PREDICTIVE VALUE OF SIMPLE BIOMARKERS OF MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE IN EMERGENCY DEPARTMENT IN SUEZ CANAL UNIVERSITY HOSPITAL IN ISMAILIA

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ABSTRACT

Background: Heart failure (HF) has become one of the most significant problems in healthcare in the western world. There are over 26 million people who suffer from heart failure in the world. Half of all patients diagnosed with heart failure die within four years. It is critical to predicting if a patient will die soon so that an effective prevention can be employed. However, characteristics and outcome of HF patients are not well investigated in developing countries like Egypt. **Methods:** Was to assess the short-term predictive value of simple biomarkers (such as d-dimer, CRP& ESR) regarding cardiovascular mortality and major cardiovascular events in patients with severe heart failure. This is a cross-sectional study which included 141 patients. **Results:** According to ESR, CRP and d-dimer as predictors of hospital admission within one-month follow-up: 45.9% of the patients had moderately elevated ESR, 72.1% of the patients had high CRP and 13.1% of the patients had positive d-dimer. According to ESR, CRP, d-dimer as predictors of mortality within one month follow up: 83.3% of the patients had moderately elevated ESR within the first hour, 83.3% of the patients had high CRP, and 33.3% of the patients had positive d-dimer. **Conclusion:** ESR may be a good predictor of mortality within one month follow-up, while CRP, d-dimer are not.

KEYWORDS: Heart failure mortality, ESR, CRP, d-dimer, Biomarkers.

Introduction

Heart failure (HF) has become one of the most important problems in healthcare in the western world. The prevalence of heart failure is about 2%-3% of the adult population, and it increases with age. There are over 26 million people who suffer from heart failure in the world, and there are over 3.5 million newly diagnosed people every year in Europe alone [1]. Half of all patients diagnosed with heart failure die within four years. It is fascinating to predict if a patient dies soon so that an effective prevention can be employed. However, characteristics and outcome of HF patients are not well described in developing countries like Egypt. Documenting patients' characteristics and the outcome might improve management of comorbidities associated with heart failure patients in Egypt as well as the disease outcome.[2] So, The aim of this study was to assess the short-term predictive value of simple biomarkers (such as d-dimer, CRP & ESR) regarding cardiovascular mortality and major cardiovascular events in patients with severe heart failure.

Study hypothesis:

d-dimer, ESR & CRP can predict major cardiovascular events and mortality in patients with severe heart failure?

Methods

$SampleSize$

$$n = \left[\frac{Z\alpha\backslash2 + Z\beta}{\frac{1}{2}\log\frac{1+r}{1-r}} \right]^2 + 3 [21]$$

Where
n= sample size

Zα /2 = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail).

Zβ = 0.84(The critical value that separates the lower 20% of the Z distribution from the upper 80%).

r = correlation between concentration of D-Dimer and CRP>30 mg/L as a criterion of heart failure. (r = 0.52) [19]

According to the previous equation, n=128.1.

Moreover, expected drop out of 10% will be added.

So, the required sample size was 141 subjects.

The study included 141 patients with inclusion criteria of (above the age of 18 years old, both sexes) attending emergency department presenting with NYHA class III or IV, systolic heart failure with ejection fraction <40% with symptoms (shortness of breath, and/or peripheral oedema, and/or fatigue) or has grade III diastolic dysfunction. The exclusion criteria included any disease can elevate d-dimer, c-reactive protein, and ESR, pregnancy, malignancy & end organ failure (except heart). Electrocardiogram and echocardiography were done. Blood samples were drawn, and CBC, RBS, serum creatinine, serum sodium, serum potassium, ESR, CRP, and d-dimer were analyzed. BD Sedi-15™ instrument measured ESR; CRP was measured Cobas C 501 and d-dimer by latex agglutination test. Follow-up was done for one month.

Funding:

Data analysis:

The data were entered, cleaned and analyzed using SPSS software version 18.0. Descriptive statistics like frequency distribution and percentage calculation was made for most of the variables. Chi-Square and odds ratios (OR) test was used to examine the relationship between two qualitative variables. A P< 0.05 was considered statistically significant.

