The Management, Early and One Year Outcome in Hospitalized Patients with Heart Failure: A National Heart Failure Survey in Israel – HFSIS 2003*

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Key words: heart failure, prognosis, one year mortality

Abstract

Background: Despite improved management of heart failure patients, their prognosis remains poor.

Objectives: To characterize hospitalized HF patients and to identify factors that may affect their short and long-term outcome in a national prospective survey.

Methods: We recorded stages B-D according to the American College of Cardiology/American Heart Association definition of HF patients hospitalized in internal medicine and cardiology departments in all 25 public hospitals in Israel.

Results: During March-April 2003, 4102 consecutive patients were recorded. Their mean age was 73 ± 12 years and 57% were males; 75.3% were hypertensive, 50% diabetic and 59% dyslipidemic; 82% had coronary artery disease, 33% atrial fibrillation, 41% renal failure (creatinine ≥ 1.5 mg/dl), and 49% anemia (hemoglobin ≤ 12 g/dl). Mortality rates were 4.7% in-hospital, 7.6% at 30 days, 18.7% at 6 months and 28.1% at 12 months. Multiple logistic regression analysis revealed that increased 1 year mortality rate was associated with NYHA III–IV (odds ratio 2.07, 95% confidence interval 1.78–2.41), age (for 10 year increment) (OR 1.41, 95% CI 1.31–1.52), renal failure (1.79, 1.53–2.09), anemia (1.50, 1.29–1.75), stroke (1.50, 1.21–1.85), chronic obstructive pulmonary disease (1.25, 1.04–1.50) and atrial fibrillation (1.20, 1.02–1.40).

Conclusions: This nationwide heart failure survey indicates a high risk of long-term mortality and the urgent need to develop more effective management strategies for patients with heart failure discharged from hospitals.

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Heart failure is an increased burden on healthcare systems. The prevalence of HF increases with age and is estimated at 0.4–2.5% [1-4]. In the United States HF diagnosis at discharge (DRG, diagnosis-related groups) ranks first among patients aged 65 and older, and fourth among all patients. Fifty percent of HF patients are > 65 years old [5]. The annual mortality from HF as a primary or contributory cause is about 300,000 deaths [4].

Two large surveys in hospitalized HF patients were recently published. The EuroHF was conducted in most countries in Europe but included only a few hospitals in each country [5,6]. The ADHERE survey focused on patients with acute decompensated heart failure in 275 hospitals in the USA [7-9]. While these studies provided short-term outcome reports, long-term outcome results are not available.

The Heart Failure Survey in Israel – HFSIS 2003 was the first national prospective survey with the purpose of characterizing the clinical profile of consecutive symptomatic as well as asymptomatic hospitalized HF patients, evaluating their management, and assessing their early and long-term outcome.

* This survey was conducted cooperatively by: the Israel Society of Internal Medicine, the Israel Heart Society, the Working Group on Heart Failure, and the Israel Center for Disease Control (ICDC), Ministry of Health – under the auspices of the Israel Medical Association. Data processing and analysis was conducted by the Israel Society for Prevention of Heart Attacks (ISPHA).

HF = heart failure
OR = odds ratio
CI = confidence interval

Patients and Methods

Heart failure definition

Heart failure was defined according to the American College of Cardiology/American Heart Association staging system [3]: A. Patients at high risk for developing HF, but without structural heart disease or HF symptoms; B. Patients with structural heart disease, but without HF symptoms; C. Patients with structural heart disease with prior or current symptoms of HF; D. Refractory HF patients who require specialized interventions.

Study population

The patients in this cohort were derived from a prospective nationwide survey conducted during March–April 2003 in 93 of 98 internal medicine departments and 24 of 25 cardiology departments in all 25 public hospitals in Israel. Included in the study were heart failure patients with stages B-D according to the ACC/AHA definition [3].

Heart failure diagnosis

Heart failure was diagnosed by the local survey team according to the following: a) clinical presentation (symptoms/physical examination), b) chest X-ray, c) echocardiography, d) radionuclide study, and e) cardiac catheterization. Results of echocardiography, radionuclide scintigraphy and catheterization findings were obtained either during or within the 6 months prior to the index hospitalization, unless the patient had a recent cardiac insult. Patients were included in our survey irrespective of whether HF was the reason for hospitalization or their main complaint. Asymptomatic HF patients (stage B) with abnormal echocardiography were included.

