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Hepatitis C Seropositivity and Short -Term Clinical Outcome of Acute Heart Failure Patients

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ABSTRACT

Background: Heart failure (HF) is a major public health problem affecting around 37.7 million people globally with frequent hospital admissions, reduced quality of life and shortened life expectancy.

Objective: The aim of this study is to compare between the short-term clinical outcome of hepatitis C seropositive acute heart failure patient's vs the seronegative acute heart failure patients.

Patients and Methods: The study is a prospective cohort study that included 150 patients admitted at cardiovascular department in Specialized Medical Hospital (Mansoura University), presented by symptoms and signs of acute heart failure. Patients of the study were classified to two groups; hepatitis C seropositive acute heart failure patient's vs the seronegative acute heart failure patients.

Results: High prevalence of abnormal liver function tests (LFTs) was found in our patients with acute heart failure reaching 77.5% of the study population. Abnormal LFTs were higher in hepatitis C virus (HCV) positive compared to HCV negative. In our study, statistically significant correlation was found between cardiovascular mortality and major adverse cardiovascular events (MACE) with chronic kidney disease (CKD) and albumin as regarding HCV positive patient. However, no statistically significant correlation was found between cardiovascular mortality and MACE with any of liver function, CBC, CKD as regarding HCV negative patient.

Conclusion: The higher prevalence of abnormal liver function tests in our study in comparison with other studies may be explained by more aggressive HF exacerbation in our patients associated subclinical hepatitis C affection in our patients with HF. Our patients with acute heart failure had younger age than other studies. The present controversy results need large long-term study in the future.

Keywords: Hepatitis C, Acute Heart Failure, Egypt, Cohort study, liver function tests.

INTRODUCTION

Heart failure (HF) is a major public health problem affecting around 37.7 million people globally with frequent hospital admissions, reduced quality of life and shortened life expectancy [1,2]. One of the most common reasons for hospital admission resulting in more than one million admissions each year is acute heart failure making it a life-threatening medical emergency [3].

The most common diagnosis in hospitalized elder patients aged more than 65 years representing 1-2% of all hospital admissions is HF [4].

HF is defined by the American Heart Association and American College of Cardiology as a complex clinical syndrome that can be caused by any structural or functional cardiac disease that impairs ventricular relaxation or contraction [5]. Hepatitis C virus (HCV) is the cause of many different forms of heart diseases worldwide. The burden of HCV-derived heart diseases is global, with higher prevalence in Asia, Africa, and low/ middle-income countries [6]. Egypt has the highest prevalence of HCV in the world, apparently due to previous mass parenteral anti Schistosomal therapy [7].

The myocardium may be the target of several types of viral infections. The importance of HCV infection has been noted in patients with hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, myocarditis and left ventricular (LV) diastolic dysfunction [8].

HCV can also directly damage cardiac structures causing myocarditis and cardiomyopathy. The prevalence of anti-HCV antibodies was greater in subjects with myocarditis and HF than in the general population, therefore HCV infection may be a cause of myocarditis and HF in regions with high HCV prevalence [9]. Another study showed diastolic dysfunction in HCV infected patients suggesting a subclinical cardiac involvement [10].

The aim of this study is to compare between the short-term clinical outcome of hepatitis C seropositive acute heart failure patient's vs the seronegative acute heart failure patients.

PATIENTS AND METHODS

Our study included 150 patients who were presented to Specialized Medical Hospital (Mansoura University) by symptoms and signs of acute heart failure within the time period of April 2019 to April 2021.

Type of the study: Prospective cohort study.

Inclusion criteria:

All patients admitted to hospital presented by acute heart failure either: (1) De novo HF. (2) Acute on top of chronic HF. The studied patients were divided according to HCV serology status into two groups, group A with HCV positive tests and group B with HCV negative tests.

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Exclusion criteria:

Patients with chronic decompensated liver cell failure, patients with end stage kidney disease (creatinine clearance less than 30 ml/minute), and patients with malignant tumors (Hepatic or Extrahepatic).

