admitted to an intensive care unit, the following admission characteristics were capable of independently predicting a higher level of in-hospital lethality: atrial fibrillation, severe hyponatremia, previous history of stroke, advanced age, and renal dysfunction. Patients with advanced heart failure (stages C and D[52,53]) not included in heart transplantation programs deserve special attention in relation to those with heart failure that are seen in ambulatory settings, since their clinical profile and prognostic factors may present peculiarities that have not been observed in previous studies.

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