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Clinical and laboratory characteristics of short-term mortality in Egyptian patients with acute heart failure



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KEYWORDS

Acute heart failure; Predictors; Short term; Mortality; Egypt **Abstract** *Objective:* To identify the clinical and laboratory predictors of short-term mortality in patients with acute heart failure (AHF).

Subjects and methods: We conducted a prospective, single center study on 120 consecutive patients presented with acute heart failure to the emergency department. All patients had clinical, laboratory, electrocardiographic and echocardiographic evaluation. Short-term mortality was reported within 30 days of presentation.

Results: Mean age was 59.29 ± 10.1 years, 55.8% were males and 50.8% were smokers. The common AHF presentations were dyspnea (91.7%), chest tightness (62.5%) and lower limb edema (54.2%). Ischemic heart disease, diabetes and hypertension were present in 72.5%, 43.3% and 35% of patients, respectively.

Short-term mortality was reported in 29 patients (24.16%); most of them died in-hospital (19 patients, 65.52%). The following parameters were significantly associated with short-term mortality: hypoxia (P < 0.001), tachycardia (P < 0.01), raised jugular venous pressure (JVP) (P < 0.001), low systolic blood pressure (P < 0.01), prolonged PR interval (P < 0.007), atrial fibrillation (AF) (P < 0.038), left bundle branch block (LBBB) (P < 0.04), impaired kidney function (P < 0.007), anemia (P < 0.029), hyponatremia (P < 0.006), hypoalbuminemia (P < 0.005), dilated left ventricle (LV) (P < 0.001), low LV ejection fraction (LVEF) (P < 0.001), and dilated left atrium (LA) (P < 0.002).

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ROC curve analysis showed that low LVEF ($\leq 24\%$), dilated LV end diastolic diameter (LVESD) ≥ 66.5 mm, dilated LV end systolic diameter (LVESD) ≥ 53.5 mm, dilated LA diameter ≥ 48 mm, increased serum creatinine ≥ 1.6 mg/dl, and decreased serum albumin ≤ 3 g/dl can significantly predict short-term mortality in patients with acute heart failure.

Conclusion: Variable clinical, laboratory, electrocardiographic and echocardiographic parameters were associated with short-term mortality. Our study showed that low LVEF, dilated LV diameter, dilated LA diameter, impaired kidney function and low serum albumin can predict short-term mortality in patients with acute heart failure.

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1. Introduction

Heart failure is an increasing epidemic with substantial morbidity and mortality burden. Its prognosis is still poor despite the advances in evidence-based medical treatment and device therapy.¹ Mortality varies between different studies; a large study on Egyptian HF patients has reported that all-cause mortality of HF was 5%² while EURO HF survey reported that AHF mortality varied from 8% to 20%.³ The risk of mortality and re-hospitalization is greater in acute than in chronic stable HF; the prognosis is still poor even after hospital discharge.^{1,4}

Clinically, blood pressure (BP) is inversely correlated with mortality; high admission systolic BP is associated with a significantly lower in-hospital and post-discharge mortality.⁵ Different studies have reported that wide QRS complex was present in about 40% of patients with low LVEF hospitalized for AHF and was associated with increased early and late post-discharge mortality and hospitalization.^{5,6}

Approximately, 30% of AHF patients have worsening renal function during hospitalization which is one of the most important predictors of early HF mortality.⁷ Similarly, 25% of AHF patients have hyponatremia which carries a significant mortality risk after discharge.^{8,9}

To our knowledge, no prospective studies were conducted to identify the clinical and laboratory predictors of short-term mortality among Egyptian patients presented with AHF.

2. Methods

2.1. Study design

This is a single center, prospective observational study. It was approved by the faculty of medicine - Suez Canal university ethical review board.

2.2. Population and data collection

Initially, we enrolled 138 consecutive patients who fulfilled the enrolment criteria, presented with AHF to the emergency department of Suez Canal University hospital from January 2012 to September 2012. AHF refers to rapid onset or worsening of symptoms and/or signs of HF. It is a life-threatening medical condition requiring urgent evaluation and treatment, typically leading to urgent hospital admission.¹ All patients have given written informed consent. Only patients with low LVEF were recruited and followed up. However, only 120

patients have completed their follow-up, while 18 patients had incomplete data or had withdrawn from the study.

Patients were excluded if they were younger than 18 years old or unable to provide informed consent. We have also excluded patients with liver failure, cancer, renal failure on hemodialysis, post-traumatic shortness of breath or presented with acute coronary syndromes.