All patients with acute heart failure were subjected to;

1) **Full history taking:** With special focus on sex, age, smoking, diabetes mellitus, hypertension, ischemic heart disease, chronic liver disease, and symptoms of heart failure (dyspnea, low cardiac output symptoms and systemic congestion).
2) **General Examination:** With special emphasis on blood pressure, heart rate, respiratory rate, lower limb edema, neck veins congestion, jaundice, bleeding manifestations, enlarged tender liver and ascites.
3) **Local Examination:** Includes scars of previous cardiac surgery, heart sounds, heart murmurs, galloping sounds, basal crackles on the lung bases.
4) **Electrocardiography.**
5) **Echocardiography.**
6) **Laboratory investigations:** Venous samples were drawn from all patients on admission before starting medications and the followings were done: serum creatinine level for estimation of creatinine clearance, viral Hepatitis markers (HCV antibodies by ELISA). Liver functions tests (LFTs): serum albumin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), prothrombin time, international normalized ratio (INR), serum bilirubin (total), complete blood picture (white blood count, platelet count, hemoglobin).

Ethical consent:

An approval of the study was obtained from Mansoura University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Data were analyzed using the computer and using using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 21). The normality of data was first tested with one-sample Kolmogorov-Smirnov test. For the statistical significance of difference, means of two sets of numerical data had been compared by the Student's t-test. The Mann-Whitney U-test was employed for comparing the two groups, as it is appropriate for non-parametric continuous data. We used the chi-square test to compare means across groups in our categorical data analysis (X^2). P-value $\leq$0.05 was considered significant, P-value $\leq$0.01 was considered as highly significant, P-value >0.05 was considered insignificant.

RESULTS

Our study included 150 patients who were presented to Specialized Medical Hospital (Mansoura University) by symptoms and signs of acute heart failure within the time period of April 2019 to April 2021.

Baseline patient history criteria:

Our study included 150 patients, the two studied groups group A with HCV positive 75 patients and group B with HCV negative 75 patients, their ages ranged between 20 years and 75 years with mean ± SD were (57.05±11.10 and 60.22±10.51) respectively. In our study population, gender distribution of the two studied groups A and B were: 57 patients (76.0%) and 49 patients (65.3%) were males, 18 patients (24.0%) 26 patients (34.7%) were females, respectively.

In our study population, group A with 37(49.3%) were diagnosed with diabetes mellitus, 39 (52.0%) have arterial hypertension, 33 (44.0%) were smokers, 11 (14.7%) have CKD, and group B with 48 (64.0%) were diagnosed with diabetes mellitus, 27 (36.0%) have arterial hypertension, 35 (46.7%) were smokers, 11 (14.7%) have CKD. There was non-significant difference between A and B group as regard age and sex.

