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Association of liver and renal function impairment with major cardiac events in heart failure patients

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Abstract

Aim: We aimed to show whether liver and renal function tests impairment have an effect on cardiovascular major adverse events (MACE) in patients with chronic heart failure (CHF).

Materials and Methods: 514 Patients with Ejection Fraction (EF) <40% were screened retrospectively. Biochemical and hemogram parameters of the patients at the first admission were recorded. GFRs were calculated with the MDRD formula. Patients were classified into four groups based on whether they had just a kidney injury, only a liver damage, both a kidney and liver injury, or neither a kidney and liver injury. Exitus, stroke, and hospitalization were taken as major cardiovascular adverse events, and whether they had a major cardiovascular adverse event within one year was recorded.

Results: There was no difference between the groups in terms of exitus. When the groups were compared, a difference was found between the groups in terms of stroke, hospitalization, and MACE rates (p=0.001; p= 0.017; p=0.004, respectively). Stroke rate (13.8%) in the only kidney injury group; hospitalization (24%) and MACE (38%) in the liver + kidney injury group were found. As a result of binary logistic regression analysis, it was found that creatinine and EF predicted hospitalization for CHF, stroke, and MACE.

Conclusion: In heart failure patients, the rate of stroke was higher in the group with only kidney injury, and the rates of hospitalization and MACE were higher in the group with both liver and kidney injury. It was found that creatinine and EF predicted hospitalization, stroke, and MACE from CHF.

Introduction

Chronic heart failure (CHF) is a serious clinical syndrome caused by decreased cardiac pumping and filling functions and the effects of neurohormonal mechanisms. It is caused by the progression of various heart diseases [1]. The American Heart Association predicts an approximately 46% increase in CHF from 2012 to 2030. In 2030, It is estimated that over 8 million adults will have heart failure in the United States [2, 3]. According to the HAPPY study in Turkey, It is found that over 2 million adults have heart failure [4].

Chronic heart failure is an important cause of morbidity and mortality worldwide [2, 3, 5]. Heart failure is a common disease with high mortality and recurrent hospitalization rates. However, it is difficult to predict how the disease will progress [6]. There is a need to predict survival and hospitalization in patients with CHF [7-10]. Based on the mortality estimation results, physicians can tailor heart failure treatments to patients of varying degrees. Mortality estimation may prevent inappropriate treatment of low-mortality patients and may affect the clinical outcomes of patients with high mortality. It can also reduce unnecessary costs [11]. Predicting major cardiovascular adverse events such as mortality, recurrent hospital admissions, stroke, and recurrent hospitalizations in patients with CHF is absolutely essential to help clinicians make optimal decisions in the treatment process.

The coexistence of CHF and kidney disease is a very common condition [12, 13]. These patients have common risk factors such as diabetes and hypertension [14, 15]. Also, CHF and liver disease often occur together. The reason for this is that systemic diseases affect both organs, and there are complex cardiohepatic and cardiorenal pathologies [16].

The main purpose of this study is to evaluate the negative impact of kidney or liver damage, which often accompanies heart failure, on cardiovascular prognosis. In addition, it is

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to show whether liver and renal function tests impairments predict major cardiovascular adverse events in heart failure patients.

Materials and Methods

Ethics committee approval was obtained from Ordu University (12.12.2022-24) before starting the research. Five hundred and fourteen heart patients who had diagnosed between January 2015 and December 2021 with reduced heart failure (Ejection Fraction <40% [17]) were included in the study. Patients with moderate heart failure (ejection fraction 40-50%), heart failure with preserved ejection fraction (ejection fraction >50%), malignancy were excluded from the study. Sociodemographic characteristics, chronic diseases, smoking, New York Heart Association (NYHA) classifications [18], biochemical and hemogram parameters, ejection fractions, and rhythms on EKG were recorded. Patients who died, had a stroke and were hospitalized within 1 year after admission to the cardiology clinic were recorded. Patients were divided into four groups as those with only kidney injury, only liver injury, kidney + liver injury and no kidney + liver injury. Glomerular filtration rate was calculated with the MDRD formula (Modification of Diet in Renal Disease Study) (MDRD: 175 × plasma creatinine−1.154 × age−0.203 × 0.742 (if female) × 1.21 (if black) [19]. Alanine aminotransferase (ALT) >33 U/L, and aspartate aminotransferase (AST) >32 U/L were evaluated as liver damage. Biochemical parameters were studied on an ARCHITECT c8000 clinical analyzer (Abbott, IL, USA). The hemogram was studied on a CELL-DYN Ruby automated hematology analyzer (Abbott, IL, USA). Exitus, stroke and hospitalization status were taken as major cardiac events.