2.3. Study protocol

Clinical, laboratory, electrocardiographic and echocardiographic evaluation was performed on all patients. The initial evaluation was conducted by the on-site emergency and cardiology physicians. Then, patients were admitted to the cardiac care unit for proper management All patients were medically managed according to our institutional guidelines for HF management. Blood samples were collected from patients at the time of admission for laboratory analysis including complete blood count, kidney and liver functions, electrolytes and serum albumin. Standard 12-lead electrocardiography (ECG) and transthoracic echocardiography were performed to all patients according to the recommendations of American Society of Echocardiography guidelines.

Ischemic etiology of HF was considered in patients with angiographically documented ischemic heart disease (IHD), i.e. at least 75% obstruction of at least one coronary artery or 50% obstruction of the left main artery. Some of these patients had history of previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Other criteria included history of myocardial infarction admission, reduced LVEF \leq 50% with evidence of regional wall motion abnormalities detected by echocardiography and the presence of ECG changes suggestive of myocardial infarction.

2.4. Short-term mortality

We defined short-term mortality as 'mortality within 30 days of AHF presentation, either during admission or after hospital discharge'. Discharged patients were followed up at the outpatient clinic and by telephone contact until 30 days from hospital presentation. Research physician who followed up mortality was blinded to all patients' initial data.

2.5. Statistical analysis

Numerical values were expressed as mean \pm standard deviation (SD). Continuous variables were compared between groups using unpaired t-test (for normally distributed variables). Comparative univariate analyses were performed using Chi-squared test, and P-value of < 0.05 was considered significant. Short-term mortality (death within 30 days of admission) was considered as the study endpoint. Receiver operating characteristic (ROC) analyses were used to determine the sensitivity and specificity of the clinical and laboratory parameters in prediction of short-term mortality in patients with acute heart failure. Predictors of short-term mortality were compared according to their sensitivity and specificity using area under the curve analysis. Statistical analyses were performed using SPSS 22.0 software, focused on the relationship between the different patients' variables and shortterm mortality.

3. Results

Mean age of the recruited patients was 59.29 ± 10.1 years, more than half of them (55.8%) were males, 50.8% were smokers and the mean body mass index was 27.9 ± 4.7 kg/m² (Table 1). More than half of AHF patients (58.3%) were from urban areas.

The most frequent clinical presentations were dyspnea (91.7%), chest tightness (62.5%) and lower limb edema (54.2%). Other associated complaints were sweating, frothy cough and fainting.

The most common co-morbidities were ischemic heart disease (IHD) (72.5%), diabetes mellitus (43.3%) and hypertension (35%). Other reported medical illnesses were valvular heart disease (16.5%), chronic liver dysfunction (9.16%), chronic renal impairment (8.3%) and chronic obstructive pulmonary disease (COPD) (5.83%). Most of the recruited HF patients had many co-morbidities.

Twenty-nine patients (24.16%) had short-term mortality. Of those patients, 10 patients (34.5%) died after discharge and 19 patients (65.5%) died in-hospital: 2 patients (6.9%)

died on the admission day, 14 patients (48.3%) died within the first week after admission and 3 patients (10.3%) died in-hospital but after 1 week of admission (Table 2, Fig. 1).

Males constituted 72.4% of patients who had short-term mortality. However, they represented only half (50.5%) of all survived AHF patients after 30 days. Cigarette smoking was associated with short-term mortality, as 22 patients (75.86%) who had short-term mortality were smokers while only 42.85% of survived patients were smokers, P value < 0.01 (Table 1).

At admission, the following clinical variables were significantly associated with short-term mortality of AHF: tachycardia (HR > 100 bpm), low systolic blood pressure (SBP), elevated jugular venous pressure (JVP) and hypoxia (Table 1).

Similarly, many electrocardiographic parameters were significantly associated with short-term mortality in AHF patients: prolonged PR interval, the presence of AF, wide QRS complex, poor R wave progression, T-wave inversion and ST segment depression and left bundle branch block (Table 3). Laboratory work-up revealed that impaired kidney function, anemia, hyponatremia and hypoalbuminemia were significantly associated with short-term mortality in AHF patient. Likewise, echocardiography revealed that low LVEF, dilated LV and dilated LA were significantly associated with short-term mortality (Table 3).

