

Characteristics, Outcomes, and Predictors of In-Hospital Mortality in Patients Hospitalized with Acute Systolic Heart Failure (HFrEF): Two-Center Registry of Acute Heart Failure from Iran

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ABSTRACT

Background: Acute Heart Failure (AHF) is a common cause of hospitalization in many countries. Rehospitalization due to AHF is also a very important economic issue for health services. Registries for AHF have been made in many countries to characterize such patients, which have provided great information about these patients for better care. To date, there is insufficient information about these patients in Iran and their rehospitalization and short- and long-term follow-up is unclear.

Objectives: This study aims to describe the results of a small registry of AHF (HFrEF) patients in Iran and their short-term follow-up.

Patients and Methods: This study aimed to describe the earliest results of the AHF registry, which was started from September 2015 in two hospitals (Afshar Heart Center in Yazd and Rajaie Heart Center in Tehran). All patients with diagnosis of AHF and HFrEF were enrolled into this registry. During six months, 352 patients with diagnosis of AHF and HFrEF were entered into this registry. The patients' demographic, clinical, and Para clinical data were collected during hospitalization and they were followed up for all-cause mortality and hospitalization for three months. Patients suffering from heart failure with preserved ejection fraction were excluded because of their small number and incomplete data.

Results: The mean age of the patients was 55 ± 16 years and 76% were male. Besides, 77% of the patients had acute decompensation of chronic heart failure and 17% had new-onset AHF. Etiology of heart failure was ischemic heart disease in 52% of the patients. Additionally, the mean left ventricular ejection fraction was 20%. Moreover, length of hospital stay was 10.5 ± 10 days and in-hospital mortality rate was 9.7%.

Conclusions: This small and limited registry of patients with AHF (HFrEF) in Iran delineated these patients' characteristics with some discrepancies and similarities with western registries. Thus, a larger nationwide registry is needed for further clarification of the issue.

1. Background

Heart Failure (HF) is a major cause of morbidity and mortality worldwide, which significantly reduces life quality and longevity and increases healthcare costs (1-3). There are multiple large registries for Acute Heart

Failure (AHF) in western and industrialized countries (4-9). However, there is limited published information about epidemiology and outcomes of patients with HF in Iran. The ADHERE registry in the U.S. is the largest registry of AHF in the world that has provided great information about these patients (4). These registries aim at evaluation of information about patients' demographic data, hospital course, in-hospital mortality, and rehospitalization and

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assessment of the relationship between mortality and rehospitalization and other variables.

Generally, there are some differences between Iranian people and those in developed countries regarding lifestyle, nutrition, and economic issues. Thus, studies have to be performed on the issue to identify similarities with and differences from other studies in this field. These differences provide information about how clinical guidelines from Western countries are used in Iran and whether these guidelines can be applied to Iranian patients.

2. Objectives

This study aims to clarify the patients' characteristics and outcomes in Iran, identify similarities and differences in comparison to other studies, and point out some prognostic factors.

3. Patients and Methods

Rajaie and Afshar HF registry is a prospective observational cohort study, which was started in Rajaie Heart Center and Afshar Heart Center, Iran from September 2015 and is currently under way in these centers. Rajaie Heart Center located in Tehran, the capital of Iran, is a referral and tertiary hospital for patients with heart diseases. Afshar Heart Center is also located in Yazd, a city in center of Iran.

The current study aimed to describe the patients with AHF who were hospitalized in these centers for six months and were followed up for death and rehospitalization for three months. The proposal was accepted by these two centers and the study was conducted by fellowships of HF. This study was approved by the local Ethics Committee of Yazd Shahid Sadoughi University of Medical Sciences (Ethics Committee No. IR.SSU.REC.134871). Indeed, informed consents were obtained from all patients.

All adult patients (age ≥ 18 years) with diagnosis of AHF and reduced Left Ventricular Ejection Fraction (LVEF) who were hospitalized in the two above-mentioned centers were included in this study. AHF was diagnosed based on typical symptoms (dyspnea, edema, and fatigue), typical signs (elevated JVP, S3, cardiomegaly, and pulmonary crackles), and abnormal cardiac function in echocardiography (1). All patients had dyspnea at rest or with minimal activity and/or severe generalized edema accompanied with severe systolic HF (LVEF $< 40\%$). Patients with acute coronary syndrome and cardiogenic shock were excluded because their data were not available. Patients with HFpEF were also excluded due to their small number. Patients who only suffered from right heart failure were excluded, as well.