Echocardiographic measurement

Echocardiography was performed with a 3.5MHz transducer in the left lateral position (Philips Medical Systems, Andover, MA). Left ventricle ejection fraction (LVEF) was calculated by Simpson's method.

Statistical analysis

The normality of the data was evaluated with the Kolmogorov-Smirnov test and the homogeneity of the variance was evaluated with the Levene test. One Way Anova Test was used for normally distributed data. Kruskal Wallis-H Test was used for the data not normally distributed. Chi-square test was applied to categorical data. In chi-square tests, if the expected frequency of a cell was below 5, the likelihood ratio chi-square value was used instead of the Pearson chi-square value. A binary logistic regression analysis was used to find factors predicting hospitalization, stroke, and MACE. While performing the regression analysis, it was arranged according to the number of cases-events, one of the parameters that were significant in the comparison of the groups. Numerical variables were expressed as mean ± SD and median [min-max], and categorical variables were expressed as percentages. Analyzes were performed using SPSS v25 (IBM Inc., Chicago, IL, USA). The results were evaluated within the 95% confidence interval and the significance level was taken as $p<0.05$.

Results

When the groups were compared, the age of the just kidney injury group and the liver+kidney injury group were found to be substantially higher than the other groups (p0.001). Male rates were high in all groups (<0.001). The rate of hypertension was significantly higher in the only kidney injury group and liver+kidney injury group (p=0.010). Hemoglobin value was significantly higher in the only liver injury group compared to the others (p=0.002). The white blood cells were found to be significantly higher in the liver+kidney injury group than the others (p=0.59). Urea and creatinine values were found to be significantly higher (respectively p<0.001; P=0.001) and GFR lower (p<0.001) in the only kidney injury group and the liver+kidney injury group. AST and ALT values were higher in the only liver injury group and in the liver+kidney injury group (p<0.001). TG was found to be higher in the only liver injury group than the others (p=0.017). EF was significantly higher in the only kidney injury group than in the only liver injury group (p=0.037). There was no difference between the groups in terms of exitus. When the groups were compared, a difference was found between the groups in terms of stroke, hospitalization, and MACE rates (p=0.001; p= 0.017; p=0.004, respectively). Stroke rate (13.8%) in the only kidney injury group and hospitalization (24%) and MACE (38%) were found in the liver+kidney injury group (Table 1). As a result of binary logistic regression analysis; It was found that creatinine and EF predicted hospitalization from CHF, stroke and MACE (Table 2, Table 3, Table 4).

Discussion

In this study, stroke, hospitalization, and MACE rates were found to be higher in groups with the only kidney injury group and the liver+kidney injury group (p=0.001; p= 0.017; p=0.004, respectively). It was also concluded that creatinine and EF predicted hospitalization from CHF, stroke and MACE.

Strong associations between kidney disease and heart failure have been demonstrated in many previous studies. This situation can be attributed to the fact that kidney disease accelerates the inflammatory process and leads to endothelial dysfunction [14, 20]. Kidney disease can worsen cardiovascular function by causing hypertension and vascular calcification. Chronic heart failure can worsen kidney function by affecting neurohormonal mechanisms and inflammatory activation, increased venous pressure and hypoperfusion. [14, 15]. The complex and interconnected interplay of heart and kidney disease has important pathophysiological consequences in both acute disease and chronic disease states. This pathophysiological process occurs by a number of common mechanisms including heart and kidney diseases, neurohormonal, bone and mineral disorders, acid-base or fluid imbalance, metabolic and nutritional changes, and the development of anemia, as well as inflammatory and immune mechanisms. Classifications such as cardio-renal syndromes have been developed to better assess the relationship between the heart and kidney. This classification helps to better understand the complex interrelated pathophysiology of heart and kidney diseases. [21].