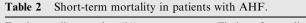
Laboratory data showed that high serum creatinine at a cutoff value of 1.6 mg/dl and low serum albumin \leq 3 g/dl can predict short-term mortality in AHF patients (Fig. 2, Table 4). The analysis of sensitivity and specificity of the echocardiographic parameters showed that LVEF at a cutoff value of \leq 24%, LV end diastolic dimension (LVEDD) \geq 66.5 mm, LV end systolic dimension (LVESD) \geq 53.5 mm, and LA diameter \geq 48 mm can predict short-term mortality in patients with AHF (Fig. 3, Table 4).

All patients $N = 120$		Survival after 30 days of admission $N = 91$ patients	Mortality within 30 days of admission $N = 29$ patients	P value
Demographic data				
Gender Male (N, %)	67 (55.83%)	46 (50.5%)	21 (72.4%)	0.03^{a^*}
Female (N, %)	53 (44.17%)	45 (49.5%)	8 (27.6%)	
Age, Mean ± SD	59.3 ± 10.1	57.2 ± 9.3	61.3 ± 11.1	0.2
BMI, Mean \pm SD	27.9 ± 4.7	27.5 ± 4.8	29.5 ± 3.9	0.04^{*}
Cigarette smoking (N, %)	61 (50.8%)	39 (42.85%)	22 (75.86%)	0.01*
Clinical Data (Mean \pm SD) Heart rate at admission <100 bpm \geq 100 bpm	$72.1 \pm 16.1 \\ 123.6 \pm 20.9$	$73.7 \pm 16.0 \\ 117.8 \pm 20.7$	65.4 ± 14.8 134.7 \pm 16.8	0.07 0.01 [*]
SBP (mmHg)	124.2 ± 25.6	136.3 ± 27.8	111.8 ± 24.9	0.01*
DBP (mmHg)	84.3 ± 26.5	89.7 ± 25.7	79.5 ± 29.3	0.07
JVP (cm)				
<4	3.3 ± 0.5	3.3 ± 0.5	3.3 ± 0.5	0.9
≥ 4	$5.4~\pm~0.7$	5.8 ± 0.6	5.8 ± 0.6	0.001^{*}
Oxygen saturation (%) Lower limb edema (N, %)	83.6 ± 6.4 108 (90%)	85.8 ± 4.3 81 (89%)	76.4 ± 6.7 27 (93.1%)	0.001 [*] 0.5

 Table 1
 Demographic and clinical findings in patients with AHF.

^{*} Statistically significant difference, N: number, SD: standard deviation, BMI: body mass index, bpm: beat per minute, MAP: mean arterial blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure and JVP: jugular venous pressure.

^a Gender difference within HF patients with short-term mortality.



Total mortality, number (%)	Timing of mortality		Number (%)
N = 29 (24.16%)	In-hospital, $N = 19$ (65.5%)	Admission day	2 (6.9%)
		$> 1 \text{ day} \le 1 \text{ week}$	14 (48.3%)
		>1 week \leq 30 days	3 (10.3%)
	Post-discharge and \leq 30 days		10 (34.5%)

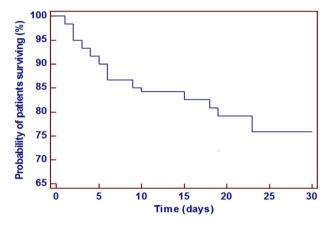


Fig. 1 Kaplan-Meier 30-day survival curve in patients with AHF.

LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, EF: left ventricular ejection fraction, FS: left ventricular fraction shortening and LAS: left atrial size.

4. Discussion

We reported that short-term mortality (death within 30 days of admission) was approximately one quarter of the recruited AHF patients (29 patients, 24.16%). This relatively high mortality rate was also reported in the Euroheart survey which reported that the in-hospital mortality rates for acute HF across Europe range from 8% to 20%. They concluded that AHF represents a period of high risk for patients, during which the likelihood of mortality and re-hospitalization is significantly greater than patients with chronic stable HF.³ The reported survival rate of patients with AHF decreases over time, from admission till 3 months with more decrease till one year.^{3–11}

There are different rates of mortality across different studies; the Euro Heart Failure Survey (EHFS) II reported the short-term mortality 8.1% and the long term mortality was 20.5% in HF patients.³ On the other hand, the reported mortality rate for AHF in USA was 11.3% at 30 days and 33.1% at 1 year.¹¹ The PROTECT trial reported a 7-day mortality rate as less as 1.8% for AHF patients.⁴

Table 3	Electrocardiographic,	echocardiographic and	laboratory findings in	patients with AHF.