All included patients underwent clinical evaluation, complete laboratory examination, and echocardiography by experienced cardiologists. In addition, their baseline information regarding demographics, medical history, and physical examination was collected at the time of admission.

Diabetes was defined as a previous diagnosis of this condition and was categorized as requiring insulin, oral hypoglycemic agent, and diet control. Besides, hypertension was defined as the previous history of this disease or current or previous use of antihypertensive drugs. Patients with the history of myocardial infarction, significant stenosis in at least one major coronary artery, and history of

coronary revascularization were categorized as ischemic cardiomyopathy. Moreover, edema was defined severe if it was present over both legs and had deformed them. Worsening Renal Function (WRF) was defined as a ≥ 0.3 mg/dL increase in serum creatinine in at least two samples during the index hospitalization up to discharge from hospital. It should be noted that serum creatinine level was measured every day. Anemia was defined according to the criteria suggested by World Health Organization (WHO); i.e., Hb < 13 g/dL in men and < 12 g/dL in women¹⁸. Furthermore, hyponatremia was defined as Na⁺ < 135 mmol/l. Echocardiography was done for all patients on the first day of admission and all data were gathered according to American Society of Echocardiography (ASE) guidelines. All-cause mortality during the initial hospitalization was recorded, as well. All patients were followed up for three months through telephone and mortalities or hospitalizations were recorded.

3.1. Statistical Analysis

Continuous variables were presented as mean \pm standard deviation and categorical ones as frequency (percentage). Predictors of in-hospital mortality were firstly assessed by univariate analysis using binary logistic regression and Enter model. Then, all variables with p-values less than 0.2 were entered into multiple logistic regression analysis (backward model). Additionally, three-month survival was derived using Kaplan-Meier method. All analyses were performed using the SPSS statistical software, version 16.

4. Results

This study was performed on 352 patients with AHF (233 patients from Rajaie Heart Center and 119 patients from Afshar Heart Center) with the mean age of 55 ± 16 years. Totally, 76% of the patients were male and 77% had previous history of HF. The patients' characteristics have been summarized in Table 1. According to the results, 90% of the patients were NYHA class III or IV and 23% had severe generalized edema. Signs and symptoms of the patients have been shown in Table 2. The mean LVEF was $20 \pm 6\%$ and 23% of the patients had concomitant severe systolic right ventricular dysfunction. Moreover, the most common presentation was acute decompensation of chronic HF (77%) followed by acute de novo HF (18%), acute pulmonary edema (4%), and cardiogenic shock (1%). Drugs used during hospitalization and some laboratory data have been listed in Tables 3 and 4, respectively.

Length of hospital stay was 10.5 ± 10 days and in-hospital mortality rate was 9.7%. The results of univariate analysis indicated that systolic blood pressure < 90 mmHg ($P = 0.007$), admission BUN ≥ 50 mg/dL ($P = 0.010$), and WRF during hospitalization ($P = 0.001$) were significantly associated with higher in-hospital mortality. However, no significant association was found between in-hospital mortality and age, gender, etiology of ischemic HF, LVEF, cardiomegaly, and anemia. The results of multiple logistic regression analysis (backward model) showed a significant association between in-hospital mortality and systolic blood pressure < 90 mmHg ($OR = 4.48$ (95% CI: 1.21 - 16.55), $P = 0.024$) and WRF ($OR = 9.33$ (95% CI: 1.99 - 43.56), $P = 0.004$).

Table 1. Characteristics of All Patients with AHF

Patients' Characteristics	Total (n = 352)
Age (years, SD)	55 ± 16
Male, n (%)	267(76)
Ischemic cardiomyopathy, n (%)	183(52)
Comorbidities	
Diabetes, n (%)	131(37)
Hypertension, n (%)	94(27)
Smoking, n (%)	98(28)
Dyslipidemia, n (%)	125 (36)
COPD, n (%)	40(11)
Previous MI, n (%)	85(27)
Hypothyroidism, n (%)	28(8)
Hyperthyroidism, n (%)	2(.5)
ECG and chest X ray	
Atrial Fibrillation, %	22
LBBB, %	19
Cardiomegaly, %	74
Pleural Effusion, %	14
Previous intervention	
ICD, %	12
CRT, %	2.8
PCI, %	15
CABG, %	24
Predisposing factors	
Pneumonia, %	7
Arrhythmia, %	15
Non-compliant with drugs, %	22
Acute coronary syndrome	22
In hospital death, n (%)	34(9.7)
Length of hospital stay, mean days (SD)	10.5 ± 10