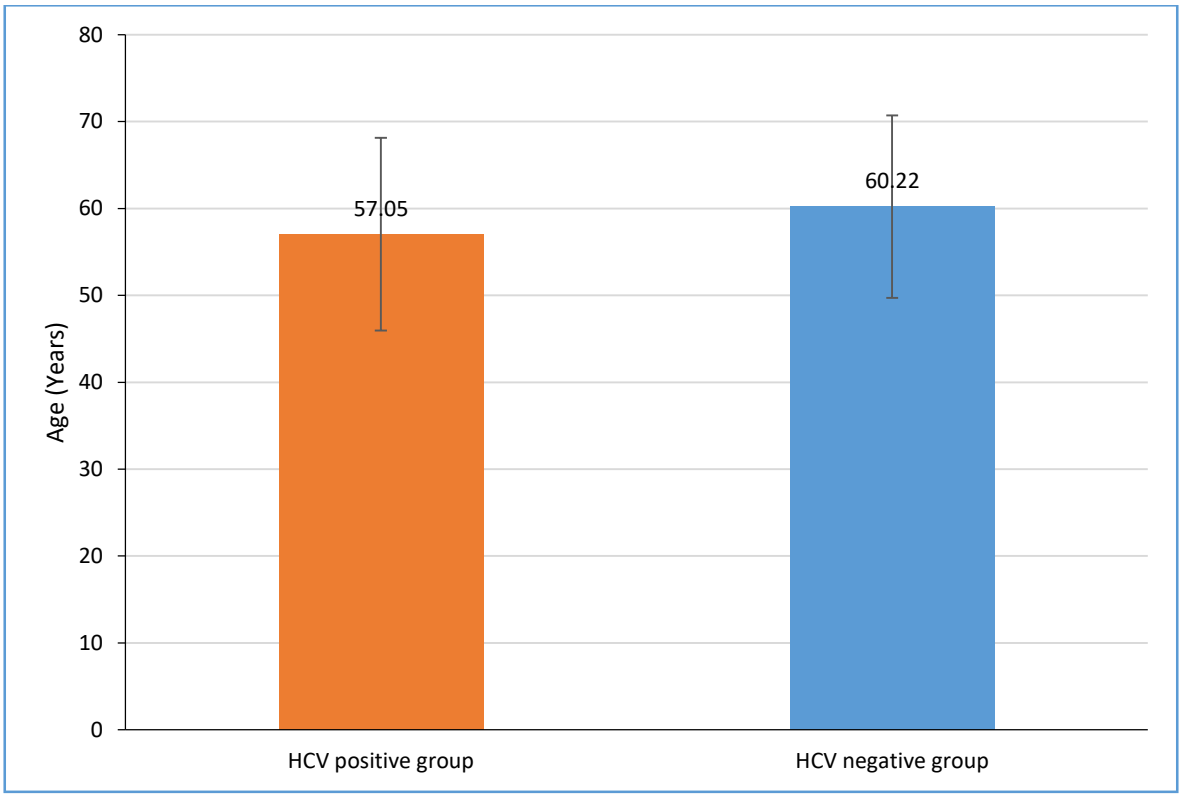

Figure (1): Age distribution among the two studied groups.

There was significant difference between A and B group as regard LAH and Atrial fibrillation and Poor R wave progression and there was non-significant difference between A and B group as regard ST segment, T wave changes, LBBB, RBBB, IVCD, First degree heart block and Prolonged QT.

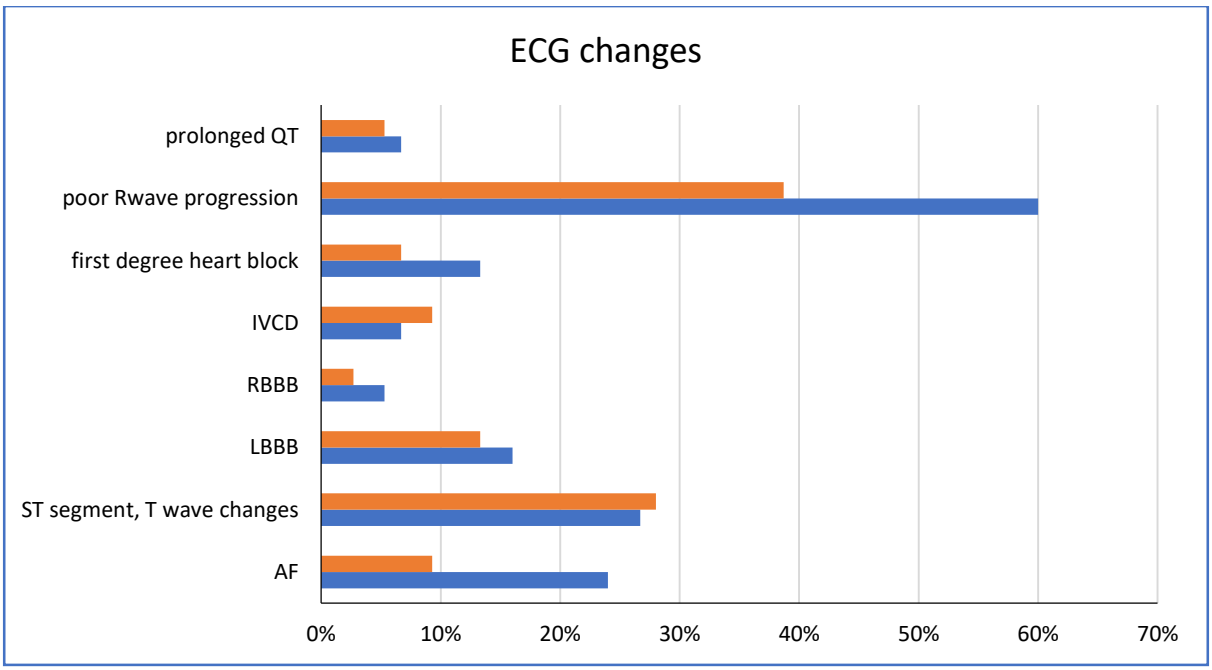

Figure (2): ECG changes among two studied groups.

There was significant difference between A and B group as regard Death, change in NYHA class and there was non-significant difference between A and B group as regard Re-hospitalization, Non-fatal AMI and Stroke.