	All patients $N = 120$	Survival after 30 days of admission $N = 91$ patients	Mortality within 30 days of admission $N = 29$ patients	P value
Electrocardiographic data				
Prolonged PR interval	34 (28.8%)	19 (20.9%)	15 (51.7%)	0.007^*
Wide QRS complex	53 (44.2%)	28 (30.8%)	25 (86.2%)	0.001^{*}
Poor R wave progression	68 (56.7%)	41 (45.1%)	27 (93.1%)	0.001^{*}
Atrial fibrillation	25 (20.8%)	15 (16.5%)	10 (34.5%)	0.038^{*}
T-wave inversion	57 (47.5%)	32 (35.2%)	25 (86.2%)	0.001^{*}
ST segment depression	59 (49.1%)	36 (40.4%)	23 (79.3%)	0.001^{*}
LBBB	38 (31.7%)	24 (26.4%)	14 (48.3%)	0.04^*
Echocardiographic data (mean \pm	SD)			
LVEDD (mm)	72.4 ± 30.4	66.2 ± 12.5	91.7 ± 53.9	0.001^{*}
LVESD (mm)	59.6 ± 22.6	54.6 ± 13.4	75.2 ± 35.6	0.001^{*}
LVEF (%)	31.4 ± 10.9	34.3 ± 10.2	22.3 ± 7.08	0.001^{*}
LVFS (%)	20.4 ± 6.2	21.8 ± 5.9	15.8 ± 4.6	0.001^{*}
LA size (mm)	$47.8~\pm~8.3$	46.5 ± 7.6	51.8 ± 9.4	0.002^{*}
Laboratory data				
Serum Creatinine (>1.5 mg/dl)	65 (54.2%)	42 (46.2%)	23 (79.3%)	0.007^*
BUN ($> 50 \text{ mg/dl}$)	77 (64.2%)	50 (54.9%)	27 (93.1%)	0.0001^{*}
Hemoglobin (<10 mg/dl)	17 (14.2%)	9 (9.9%)	8 (27.6%)	0.029^{*}
Serum Albumin ($< 3 \text{ g/dl}$)	68 (56.7%)	45 (49.5%)	23 (79.3%)	0.005^{*}
Serum Na ($< 130 \text{ mEq/l}$)	75 (62.5%)	51 (56.0%)	24 (82.8%)	0.006^{*}
ALT (IU/L) mean \pm SD	28.73 ± 21.02	26.43 ± 15.47	30.49 ± 20.76	0.15
AST (IU/L) mean \pm SD	36.74 ± 21.62	35.37 ± 16.14	38.68 ± 22.43	0.12

LBBB: left bundle branch block, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LVEF: left ventricular ejection fraction, LVFS: left ventricular fraction shortening, LA: left atrium, BUN: blood urea nitrogen, ALT: Alanine amino-transferase and AST: Aspartate aminotransferase.

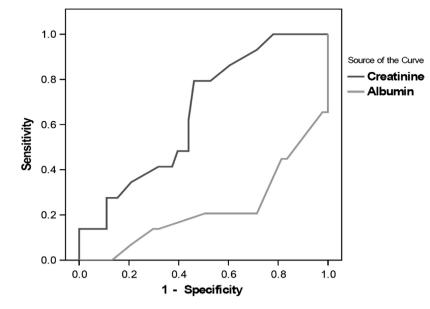


Fig. 2 ROC curve analysis for serum creatinine and serum albumin for prediction of short-term mortality in patients with AHF.

 Table 4
 Sensitivity and specificity of selected laboratory and echocardiographic parameters for prediction of short-term mortality in patients with AHF.

Parameter	Cutoff value	Sensitivity	Specificity	95% CI	P value
Serum Creatinine, mg/dl	≥1.6	62%	56%	0.5-0.8	0.01*
Serum Albumin, g/dl	≤ 3	79%	71%	0.1-0.3	0.001*
LVEF (%)	≤ 24	86%	84%	0.07 - 0.2	0.001*
LVFS (%)	≤ 18	86%	75%	0.1-0.3	0.001^{*}
LVEDD, mm	≥66.5	89%	60%	0.6-0.8	0.001*
LVESD, mm	≥53.5	75%	60%	0.6-0.8	0.001*
LA size, mm	≥ 48	72%	60%	0.5-0.8	0.01*

* Statistically significant difference, AUC: area under the curve, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LVEF: left ventricular ejection fraction, LVFS: left ventricular fraction shortening, LA: left atrium.