Heart failure was classified according to HF discharge diagnosis: 1. Main (primary) diagnosis; 2. Secondary diagnosis; 3. Past diagnosis, currently inactive. For analysis purposes, diagnoses 2 and 3 were combined as "secondary diagnosis." Heart failure was also defined as: 1. Acute HF, 2. Exacerbation of chronic HF, 3. Chronic HF. For analysis, 1 and 2 were also combined as acute HF.

Detailed data on patients' characteristics, in-hospital course, and management were collected and recorded on pre-specified structured forms. Mortality during the first year after the index hospitalization was assessed in 99% of patients by matching their identification numbers with the Israeli registry. The protocol was approved by the ethics committee at each of the participating hospitals.

Statistical analysis

All analyses were performed using SAS software. The chi-square and *t*-test were used to determine the significance of the differences between proportions and means, respectively. Medications on admission and at discharge were compared using categorical data modeling for repeated measurement analyses (PROC CATMOD). Multivariate stepwise logistic regression analyses (SAS LOGISTIC Procedure) were performed to examine variables independently associated with in-hospital and 1 year mortality. The results are reported in terms of odds ratio with 95% confidence interval.

ACC = American College of Cardiology

Table 1. Patients' characteristics

	N (n=4102)	%
Male gender	2338	57.0
Age (yrs), mean ± SD	73.4 ± 12.2	
Male	71.5 ± 12.4	
Female	75.9 ± 11.4	
≤ 50	187	4.8
51–65	725	17.7
66–75	1150	28.0
> 75	2030	49.5
Hypertension	3088	75.3
Diabetes mellitus	2050	50.0
Dyslipidemia	2403	58.6
Obesity	949	23.1
Current smoking	417	10.2
Coronary artery disease	3372	82.2
Acute coronary syndrome	1505	36.7
Valvular heart disease	1473	35.9
Cardiomyopathy, non-ischemic	565	13.8
Atrial fibrillation	1360	33.2
Renal failure (creatinine ≥ 1.5 mg/dl)	1672	40.8
Anemia (hemoglobin ≤12 g/dl)	2026	49.4
Chronic obstructive pulmonary disease	803	19.6
Stroke/transient ischemic attack	511	12.5

Results

During March–April 2003, 4514 hospitalizations of 4102 consecutive unselected HF patients in stages B-D were recorded. The majority of patients (79.3%) were hospitalized in internal medicine departments, 18.6% in cardiology wards, and 2.1% were transferred from other departments. The mean hospitalization duration was 5.9 ± 6.0 days, while the median was 4 days (25%–75%, range 3–7 days). Table 1 presents the patients' clinical characteristics. Mean age was 73.4 ± 12.2 years and 57% were males; 75.3% were hypertensive (defined by the local treating team or recorded blood pressure ≥ 140/90 mmHg), 50% were diabetic and 58.6% were dyslipidemic; 82.2% had coronary artery disease, 36.7% acute coronary syndrome, 41% renal failure (creatinine ≥ 1.5 mg/dl), 49.4% anemia (hemoglobin ≤ 12 g/dl), and 33% atrial fibrillation.

Functional class

Patients' pre-hospitalization New York Heart Association functional class was as follows: I – 798 patients (19.9%), II – 1572 (39.3%), III – 1276 (31.7%) and IV – 362 (9.0%). Killip classification was used to describe not only acute myocardial infarction patients on admission, but all HF patients during the entire hospitalization course. Our patients' Killip class was: I – 905 patients (22.0%), II – 1443 (35.2%), III – 1527 (37.2%) and IV – 224 (5.4%). Acute HF of new onset or acute exacerbation of chronic

AHA = American Heart Association

HF occurred in 18.1% and 40.2%, respectively, while chronic HF occurred in 41.7% of the patients.

Echocardiographic findings

Echocardiography was performed in 3236 patients (78.9%). Left ventricular ejection fraction measurement was available in 2845 patients (69.4%). Preserved LVEF (≥ 40%) was recorded in 47.9%, of whom 763 patients (26.8% of all patients) had normal LVEF (≥ 50%). Reduced LVEF (< 40%) was recorded in 52.1%, of whom markedly reduced LVEF (< 30%) was noted in 743 patients (26.1%).