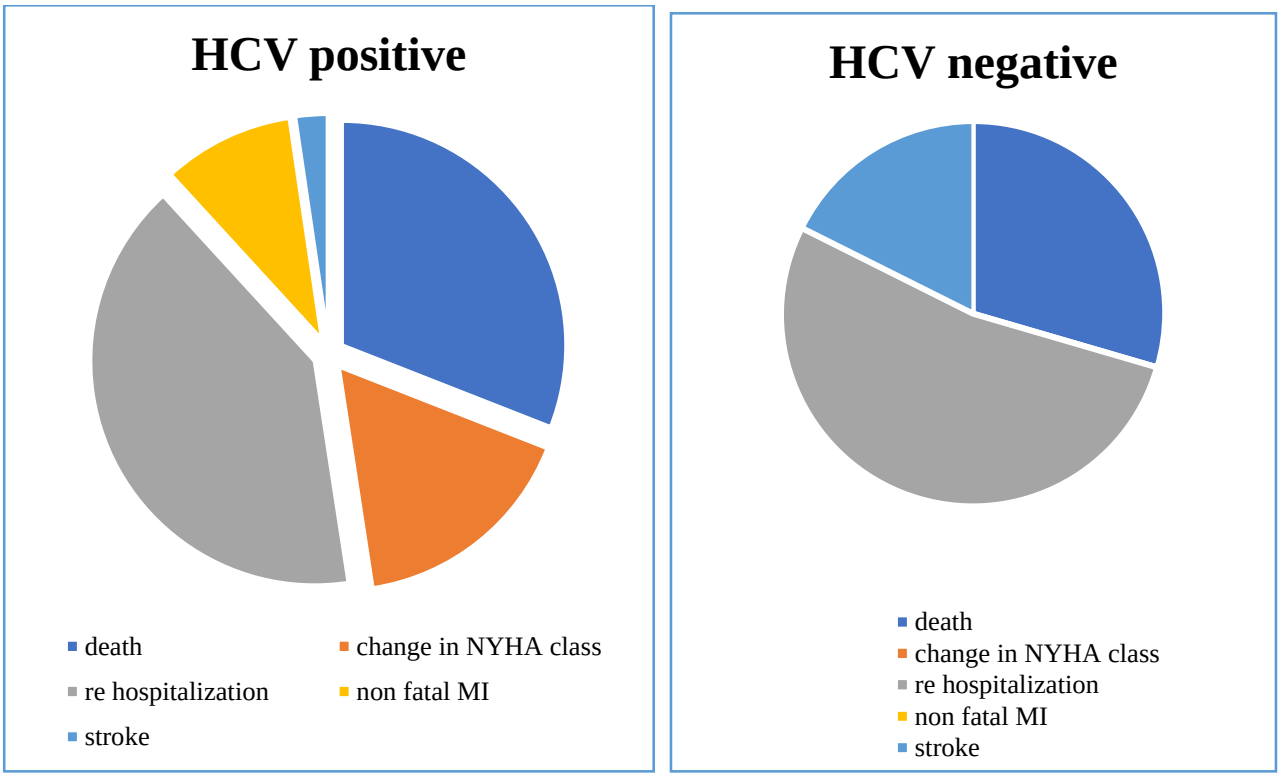

Figure (3): Outcome among the two studied groups.

There was significant difference between MACE with HCV positive patient and CKD, and Albumin, otherwise not significant regarding ALT, AST, total bilirubin, PLT, Hb, TLC, Age, SBP, and pulse.

Table (1): Comparison between MACE with HCV positive and the following parameter.

Variable	MACE		Test of significance	p-value
	Yes (n=23)	No (n=52)		
CKD	8 (34.8%)	6 (11.5%)	χ^2=5.67	**0.017*s**
ALT (U/L)	35 (6-127)	34 (13-132)	Z=0.34	0.734 ns
AST (U/L)	32 (11-213)	31 (10-126)	Z=0.316	0.752 ns
T. bilirubin (µmol/L)	1.64±0.57	1.5635±.64535	t=0.511	0.611 ns
Albumin (g/L)	3.04±0.51	3.33±0.52	t=2.26	**0.027*s**
PLT (mcL)	216.35±52.33	210.02±49.64	t=0.314	0.755 ns
Hb (g/dL)	11.15±1.76	11.82±1.83	t=1.47	0.144 ns
TLC	8.00±1.61	7.51±1.36	t=0.864	0.390 ns
Age (Years)	54.65± 8.29	58.11± 12.06	t=1.25	0.215 ns
SBP (mmHg)	126.09±4.34	130.87±4.37	t=0.443	0.659 ns
Pulse	105.87±12.09	102.71±12.25	t=1.03	0.305 ns