Abbreviations: LBBB, left bundle branch block; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronized therapy; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft

Table 2. Frequency of Symptoms and Signs in Patients with AHF

Signs and Symptoms	Frequency (%)
Dyspnea	98%
Orthopnea	67%
PND	47%
Fatigue	63%
Elevated JVP	88%
HeartS3	23%
Systolic murmur	47%
Rales	46%
Mild to moderate edema	73%
Severe edema	23%
Ascites	19%
Systolic BP, mm/Hg (mean, SD)	115 ± 24
Diastolic BP, mm/Hg (mean, SD)	74 ± 16
Heart rate (mean, SD)	87 ± 20
Respiratory rate (mean, SD)	18 ± 4

Abbreviation: PND, paroxysmal nocturnal dyspnea; JVP, jugular venous pressure

After three months, 84% of the patients were followed up by telephone and the remainders were lost to follow-up. The three-month survival curve has been depicted in Figure 1.

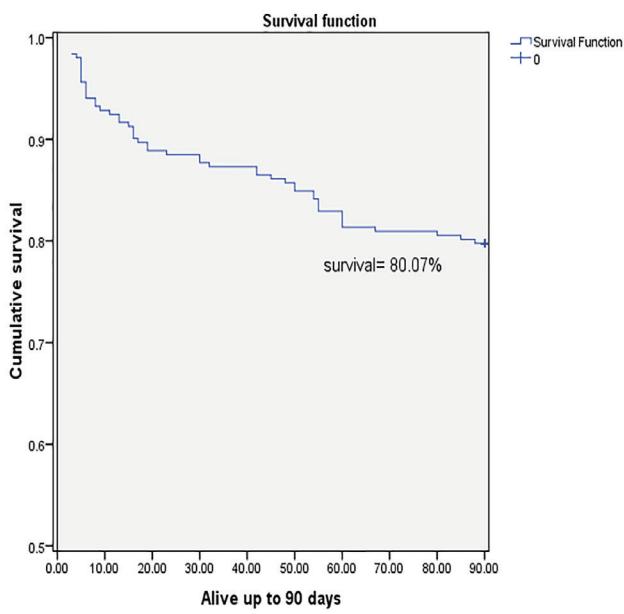
Table 3. Pharmacotherapy of Patients during Hospitalization

Drugs Used in Patients	Frequency
Beta blockers, %	83
ACEI or ARB, %	85
Spironolactone, %	72
IV Furosemide, %	88
Total daily furosemide dose, mg	158 ± 55
Metolazone, %	20
Digoxin, %	34
Warfarin, %	23
Atorvastatin, %	38
Amiodarone, %	13
Aspirin or clopidogrel, %	40
Hydralazine, %	20
Parenteral Iron therapy, %	16
IV vasodilator, %	11
Inotropes, %	22

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor antagonist

Table 4. Laboratory Data of AHF Patients

Laboratory Variables	Mean ± SD
Hemoglobin, mg/dL	12.9(2)
Creatinine at admission, mg/dL	1.34(0.7)
BUN at admission, mg/dL	30(20)
Na+, mmol/L	136(5)
NT-proBNP, mean pg/mL	6669
BNP, mean pg/mL	1220
Uric acid, mg/dL	7.6(2)
HbA1c, mg/dL	6.7(1.7)
Anemia, proportion (%)	43.9
Hyponatremia, proportion (%)	31

**Figure 1.** Kaplan-Meier Survival Analysis for Death during the Three-Month Follow-up

During this period, 30% of the patients were readmitted due to worsening HF and 8.2% died. The total mortality rate (in-hospital and after discharge) was 20%.

5. Discussion

This study was the first report of an AHF registry in Iran, a two-center database that was primarily used to define the patients' clinical and Para clinical characteristics and determine some prognostic factors. It should be mentioned that these centers are referral and tertiary ones for patients with heart diseases.

The mean age of our patients was 55 ± 16 years, which is obviously different from registries done in the U.S., European countries, Korea, and Japan (4-9). In these large registries from developed countries, the mean age of patients was around 70 years. This difference might be due to exclusion of HFpEF patients from the present study. It might also reflect the true difference between our population and those from developed countries. In one study performed on AHF patients in Saudi Arabia (10), the mean age was 60 years. Another study in India (11) also revealed that patients' mean age was 61 years. One other study in Africa (12), too, reported the mean age to be 52 years, which is close to that reported in the current study. This also supports the true difference between our population and those from developed countries. Moreover, the mean age of Iranian patients with acute myocardial infarction was about 62 years (13, 14), which is lower compared to developed countries. This might be due to the HF patients' lower age.