Ethical Approval:

Confidentiality and anonymity we are maintained according to the regulations mandated by Research Ethics Committee of Faculty of Medicine Suez Canal University. The study subjects were explained the purpose of the study, assured privacy, and a written consent was obtained from them.

Results

The study revealed that the patient's age was 61.5±12.7 with a range of (27-80), 51.8% of the patients were males, 14.9% of them were smokers. The mean age of the studied patients was 61.5±12.7 with a broad range of (27-80), 36.2% of the patients were in the age group 70-≤ 80 years old, 51.8% of the studied

Table 1 Characteristics of the study population:

Variable		Number	Percent
Age(years)	20-<30	4	2.8%
	30-<40	0	0%
	40-<50	24	17%
	50-<60	20	14.2%
	60-<70	42	29.8%
	70-≤ 80	51	36.2%
	Mean & standard deviation	61.55± 12.74	
	Range	27-80	
Sex	Male	73	51.8%
	Female	68	48.2%
Smoking	Smoker	21	14.9%
	Non,smoker	108	76.6%
	Ex-smokers	12	8.5%

patients were males, 14.9% of the studied patients were smokers.(Table 1)

According to the vital signs of the studied patients regarding the time of presentation in the emergency department, 68.8% of the patients were normotensive 17.7% of the patients presented by tachycardia (>90 bpm). According to presenting symptoms, 31.9% of the studied patients were presented by dyspnoea and orthopnoea. Regarding history of chronic medical illnesses, 56.7% of patients were hypertensive, 46.1% of patients were diabetic, 59.6% of patients had ischemic heart disease, 45.4% of patients had valvular heart disease, 22.7% of patients had impaired renal function and 14.2% of patients had history of cerebrovascular stroke (Figure 1).
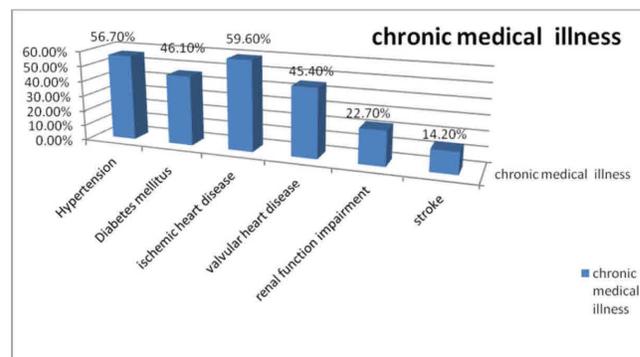

Figure (1): Distribution of studied patients according to history of chronic medical illness

The study showed that there was no relation between some comorbidities and mortality.

Regarding the relation between each chronic illness and mortality, the study showed that hypertension associated with 50% of all deaths, diabetes associated with 16.7% of all deaths, ischemic heart disease associated with 33.3% of all deaths, valvu-

lar heart disease associated with 50% of all deaths and renal impairment associated with 50% of all deaths. Regarding the presenting signs at time of presentation, 39.7% of the patients had bilateral lower limb edema, 57.4% had raised jugular venous pressure, 60.3% of patients had bilateral basal crepitations in chest auscultation, 39.4% of patients had cardiac murmurs, 5.6% of patients had s_3 or s_4 in heart auscultation and only 17% had enlarged tender liver.

According to electrical changes in ECG, the most common electrical changes in the electrocardiogram of the studied patients were ischemic changes (26.2%) followed by left bundle branch block. According to ejection fraction, the mean of ejection fraction of the study population was at 29.7%± 8.18% with a wide range of (15-40%).

Regarding the laboratory investigations at time of presentation in the emergency department, 28.4% of the patients had anemia, 34.8% of patients had leukocytosis, 48.9% of patients had elevated random blood sugar, 19.9% of patients had elevated serum creatinine, 40.4% of patients had hyponatremia, 6.3% of patients had hyperkalemia, 62.4% of patients had moderately elevated ESR and 82.3% of patients had high CRP.

According to ESR, CRP, d-dimer as predictors of hospital readmission within one-month follow-up, 65.6% of the patients had moderately elevated ESR, 72.1% of the patients had high CRP and 13.1% of the patients had positive d-dimer (Table 2).