Z: Mann Whitney test, *S Significant p ≤0.05, ns = non-significant at p value > 0.05

DISCUSSION

HF has become a substantial public health problem, affecting 2% of the adult population, and the number of hospital admissions related to HF has tripled since the 1990 [11].

In HF, the prevalence of abnormal LFTs is 30 % to 60 % and are related to poor outcomes. HF may lead to liver disease, which adversely affects prognosis and complicates management of HF [12]. Laboratory tests show increased ALT and LDH, usually 1 to 3 days after hemodynamic deterioration. An ALT to- LDH <1.5 denotes cardiogenic acute liver injury. Frequently, patients exhibit a bleeding diathesis derived from deficiency of liver coagulation factors. An increase in bilirubin denotes hepatocellular injury or cholestasis [13].

Liver function abnormalities caused by HF have variable ranges. Elevation of serum bilirubin is the most common abnormality reaching 30-70% of cases while serum transaminases as AST) and ALT are elevated in 12-33% of patients **[1].** The hepatitis C virus itself, along with impairment of liver function, can cause damaging effects to the heart and circulatory system [14]. Baseline values of AST, ALT, and albumin were also related to the risk of 180-day all-cause mortality [15].

In our study, abnormal LFTs in patients admitted by acute heart failure were common reaching 77.5% of study population. Abnormal total bilirubin

(1.59±0.62) and (1.22±0.87), ALT (36.72±20.29) and (42.52±40.92), AST (39.21±28.79) and (42.52±40.92), serum albumin (3.24±0.53) and (3.47±0.43) and INR (1.29±0.25) & (1.18±0.29) between group A and B of patients respectively. **van Deursen *et al.* [12]** study revealed that abnormal LFTs were 77.5% of patients. Total bilirubin in 19%, ALT in 12%, AST in 21%, and serum albumin in 25% of patients. **Nikolaou *et al.* [16]** reported that abnormal testes were detected in 20% of patients. In **Biegus *et al.* [17]** study, abnormal tests at admission were AST, ALT, and albumin were present in 20%, 12%, and 40% of patients. **Samsky *et al.* [1]** founded that abnormal bilirubin was detected in 42%, ALT in 22%, AST in 30% of cases of acute heart failure.

The higher prevalence of abnormal LFTs in our study in comparison with other studies may be explained by more aggressive HF exacerbation in our patients, associated subclinical hepatitis C affection in our patients with HF and the small sample size of our study.

In our study hypoalbuminemia is more common in patients with group A with mean ± SD (3.24±0.53) compared to patients with group B with mean ± SD (3.47±0.43) with statistical significance. **Kinugasa *et al.* [18], Uthamalingam *et al.* [19], Biegus *et al.* [17] and Ancion *et al.* [20]** studies revealed that in patients admitted to hospitals by acute HF, low serum albumin is common and is associated with increased risk of cardiovascular mortality. **Nikolaou *et al.* [16] and Bonilla-Palomas *et al.* [21]** studies demonstrated that low serum albumin in hospitalized patients with HF is associated with increased risk of pulmonary edema, heart failure decompensation and recurrent hospitalization. In the opposite side, **Grodin *et al.* [22]** study showed that serum albumin level was not associated with mortality, rehospitalization or ER visits as serum albumin levels were largely within the normal range in this acute HF cases.

In our study, serum total bilirubin was lower in patients with cardiovascular mortality with group A mean ± SD (1.59±0.62) and with group B (1.22±0.87) with statistical significance. However, **Dai *et al.* [23] and Samsky *et al.* [1]** studies revealed that increased total bilirubin is associated with increased risk of heart failure rehospitalizations. This difference between our results and those of other studies may be related to small sample size, the population difference between our Egyptian patients and other studies and the retrospective nature of the previous studies. The confirmation of this controversy needs large long-term study in the future.

