ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The Relationship between the Presence of Cardiohepatic Syndrome and Mortality in Heart Failure with Reduced Ejection Fraction

Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliğinde Kardiyohepatik Sendrom ve Mortalite İlişkisi

ABSTRACT

Objective: Heart failure (HF) is a major health burden that commonly affects liver function. Therefore, cardiohepatic syndrome (CHS) has been defined to describe the relationship between the heart and the liver. In this study, we aimed to evaluate the effect of CHS on long-term mortality in HF with reduced ejection fraction (HFrEF).

Methods: Patients followed at the outpatient HF clinic of our hospital with HFrEF between 2010 and 2018 were retrospectively analyzed. CHS was defined as elevation of at least two of three cholestasis parameters (total bilirubin, alkaline phosphatase, and gamma-glutamyl transferase) above the upper limit of normal. Patients were divided into two according to the presence of CHS. The endpoint was all-cause mortality. Patients were followed up for a median of 4.4 (3.3–5.9) years.

Results: A total of 469 patients were included in the study. The mean age of the group was 52.2 ± 11.9 years and 75.5% of the patients were males. About 22.4% (n = 105) of the patients had CHS. Patients with CHS were older and had more comorbidities than patients without CHS. Furthermore, significantly worse left and right ventricular functions were observed in CHS (+) group. All-cause mortality was significantly higher in CHS (+) group (61.9% vs. 19.5%, P < 0.001). Multivariate analysis revealed the presence of CHS (HR: 2.92, 95% CI: 2.09–4.07, P < 0.001) as an independent predictor of long-term mortality.

Conclusion: The presence of CHS is associated with increased long-term mortality in outpatients with HFrEF. As an easy parameter to assess from routine laboratory parameters, CHS should be used to evaluate the long-term prognosis of patients with HFrEF.

Keywords: Alkaline phosphatase, cardiohepatic syndrome, gamma-glutamyl transferase, heart failure with reduced ejection fraction, mortality, total bilirubin

ÖZET

Amaç: Kalp yetersizliği, karaciğer fonksiyonlarını sıklıkla etkileyen önemli bir sağlık sorunudur. Bu nedenle, kalp ve karaciğer arasındaki ilişkiyi belirtmek için kardiyohepatik sendrom (KHS) tanımlanmıştır. Bu çalışmada, düşük ejeksiyon fraksiyonlu kalp yetersizliği (DEF-KY) hastalarında KHS'nin uzun dönem mortalite üzerine olan etkisini değerlendirmeyi amaçladık.

Yöntem: Hastanemiz kalp yetersizliği polikliniğinde 2010-2018 yılları arasında DEF-KY ile takip edilen hastalar retrospektif olarak incelendi. KHS, üç kolestaz parametresinden (total bilirubin, alkalen fosfataz, gama-glutamil transferaz) en az ikisinin normalin üst sınırının üzerinde olması olarak tanımlandı. Hastalar KHS varlığına göre ikiye ayrıldı. Çalışmanın sonlanım noktası tüm nedenlere bağlı ölüm olarak belirlendi. Hastalar ortanca 4,4 (3,3–5,9) yıl takip edildi.

Bulgular: Çalışmaya toplam 469 hasta (yaş ortalaması 52,2 ± 11,9 yıl; %75,5'i erkek) dahil edildi. Hastaların %22,4'ünde (n = 105) KHS vardı. KHS (+) hastalar daha yaşlıydı ve daha fazla komorbiditeye sahipti. Ayrıca KHS (+) grupta anlamlı olarak daha kötü sol ve sağ ventrikül fonksiyonları gözlendi. Tüm nedenlere bağlı mortalite, KHS (+) grupta anlamlı olarak daha yüksekti (%61,9'a karşı %19,5, P < 0,001). Çok değişkenli analiz, KHS varlığını (HR: 2,92, %95 güven aralığı: 2,09–4,07, P < 0,001) uzun dönem tüm nedenlere bağlı mortalitenin bağımsız bir belirleyicisi olarak ortaya koydu.

Sonuç: KHS varlığı, ambulatuar DEF-KY'li hastalarda artmış uzun dönem mortalite ile ilişkilidir. Rutin laboratuvar parametrelerinden değerlendirilmesi kolay olan KHS, DEF-KY'li hastaların uzun dönem prognozunu değerlendirmek için kullanılabilir.