In HF registers from developed countries, about 40 - 50% of patients with HF suffered from HFpEF (4, 7). However, the number of patients with HFpEF was very low in our registry and, consequently, their data were excluded from analysis. This low frequency of HFpEF patients could be attributed to registration of patients from two heart hospitals. These patients are normally old and hospitalized in general hospitals. Thus, finding and registration of these patients requires cooperation among many hospitals. From another point of view, the low frequency of HFpEF patients might be due to the younger population of Iran. This is supported by lower prevalence of HFpEF in registries from Africa (12) and Asia (10, 11) in comparison to those from developed countries.

The number of female patients was low in the present study, which could result from the low number of HFpEF patients who are usually old female ones.

The etiology of HF was ischemic heart disease in nearly half of the patients, which is comparable with many other studies conducted on the issue (4, 7).

Hypertension as a major risk factor for HF was seen only in 27% of the current study patients, which is considerably lower than 50 - 57% reported in large western registries (4, 7). Our patients were significantly young, suffered from severe systolic dysfunction, and did not have HFpEF. Hypertension is seen less in these populations. In OPTIMIZE registry also, hypertension was less frequent in systolic HF in comparison to HFpEF (15).

Elevated Jugular Venous Pressure (JVP) was the most common sign in the present study patients (88%). However, it was reported in only 33% of patients in OPTIMIZE registry (15). Our patients were examined and treated by fellowships of HF. It seems that careful examination might

increase the positivity of this important sign. On the other hand, Left Bundle Branch Block (LBBB) was seen in 19% of our patients and all these patients' LVEF was $< 30\%$. Nonetheless, implantation of Implantable Cardioverter Defibrillator (ICD) and Cardiac Resynchronization Therapy (CRT) were done in minority of the patients. This is mostly due to financial issues and lack of such devices in our country.

In the current study, thyroid disease was detected in 10% of the patients. This disease may affect the course of treatment, which indicates the necessity of thyroid evaluation in all patients with advanced systolic HF. The results also revealed a relationship between thyroid dysfunction and WRF, which was noted by Merla, as well (16).

In the current study, evidence-based drugs like beta blockers, Angiotensin Converting Enzyme Inhibitor (ACEI), Angiotensin Receptor Antagonist (ARB), and Mineralocorticoid Receptor Antagonist (MRA) were used in the majority of patients. Use of Inotrope was also similar to other studies conducted on the issue (5, 8, 10).

In the present study, the rate of in-hospital mortality was 10%. This measure varied from 4% to 13% in the previous studies (4, 10, 17), which could be attributed to differences in design and population of studies. Among multiple interactive variables that had a significant association with in-hospital mortality in univariate analysis, systolic blood pressure < 90 mmHg and WRF had a significant impact on in-hospital mortality in multivariate analysis. In OPTIMIZE registry, older age and lower systolic blood pressure were significant predictors of in-hospital mortality (15).

Echocardiographic study in our patients showed no significant association between LVEF and in-hospital mortality. It seems that LVEF is not a reliable predictor of poor outcomes in advanced systolic HF, which needs to be explored in future studies.

In the present study, WRF during hospitalization was found in 40% of the patients. Indeed, it had a significant impact on in-hospital mortality and 3-month survival, which is consistent with the results of some other studies (18-20).

Anemia was also detected in 44% of the patients, but it had no prognostic importance in this study. However, several other studies have referred to its prognostic importance (21, 22). The difference between the results could be possibly due to the small population of our study.

The present study has some strengths and limitations. This study was performed on a prospective registry and all patients were examined and treated under supervision of HF specialists in a heart center. This might cause less variability in the data. On the other hand, the results of a two-center study on a special population cannot be generalized to the entire community. Indeed, we did not have access to all medical options and left ventricular assist devices, which could affect the medial course and mortality.

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Authors' Contribution

Ahmad Amin, Nasim Naderi, and Sepideh Taghavi

proposed the study concept and design. Mohammad Hossein Soltani, Shima Asis, Abbas Andishmand, Elahe Abbasi, and Leila Hadiani were responsible for acquisition of data. Mahdieh Nemayandeh analyzed the data. Hamid Reza Dehghan played a role in IT technical support. Mohammad Hossein Soltani wrote the paper.

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