According to ESR, CRP, d-dimer as predictors of mortality within one-month follow-up, 83.3% of the patients had moderately elevated ESR within the first hour, 83.3% of the patients had high CRP, and 33.3% of the patients had positive d-dimer (Table 3).

Discussion

Regarding the blood pressure of the studied patients at time of presentation their results match the results of a study performed in 2009, in which 91% of the studied population were normotensive and systolic blood pressure values above 140 mmHg was recorded in only five percent of the study patients' population. [2] Unfortunately, this cannot be naively interpreted as good news, since in this subset of patients; all medications such as beta blockers and ACEI may cause a decrease in blood pressure limiting the physicians' ability to achieve the target doses of medications.[2]

According to the presenting pulse at the time of examination, did not match the results of another study which showed that most of the patients presented by tachycardia.[4] The results of this study may be because most of the studied patients were on β-blockers. Regarding the presenting symptoms at the time of presentation in the emergency department, most of the studied patients were presented by dyspnea and orthopnea together. While in another study, most of the patients presented by dyspnea as the main complaint.[4] This can be explained by the fact that the heart spent much of its compensatory reserve. [5]

The results regarding history of chronic illnesses, match the results of another study which revealed that 57.5% of patients had hypertension, 52% had diabetes mellitus, 65% of patients had ischemic heart disease with varying degrees of severity, 15.5% had valvular heart disease, 34% of patients had impaired renal function and 8.5% had cerebrovascular stroke. [2, 3] In our study, more than half of patients had ischemic heart disease and developed HF, in spite of all the recent advances in the arena of management of coronary heart disease.

The study showed that no relation between some comorbid illnesses and mortality, unlike the results of a study performed by Bin Tong& Chris Stevenson which showed that 13.2% of all deaths due to two comorbid illnesses.[6] The observed excess rate of comorbidity in deaths suggests that the coexistence of these diseases is caused by associations between these diseases and risk factors for these diseases.

The study showed that hypertension was associated with 50%, diabetes associated with 16.7%, ischemic heart disease associated with 33.3%, valvular heart disease associated with 50%, renal impairment associated with 50% of all deaths. While in a study performed by Bin Tong & Chris Stevenson which showed that hypertension associated with 11.5%, ischemic heart disease associated with 28.6%, renal impairment associated with 9.1%, valvular heart disease associated with 25.5%, diabetes associated with 9% of all deaths.[6]

According to the presenting signs, the results of this study matches the results of another study which showed that in patients treated in an emergency department for heart failure, 47% had lower extremity edema detected on physical examination.[7] However, in two large registries that used review of medical records to report findings on physical examination of patients with acute heart failure decompensation, 65% to 66% had lower extremity edema.[8,9,10] Variation in the results could be due to many factors which include heterogeneity in characteristics, medical history, use of diuretics. [4]

Regarding electrical changes in the electrocardiogram, the study did not match the results of another study which revealed that left bundle branch block was the most common electrical changes in the electrocardiogram.[11]

The study showed that the mean of ejection fraction of the study population was at (29.7±8.18). Which matches the results of another studies.[12]

Regarding anemia, leukocytosis, random blood sugar, elevated serum creatinine, hyponatremia, hyperkalemia and elevated ESR, our study did not match the results of the study performed by Clement E.L. Makule which showed that 33.3% of patients had anemia, 6.6% of patients had leukocytosis, 4.3% of patients had elevated random blood sugar, 36% of patients had elevated serum creatinine, 13.9% of patients had hyponatremia, 7.6% of patients had hyperkalemia, 25.8% of patients had moderately elevated ESR.[5]

Our present study shows that 82.3% of patients had high CRP. Which did not match the results of another study performed by Eric S. Williams et al. who found in that 39.6% of patients had high CRP. The relationship of HF to elevated CRP levels was first reported decades ago.[13] Since then, several mechanisms have been postulated to explain the association between inflammatory markers and HF. Interleukin-6 is a powerful stimulus of CRP production in hepatocytes and is produced by a many of cell types. [13]