Table 1. Comparison of groups.

	Only liver injury mean±SD (N)	Only renal injury mean±SD (N)	Liver+renal injury mean±SD (N)	No liver+renal injury mean±SD (N)	p
Age, year	57.14±10.27	66.92±10.91	67.98±11.77	62.19±10.43	<0.001[a,c,d,e]
Gender %					
Female	%14.30 (3)	%44.30 (132)	%44 (22)	%22.10 (32)	<0.001*
Male	%85.70 (18)	%55.70 (166)	%56(28)	%77.90(113)	
Diabetes Mellitus,%(n)	%38.10(8)	%34.40(98)	%28(14)	%31.40 (44)	0.616
Hypertension, %(n)	%28.60 (6)	%58.50(155)	%67.40(31)	%44.20(61)	0.010*
Hyperlipidemia, %(n)	%14.30 (3)	%20.40(56)	%17.80(8)	%11.40(16)	0.752
Cigaret,%(n)	%42.90(9)	%27.50(64)	%27.50(11)	%36.10(43)	0.323*
Rhythm, %(n)					
Sinus	%57.10(12)	%53.90(159)	%52(26)	%54.50(79)	0.923
Atrial fibrillation	%42.90(9)	%46.10(136)	%48(24)	%45.50(66)	
Hemoglobin, g/dl	14.78±1.48	13.47±2.03	13.21±2.66	13.80±1.79	0.002[d, f]
White blood cell, 10*3/UL	7.49±2.42	8.29±4.11	10.01±4.70	7.95±3.60	0.059
Platelets, 10*3/UL	239.57±62.31	230.58±88.66	218.68±89.70	232.05±78.74	0.742
Fasting Blood Sugar,mg/dl	106.84±16.90	119.38±57.26	117.36±40.82	108.56±31.58	0.611
Urea, mg/dl	33.43±13.24	41.20±28.75	47.07±36.31	31.03±13.84	<0.001[a,c]
Creatinine, mg/dl	0.76±0.08	1.39±1.08	1.45±1.52	0.73±0.10	0.001[a,c]
GFR	108.76±13.78	61±20.29	61.08±20.40	111.02±18.15	<0.001[a,c]
C reactive protein, mg/L	7.88±7.32	7.91±9.32	11.15±14.57	8.5±9.6	0.240
AST,U/L	70.45±57.02	22.21±13.91	100.75±137.13	23.25±13.47	<0.001[c,d,f]
ALT, U/L	98.9±106.71	19.11±7.62	89.24±75.49	19.68±7.63	<0.001[c,d,f]
T. Cholesterol	194.62±44.22	188.77±46.11	181.32±51.38	189.75±46.24	0.646
HDL- Cholesterol	38.81±12.99	40.69±11.41	37.48±13.67	41.71±12.15	0.163
LDL-Cholesterol	113.67±40.30	116.42±33.30	114.37±33.34	114.05±35.64	0.904
Triglyceride	219.29±237.25	147.27±85.04	122.08±52.51	147.85±95.83	0.017[f]
Ejection Fraction, %	27.14±5.37	31.18±7.35	30±7.58	29.94±6.58	0.037[d]
BNP	3615.82±3324.93	3288.72±3678.90	3072.27±2767.81	2756.26±2602	0.395
Troponin	0.023±0.03	0.217±2.28	0.044±0.62	0.1680±1.059	0.906
Exitus % (n)	%9.50(2)	%9.10 (27)	%14 (7)	%4.80(7)	0.193
Stroke%(n)	%0(0)	%13.80(41)	%10(5)	%3.40(5)	0.001*
Hospitalization %(n)	%0 (0)	%18.50 (55)	%24(12)	%15.20(22)	0.017*
MACE	%9.50(2)	%32.20(96)	%38(19)	%20.70(30)	0.004*

GFR: Glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BNP: brain natriuretic peptide, MACE: major cardiovascular adverse events.
[a]: no kidney+liver injury group and only kidney injury group [b]: no kidney+liver injury group and only liver injury group [c]: no kidney+liver injury group and kidney+liver injury group [d]: only kidney injury group and only liver injury group [e]: only liver injury group and kidney+liver injury group [f]: only kidney injury group and kidney + liver injury group *: chi-square test.