In-hospital treatment

During hospitalization 60.4% of the patients were treated with intravenous furosemide, 10.5% with IV vasodilators, 6.9% with blood transfusions, 6.8% with positive inotrops, and 1.7% with dialysis. Swan Ganz catheter was inserted only in 11 patients (0.3%).

Pre-hospital and discharge medications

Figure 1 presents pre-hospital and discharge medications. Diuretics were the most common discharge medication used (75.4%) with a 10% absolute increase from admission; furosemide use (73.2%) was increased by 11.2% and thiazides (5.1%) declined by 1.0%. The index hospitalization was associated with a significant increase in the use of angiotensin-converting enzyme inhibitors (6.6%), angiotensin receptor blockers (0.8%), beta-blockers (7.8%), aldosterone antagonists (4.8%), anticoagulants (3.7%) and statins (4.1%). The use of antiplatelets was increased by 8.0% (aspirin by 7.4% and clopidogrel by 6.4%). Digoxin use increased slightly (0.7%), whereas the use of calcium channel blockers declined by 1.5%. At discharge, 263 patients (6.7%) had a permanent pacemaker and 106 (2.7%) an implantable cardiodefibrillator. Almost all these devices had been implanted prior to the index hospitalization.

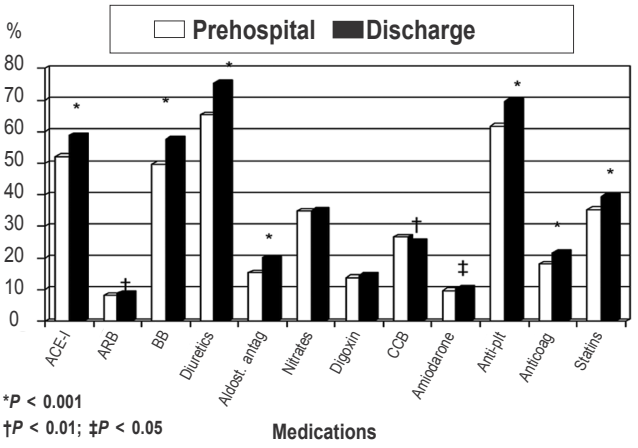

Figure 1. Medications prescribed pre-admission and at discharge

Mortality data

In-hospital mortality was 4.7% and 30 day mortality 7.6%. Variables associated with increased in-hospital mortality (by multivariate stepwise logistic regression analysis) were: renal failure (OR 2.95, 95% CI 2.11–4.16), NYHA class III–IV (2.59, 1.85–3.66), female gender (1.98, 1.43–2.74), hospitalization in coronary care unit/cardiology (1.80, 1.19–2.67), stroke/transient ischemic attack (1.63, 1.07–2.43) and age (10 years increment) (1.39, 1.19–1.63). On the other hand, hypertension (0.52, 0.37–0.73) and primary HF diagnosis (0.65, 0.47–0.90) were associated with improved in-hospital survival.

Despite relatively low early mortality, late mortality thereafter was high: 18.7% at 6 months and 28.1% at 1 year. One year mortality was similar in patients with acute or exacerbation of chronic HF versus chronic HF patients (29.2% vs. 27.4% respectively, age-adjusted OR 1.07 (95% CI 0.93–1.23), and among patients with primary HF diagnosis versus patients with secondary HF diagnosis (30.0% vs. 26.4%, respectively, age-adjusted OR 1.09, 95% CI 0.95–1.26).

The following variables were found to be associated with increased 1 year mortality: NYHA III–IV (OR 2.07, 95% CI 1.78–2.41), renal failure (1.79, 1.53–2.09), anemia (1.50, 1.29–1.75), stroke (1.50, 1.21–1.85), age (10 year increment) (1.41, 1.31–1.52), chronic obstructive pulmonary disease (1.25, 1.04–1.50) and atrial fibrillation (1.20, 1.02–1.40). In contrast, hypertension (0.65, 0.54–0.77) and hospitalization in coronary care unit/cardiology department (0.79, 0.63–0.98) were associated with decreased 1 year mortality [Figure 2A]. Prescription of ACE inhibitors, angiotensin receptor blockers, beta-blockers and calcium channel blockers (borderline) were associated with improved outcome, whereas diuretics, spironolactone and digoxin use were associated with detrimental 1