Our study showed that the mean age of the studied patients was 59.3 ± 10.1 years; more than half of them were males (55.8%). Moreover, we reported that 72.4% of HF patients with short-term mortality were males. These demographic results are consistent with the results of the Egyptian prospective HF study,² where median age was 61 years and males constituted 67.9% of recruited patients.

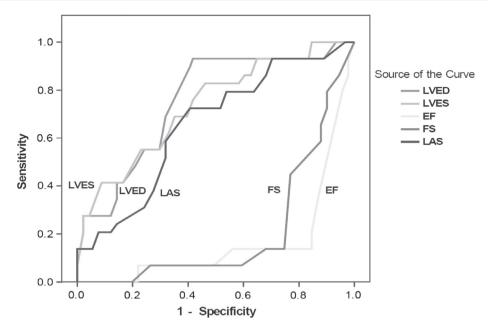
We demonstrated that ischemic heart disease (IHD) is the most common cause of HF in the studied cohort (72.5%), which is close to the prevalence of IHD (67.6%) in the Egyptian prospective HF study.² This was reported in the PRO-TECT trial which enrolled 2033 patients hospitalized with acute HF in USA with high median age (72 years-old) and high male gender contribution (67%) as well.⁴ The PROTECT trial investigators explained this by the high reported incidence of IHD in males, which is the main etiology of HF. Moreover, the high volume of primary percutaneous interventions in acute coronary syndromes could be responsible for the delayed onset of ischemic cardiomyopathy and HF presentation.⁴

In the present study 50.8% were smokers; this is slightly less than the reported prevalence of smoking (61%) in the Egyptian HF study.² We reported that majority (75.86%) of patients who had short-term mortality were smokers. This

finding is comparable to the results of the ADHERE registry which reported that the in-hospital mortality in patients with acute decompensated heart failure was 79.3% in smokers.¹⁰ Smoking boosts mortality rate due to many factors, mainly the acceleration of ischemia and exacerbation of AHF.¹⁰

In the present study, patients who died within 30 days of AHF admission had lower SBP (111.8 \pm 26.9 mmHg) than those who survived after 30 days (136.3 \pm 27.8 mmHg). Many trials, such as EuroHeart Failure Survey (EHFS) II,³ PRO-TECT study⁴ and ADHERE¹⁰ have reported that mortality rate was higher in patients with low SBP, which was highly predictive of short-term mortality risk in heart failure patients. OPTIME-CHF study revealed that one of the most important prognostic factors among patients with AHF was low SBP.⁷ This could be explained by several pathophysiological changes in advanced HF that contribute to low SBP, such as low LVEF due to ventricular remodeling, neurohormonal imbalance and HF medication effect.

According to the ECG changes, our study showed that prolonged PR interval (1st degree heart block), the presence of AF, wide QRS complex, poor R wave progression, T-wave inversion, ST segment depression and LBBB were significantly associated with short-term mortality.



LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, EF: left ventricular ejection fraction, FS: left ventricular fraction shortening and LAS: left atrial size.

Fig. 3 ROC curve analysis for different echocardiographic parameters for prediction of short-term mortality in patients with AHF.

Up to our knowledge, this is the first study to show that electrical dyssynchrony, prolonged PR interval and wide QRS complex could predict short-term mortality in Egyptian patients with AHF. PR prolongation and wide QRS duration are markers of electrical dyssynchrony. So, there are several possible explanations for the close association between these markers, poor prognosis and high mortality in HF patients. Electrical dyssynchrony could eventually lead to mechanical dyssynchrony, which in turn, contributes to more worsening of heart failure.⁶ Moreover, QRS widening means a larger extent of LV mechanical dyssynchrony, a lower LVEF, increased ventricular excitability and higher mortality. It was reported that a stepwise increase in mortality rate is noted in patients with HF as QRS duration increases progressively above 120 ms.^{5,6}

PR prolongation may cause negative hemodynamic effects, and it can reduce cardiac output and increase left atrial pressure. The Framingham Heart Study investigated 7,575 individuals and reported that PR prolongation was associated with a 1.44-fold risk of all-cause mortality.¹² In the EuroHeart Failure Survey (EHFS) II, the mortality rate was 24.1% for patients with wide QRS complex and 18.8% for patients with normal or narrow QRS complex.³ Likewise, the Korean Heart Failure Registry reported that a combined analysis of electrical dyssynchrony markers: PR prolongation and QRS prolongation are useful for short- and long-term risk stratifications of patients with AHF.¹³

Our study showed that the presence of AF is associated with short-term mortality. AF was present in 20.8% of all patients, which is slightly less than the reported prevalence of AF (24.8%) in the Egyptian HF registry.² This difference might be due to the significant large number of HF patients included in the registry compared to our study.