Table 2. Factors predicting hospitalization for CHF.

	Exp (Beta)	%95 CI	p
Age	1.015	0.989-1.042	0.250
Creatinine	1.359	1.004-1.840	0.047
ALT	0.995	0.985-1.005	0.314
EF	1.047	1.012-1.084	0.008
HB	1.020	0.893-1.164	0.770

ALT: alanine aminotransferase, Ef: ejection fraction, HB: hemoglobin.

Table 3. Factors predicting stroke.

	Exp (Beta)	%95 CI	p
Age	0.976	0.938-1.016	0.235
Creatinine	4.857	2.702-8.732	<0.001
ALT	0.988	0.966-1.010	0.272
EF	1.216	1.141-1.295	<0.001
HB	1.120	0.922-1.361	0.253

ALT: alanine aminotransferase, Ef: ejection fraction, HB: hemoglobin.

Studies have shown that chronic kidney disease is an important independent predictor of increased mortality and morbidity in CHF patients. Decreased glomerular filtration rate has been shown to independently predict mortality and accelerate the progression of cardiovascular disease and CHF [12, 21, 22]. It has been reported in the publications that the coexistence of CHF and renal failure contributes to morbidity and mortality [23-25]. It has

Table 4. Factors predicting MACE.

	Exp (Beta)	%95 CI	p
Age	1.010	0.988-1.033	0.363
Creatinine	2.728	1.775-4.190	<0.001
ALT	0.998	0.992-1.004	0.553
EF	1.046	0.1013-1.080	0.006
HB	0.970	0.865-1.087	0.599

ALT: alanine aminotransferase, Ef: ejection fraction, HB: hemoglobin.

been said that even mild decreases in GFR can strongly affect all-cause mortality in patients with HF [26]. The coexistence of CHF and kidney failure negatively affects the prognosis and the frequency of their co-occurrence is high. It has been found that 40% of patients with heart failure have chronic kidney disease [23-25].

The liver is very often damaged by heart failure due to its high metabolic activity and the consequent high oxygenation requirement. Although signs of liver damage are common in heart failure, clinically significant liver dysfunction rarely occurs [27]. Liver damage results from impaired hepatic circulation due to obstruction and/or hypoperfusion. Congestive lesion is more common. It typically presents as painful hepatomegaly, increased liver function tests, increased direct bilirubin, and increased alkaline phosphatase. Severe and prolonged hepatic hypoperfusion, often accompanied by hypoxemia and may cause an increase in total bilirubin and transaminase levels. Signs of impaired proteosynthetic liver function, as well as increased bilirubin and transaminase tests, are associated with a poor prognosis. The worst prognosis is found in patients with heart failure and primary liver disease [27]. It is known that cirrhotic cardiomyopathy causes pro-inflammation and is directly related to endothelial dysfunction due to toxic factors secondary to liver failure [28, 29]. Cirrhotic cardiomyopathy is a syndrome including systolic, diastolic and electrophysiological abnormalities that damages the endothelium [16].

It has been shown in previous publications that the length and frequency of hospitalization reduces life expectancy [30]. The increase in the frequency and duration of hospitalization also draws attention in these patients because of the progressive worsening of cardiac functions and the possible risk of infection in the hospital. Similar to stroke and total MACE, it was observed that the most important predictor of hospitalization in heart failure patients was decreased renal function. Close monitoring of renal functions is important in this patient group.

Limitations

Among the important limitations of this study, it can be considered that the study was single-centered and the number of patients was not enough. Second, we used a single liver and renal functions value instead of a timed trend for our analysis.

Conclusion

Although heart failure is an important public health problem, it is a disease with high comorbidity, initiating pathophysiological processes leading to multiorgan dysfunction, and failure of vital organs such as the liver and kidney is common. While heart failure can be the initiating factor of a negative multisystem process, it continues to be a disease that contributes to the failure of these organs. While struggling with CHF, it is also important to fight with accompanying diseases. Thus, possible complications can be prevented to the greatest extent possible. In addition, knowing the accompanying complications may lead to the determination of more effective treatment strategies.

Ethical approval

Approval was obtained from Ordu University Clinical Research Ethics Committee (12.12.2022-24).

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