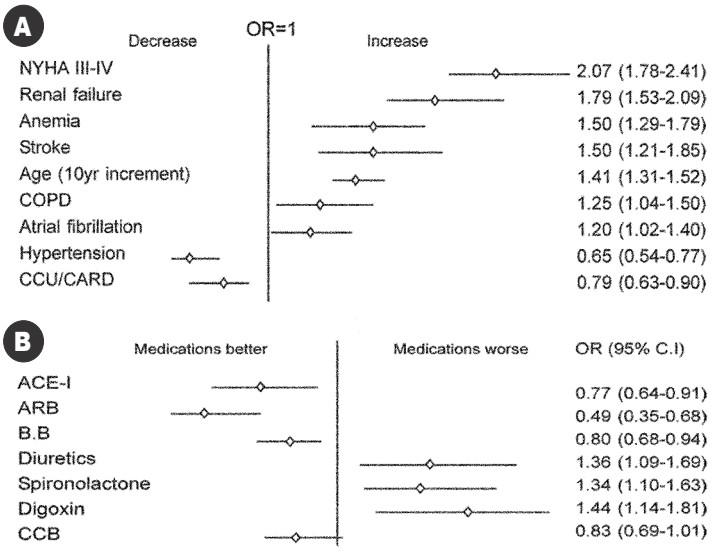

Figure 2. Parameters associated with 1 year mortality (by multivariate analysis). **[A]** Clinical, **[B]** Medications prescribed at discharge

LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
ACE = angiotensin-converting enzyme

year outcome [Figure 2B]. Aspirin (OR 0.83, 95% CI 0.70–0.99), anticoagulants (0.63, 0.50–0.80) and statins (0.67, 0.56–0.80) were also associated with reduced mortality.

Discussion

This nationwide survey of hospitalized patients with heart failure that was conducted in all public hospitals in Israel (HFSIS) has provided valuable information on patients' clinical profile and management. This study is the first prospective survey of consecutive hospitalized HF patients that presents long-term outcome. The main finding of this survey was the sharp increase in-hospital mortality from 4.7% to 28.1% at 1 year.

Comparison to ADHERE and EuroHF surveys

The baseline characteristics and the management of patients in HFSIS are similar to those in the EuroHF and ADHERE surveys [5-9] [Table 2]. About half of the patients were 75 years or older and had diabetes mellitus, and most of them had coronary artery disease and hypertension. In-hospital mortality rates were comparable: HFSIS 4.7%, ADHERE 4.2%, and EuroHF 6.9%. Long-term mortality was not available in ADHERE or in EuroHF, which reported only a high 12 week mortality of 13.5%.

Adherence to guidelines in HFSIS was fair. Although almost 80% of the patients in HFSIS underwent recent echo-Doppler study, left ventricular ejection fraction measurement was available only in 70% of the patients. However, the echo-Doppler evaluation rate was higher compared to EuroHF and the Italian IN-CHF database [10]. There was also reasonable adherence to the usage of evidence-based medications in HFSIS, such as ACE inhibitors and/or angiotensin receptor blockers (67%), and beta-blockers (58%), and their use increased during the hospitalization course by 10%.

Long-term mortality

In spite of what seems to be adequate management in the majority of patients, mortality, which was 4.7% in-hospital, sharply increased after patients' discharge to 18.7% at 6 months and 28.1% at 12 months. These high mortality rates, although not available in other prospective surveys, are supported by several retrospective community-based studies [9-15].

Predictors of mortality

The multivariate stepwise logistic regression analysis performed in HFSIS indicates that increased in-hospital mortality was associated with three clusters of parameters: a) presence of co-morbidity, especially renal failure and stroke; b) NYHA class III–IV prior to hospitalization; and c) increased age and female gender. Increased 1 year mortality was associated primarily with: a) the patient's limited functional class; b) presence of co-morbidity, e.g., renal failure, anemia, stroke and chronic obstructive pulmonary disease; and c) increased age but not gender.

These findings are supported by several recent reports indicating as well that co-morbidity, such as renal failure [11,13,14,16,17], stroke [11,13,14], anemia [14,18], and chronic obstructive pulmonary disease [11,13,14], are indeed associated with increased mortality in HF patients.