The association of AF and mortality in HF was proven extensively in the literature; EuroHeart Failure Survey (EHFS) II reported that the presence of AF in HF patients increases the odds of mortality from 14% to 57% in comparison with HF alone.^{3–14} A previous community based study recruited 937 HF patients with AF and demonstrated that AF increased the mortality by 29% in those with AF prior to HF and >2-fold increased risk in those with AF during HF.¹⁵ The SOLVD study reported that the presence of AF in HF patients boosted overall mortality by 34%.¹⁶

Our study showed that some laboratory parameters were significantly associated with short-term mortality in HF patients. This includes impaired kidney function, anemia, hyponatremia and hypoalbuminemia.

Hyponatremia in HF is a frequent finding related to worsening of HF due to activation of variable neurohormonal pathways including the sympathetic nervous system and the renin-angiotensin-aldosterone system and use of diuretics.⁸ Hyponatremia is associated with increased mortality in HF. In a cohort of 6185 HF patients with 2 years follow-up, hyponatremia was present in 13.8% and was a significant predictor of short- and long-term mortality and hospitalization.¹⁷

ROC curve analysis showed that high serum creatinine level at a cutoff value of ≥ 1.6 mg/dl and low serum albumin ≤ 3 g/dl can predict short-term mortality in AHF patients. The PRO-TECT in-hospital risk model demonstrated that serum creatinine and BUN were powerful prognostic variables in predicting HF mortality.⁴ Additional predictors of worse HF outcome beside impaired kidney function were lower values of serum albumin and serum cholesterol.⁷ OPTIME-CHF study revealed that the most important prognostic factors among patients with AHF include low SBP, high creatinine level and BUN.⁷ Finally, our study revealed that cardiac structural remodeling is associated with short-term mortality in AHF patients. Depressed LVEF, dilated LVEDD, dilated LVESD, and dilated LA size were associated with short-term mortality. ROC curve analysis showed that all these echocardiographic findings can predict short-term mortality in patients with AHF.

BEST study reported that the echocardiographic measures of LV end-diastolic volume index, could predict mortality in patients with advanced HF.¹⁸ EuroHeart Failure Survey (EHFS) II, reported that low LVEF and dilated LV dimensions were associated with a short-term mortality of 10.8% and a long-term mortality of 25.9%.³ More recently, the echo HF scores¹⁹ reported that reduced LVEF and dilated LV dimensions are predictors of short- and long-term mortality in HF patients. All these parameters are indicative of advanced LV remodeling and reflect worse progression of ventricular myocardium, so they are expected to be powerful mortality predictors in HF patients.¹⁹

5. Conclusion

We reported a relatively high prevalence of short-term mortality in our single center study of Egyptian patients with AHF and low LVEF. We reported that short-term mortality in AHF was associated with many clinical, laboratory, electrocardiographic and echocardiographic parameters. Of those parameters, depressed LVEF, increased LV diameter, increased LA size, high serum creatinine and low serum albumin were significantly associated with short-term mortality and could predict it. Other parameters that were significantly associated with short-term mortality in AHF included tachycardia, hypoxia, elevated JVP, prolonged PR interval, wide QRS complex, AF, anemia and hyponatremia. Nevertheless, larger trials should be conducted for validation of these findings. We suggest that all emergency, internal medicine and cardiology clinicians should be aware of these feasible parameters. Identifying AHF patients at risk of short-term mortality can recognize patients who should be hospitalized, closely monitored, properly managed and followed up.

Study limitations

This study is a single center, prospective study with a limited number of consecutive recruited AHF patients. We didn't include HF patients with preserved ejection fraction. Longterm follow-up was not performed as our aim was to assess short-term mortality.

Conflicts of interest

No conflicts of interest.

Disclosure

All listed authors declare no conflict of interest.

Authorship declaration

All listed authors are in agreement with the manuscript.

Financial disclosures

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