The study showed that ESR was elevated within the first hour in patients who subsequently readmitted or died within one-month follow-up (Table 2). Which matches the results of another study which showed that ESR was associated with higher rates of mortality and repeated readmission. Accelerated erythrocyte aggregation is caused by large, asymmetrical plasma proteins inhibiting the negative electrical power which normally keep the erythrocytes apart.[14] Previous studies had reported that a low ESR was associated with severe cardiac decompensation and unfavorable prognosis. While Sharma et al. demonstrated the relationship between low ERS and better prognosis in patients

Table 2 Predictors of hospital readmission in patients with severe heart failure:

	Hospital readmission		Chi–square & odd-ratio (UCL, LCL)	p-value
	Yes	No		
Abnormal ESR	40 (65.6%)	60 (75%)	1.4 & 1.5 (3.2, 0.7)	0.08
High CRP	44 (72.1%)	72 (90%)	7.57 & 3.4(8.7,1.3)	0.1
d-dimer Positive	8 (13.1%)	28 (35%)	8.7 & 3.5(8.5,1.4)	0.003*

Table 3 Predictors of mortality in patients with severe heart failure:

	Mortality		Chi–square & odds ratio (UCL, LCL)	p-value
	Yes	No		
Abnormal ECG	20 (83.3%)	97 (82.9%)	0.003 & 0.9 (3.1,0.3)	0.9
Abnormal ESR	20 (83.3%)	80 (68.4%)	2.1 & 0.4 (1.3,0.1)	0.01*
CRP High	20 (83.3%)	96 (82.1%)	0.022 & 0.9 (2.9,0.2)	0.6
d-dimer Positive	8 (33.3%)	28 (23.9%)	0.9& 0.6 (1.6,0.2)	0.3

with systolic dysfunction and stable CHF.[15] In another study, ERS was identified as a predictor of survival in patients with decompensated heart failure. In a variable percent of patients, the prognostic value of ESR is limited, because decompensation is caused by diseases that increase ESR (such as infection).

Although this study is limited by a small number of patients this finding is consistent with prior reports.[16] Our results suggest that ESR could be a useful marker of mortality in patients with CHF and acute decompensation. Indeed, because it is a cheap and easily available, ESR could be a tool for monitoring patients at risk after discharge.

Regarding CRP as a predictor of hospital readmission and mortality within one-month follow-up in patients with severe heart failure, the study showed that CRP is not related to higher rates of hospital readmission and mortality within one-month follow-up (Table 2). Which matches the results of another study which showed that CRP is associated with the impairment of ventricular function and with NYHA class, whereas it is not an independent predictor of clinical outcome in HF;[17] this is in contrast to the data of other authors who found, on a smaller number of patients, that high CRP levels, measured with a sensitive standard assay, are predictor of improvement and readmission in HF. [18]

According to d-dimer as a predictor of hospital readmission and mortality within one-month follow-up in patients with severe heart failure, the study showed that d-dimer was not related to higher rates of hospital readmission nor mortality within one-month follow-up (Table 2). In comparison to another study performed by Urban Alehagen, showed that d-dimer associated with higher rates of mortality.[19] The results of this study did not match the results of another study which concluded that d-dimer associated with higher rates of hospital readmission. The elevated levels of DD documented in heart failure patients might be interpreted as the effect of the inflammatory state detected in HF or as the mirror of hypercoagulable statutes which could increase the risk of thrombogenesis in HF. As markers of hypercoagulability and inflammation, it was conceivable to find elevated levels in hospitalized HF. Nevertheless, the levels of these markers found to be predictive of mortality, suggesting that a more pronounced increase during the acute phase identifies patients of higher risk. By the measurement of DD, patients might be selected for intensive follow-up after hospital discharge.[17]

The study showed that no relation between ECG changes and mortality, which matches a study performed in 2013 in Africa, which revealed that some ECG findings have prognostic value for risk of adverse outcomes, most of them are nonspecific and add little to the risk stratification of these patients.[20]

Conflict of Interest:
Authors have declared that no conflict of interests exists.

Authors' Statements

Competing Interests
The authors declare no conflict of interest.

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