In our study, patients with cardiovascular mortality have elevated serum transaminases with cardiovascular mortality with group A mean ± SD ALT (36.72±20.29) AST (39.21±28.79) and with group B ALT (43.26±41.60) AST (42.52±40.92) with no statistical significance. **van Deursen *et al.* [24], Ambrose *et al.* [25], Nikolaou *et al.* [16] and Biegus *et al.* [17]** studies revealed that increased serum transaminases (ALT, AST) are associated with increased short-term cardiovascular mortality. However, **Ambrose *et al.* [25] and Samsky *et al.* [1],** studies demonstrated that serum ALT has neither predictive value for cardiovascular mortality nor for all-cause mortality in decompensated HF patients, including re-hospitalization.

In our study, Platelet was lower in patients with cardiovascular mortality with group A mean ± SD (211.96 ± 80.05) and with group B (268.43±69.84) with statistical significance. Also, INR was elevated in patients with cardiovascular mortality with group A mean ± SD (1.29±0.25) & with group B (1.18 ± 0.29) with statistical significance. **Okada *et al.* [26]** study revealed that elevated INR in decompensated HF failure patients was associated with increased risk of cardiovascular mortality, re-hospitalization and worsening of NYHA class. Comparative analysis of different liver function tests in relation to different major adverse cardiac events (MACE), revealed that abnormal AST was the only variable that shows significance in re-hospitalization in the group with high AST compared with the group with normal AST. There are no significant differences in other abnormal liver function tests with other major cardiac events.

The variability of the results in LFTs and cardiovascular morbidity and mortality may be related to underlying varied pathogenesis which include either congestive hepatopathy due to right sided heart failure which is manifested by elevated bilirubin and damaged hepatic synthetic function (less albumin and high INR) and less common ischemic hepatitis by hypoperfusion due to decreased cardiac output especially in patients with cardiogenic shock and presented with markedly elevated transaminases (ALT, AST) **[27, 28].**

In order to assess the relation between abnormal LFTs and different MACE, we perform linear regression analysis between each variable of MACE and different LFTs parameters. In our study, statistically significant correlation was found between cardiovascular mortality and MACE with CKD and albumin AS regarding HCV positive patient. However, no statistically significant correlation was found between cardiovascular mortality and MACE with any of liver function, CBC, CKD AS regarding HCV negative patient. **Lee *et al.* [29],** study revealed that HCV infection is associated with increased cardiovascular mortality. A retrospective cohort of more than 10,000 HCV-positive blood donors noted an increase in cardiovascular mortality in the HCV positive group (hazard ratio [HR] = 2.2, 95% confidence interval [95% CI]: 1.41-3.46) An Asian cohort of more than 1,000 HCV-positive individuals, the REVEAL study based in Taiwan, similarly found an increased risk of mortality for extrahepatic disease, when compared to HCV-negative individuals, and in particular a higher risk of death from circulatory disease (HR = 2.77, 95% CI 1.49-5.15) **[30].**

In contrast, an Australian cohort of nearly 30,000 opioid substitution therapy recipients did not find increased cardiovascular mortality in HCV-positive individuals, although it may be argued that the population examined was different in this case to the other studies [31]. **Pateria *et al.*** [32] study that compared the occurrence of cardiovascular diseases between HCV-infected and HCV-uninfected subjects found that HCV-infected patients had increased risks of cardiovascular diseasesrelated mortality (OR 1.65; 95% CI: 1.07–2.56; P = 0.02), even greater in patients with diabetes and hypertension.

CONCLUSION

Our patients with acute heart failure had younger age than other studies. High prevalence of abnormal liver function tests was found in our patients with acute heart failure reaching 77.5% of the study population.

Platelet was lower in patients with acute heart failure with seropositive group, INR was elevated in patients with acute heart failure with seropositive group, total bilirubin was higher in patients with acute heart failure with seropositive group, hypoalbuminemia is more common in patients with seropositive group.

Re-hospitalization due to HF exacerbation was found in 17 patients (22.7%) and 9 patients (12.0%) between seropositive and seronegative groups respectively. The relation of abnormal liver function tests and short-term outcome was not statistically significant. A future large study with more prolonged follow up and several measurements of liver function tests is suggestive for more evaluation of the relation of abnormal liver function tests on cardiovascular outcome in patients with acute heart failure.

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Author contribution: Authors contributed equally in the study.

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