Table 2. Characteristics, management and outcome in large recent surveys in heart failure

	EuroHF 2000–2001 (%)	ADHERE 2002–2003 (%)	HFSIS 2003 (%)
No. of patients	11,327	105,388	4102
Male gender	53	48	57
Age (yrs)			
Mean	71	72	73
> 75	Females 51, males 30	48	49
Co-morbidity			
Hypertension	53	72	75
Diabetes mellitus	20	44	50
Coronary artery disease	68	58	82
Atrial fibrillation	13	31	33
NYHA classification			
I–II	73	13	59
III–IV	26	87	41
Echocardiography			
Echo performed	66	–	80
LVEF > 40%	55	49	48
Medications			
ACE inhibitors	62	55	59
ARB	4	14	9
Beta-blockers	37	59	58
Mortality			
In-hospital	6.9	4.2	4.7
3 months	13.5	–	13.7
6 months	–	–	18.7
1 year	–	–	28.1

NYHA = New York Heart Association, LVEF = left ventricular ejection fraction, ACE = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker.

Interestingly, hypertension was found to be associated with reduced risk of mortality, a finding corroborated also by Braunstein et al. [11] and Lee et al. [14]. This seemingly paradoxical finding may in fact reflect apparent protective treatment effects of higher use of beta-blockers, ACE inhibitors and angiotensin receptor blockers. Heart failure patients with hypertension more commonly have diastolic dysfunction with preserved left ventricular function, which is associated with a better survival.

Medications

Increased use of current class I clinical guidelines-recommended HF medications, alone or in combination – such as ACE inhibitors, angiotensin receptor blockers, beta-blockers – was associated with a significant reduction in 1 year mortality [1-6,19]. The use of calcium channel blockers, which is not recommended for patients with systolic left ventricular dysfunction, was slightly reduced during hospitalization by 1.5%, and was associated with an approximately 17% borderline significant mortality rate reduction. Surprisingly, aldosterone blockers, known to increase survival – as in the RALES [20] and EPHESUS [21] studies – were given

to only 20% of our patients at discharge, and were associated in HFSIS with a significantly increased adjusted mortality (34%). These results are supported by the recent study of Juurlink and colleagues [22] from Ontario, Canada, reporting increased associated morbidity and mortality compared to the RALES study. Thus, closer laboratory monitoring and more judicious use of aldosterone blockers may reduce the occurrence of this complication. Further randomized trials are needed to verify these clinical observations.

Two commonly used drugs were associated with increased mortality – furosemide (36%), prescribed to 73% of the patients, and digoxin (44%). Since 82% of our patients had coronary artery disease, the use of aspirin, clopidogrel and statins was associated with reduced mortality. It should be emphasized that the mortality data described for several co-morbidities and the usage of various medications are merely associative and by no means imply definitive cause and effect. Our findings should draw attention and need further validation, but they cannot detract survival benefits observed in randomized controlled studies.

Limitations of the study

HFSIS was a prospective observational survey and not a randomized interventional study. Our study was not designed to determine HF incidence or prevalence. The study period March–April does not necessarily reflect the hospitalized HF population during the whole year as seasonal variation may occur. The strength of our report, however, is the nationwide extent of its data, reflecting "real world" practice, thus avoiding selection bias of physicians, facilities or specialized HF programs.

Conclusions and implications

The high mortality rate observed in HFSIS 2003, although currently expected in HF patients in the western world [9-15], is not acceptable. In order to improve outcome it is crucial that we increase the rate and quality of diagnostic workup, and undertake strict measures to target the risk factors of HF and coronary artery disease [23]. Patients who suffer from co-morbidity should receive vigorous management, special attention and additional resources. Treatment during the hospitalization phase and in the community should be delivered by a health professional team trained in the management of this condition [24]. Notwithstanding the fair adherence to guidelines in our survey, there is a need for improvement in applying the recommendations. The guidelines should be designed to include accurate time tables, similar to those that exist for acute myocardial infarction and acute coronary syndrome, including information on when to start each medication, how to reach the recommended dose, and how to detect and treat drug-related complications, as well as when to evaluate etiology, precipitating factors and co-morbidity [24]. Usage of newer modalities, such as cardiac resynchronization therapy, implantable cardiodefibrillator, and ventricular assist device, should be increased [25]. The efficacy of management strategies should be measured by repeated large, national, non-selective prospective surveys [19].

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APPENDIX

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