Anahtar Kelimeler: Alkalen fosfataz, kardiyohepatik sendrom, gama-glutamil transferaz, düşük ejeksiyon fraksiyonlu kalp yetersizliği, mortalite, total bilirubin

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Mustafa Azmi Sungur[1]
Aylin Sungur[2]
Aycan Esen Zencirci[1]

[1]*Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Türkiye*
[2]*Department of Cardiology, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Türkiye*

Corresponding author:
Mustafa Azmi Sungur
✉ azmisungur80@gmail.com

Received: August 18, 2023
Accepted: September 19, 2023

Cite this article as: Sungur MA, Sungur A, Zencirci AE. The Relationship between the Presence of Cardiohepatic Syndrome and Mortality in Heart Failure with Reduced Ejection Fraction. *Turk Kardiyol Dern Ars.* 2024;52(3):167-173.

DOI:10.5543/tkda.2023.25477

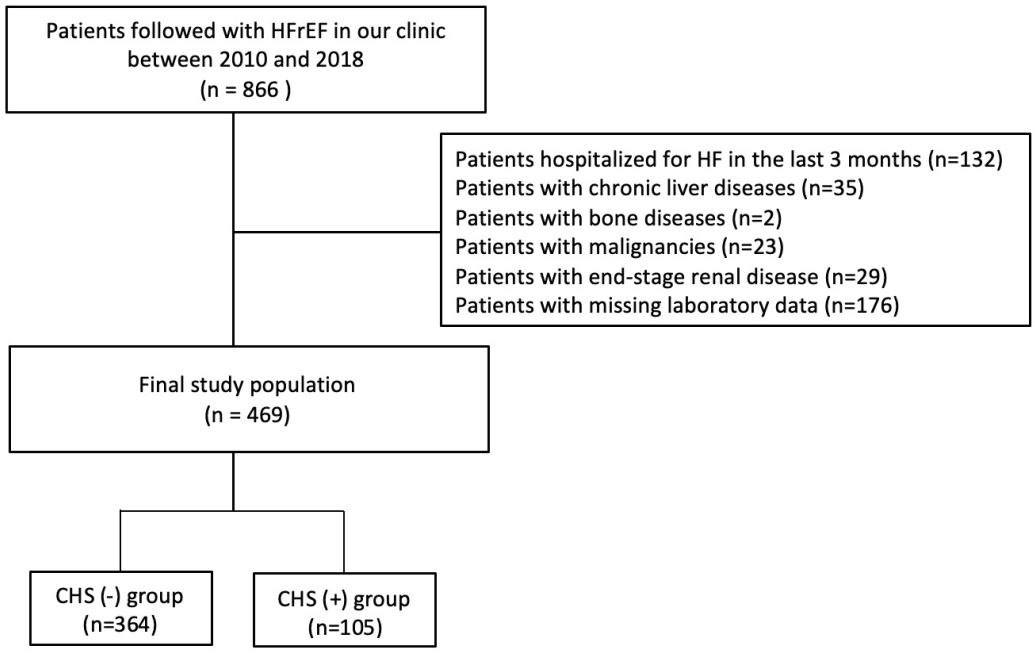


Figure 1. Flowchart of the study.
CHS, Cardiohepatic syndrome; HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction.

Heart failure (HF) is an important cause of morbidity and mortality. At present, the incidence of HF in Europe is about 5/1000 person-years in adults.[1,2] The true prevalence is likely to be higher, as studies often include cases of HF that have been diagnosed.[3] Based on studies generally in hospitalized patients, it is believed that approximately 50% of patients with HF have HF with reduced ejection fraction (HFrEF).[4,5]

The relationship between chronic HF and liver is well-defined.[6,7] The term cardiohepatic syndrome (CHS) describes liver or heart damage that occurs due to the pathology of the other. Liver has dual blood supply and receives approximately 25% of the cardiac output.[8] Therefore, the liver is more susceptible to decreased cardiac output and hepatic arterial flow. Congestion in liver usually occurs in chronic HF due to increased right-sided cardiac and thus the hepatic venous pressure.[9] The previous studies have shown that chronic HF is predominantly characterized by a cholestatic enzyme pattern while elevated transaminases are predominantly observed in acute HF. Continuous congestive stress causes an increase in serum gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and total bilirubin (TB) levels known as cholestatic parameters.[10,11] GGT level has prognostic value in HF patients regardless of age and N-terminal pro-brain natriuretic peptide.[12] Elevated TB in chronic HF has been reported as an independent predictor of cardiovascular death and all-cause mortality.[13] High ALP values were related to increased long-term mortality in chronic HF.[11] Recently, these parameters were evaluated together and CHS was defined as elevations in at least two of the three cholestatic parameters by Stolz et al.[14]

There is no information about the effect of CHS defined in this way on prognosis of patients with HFrEF. In this study, we aimed to evaluate the effect of CHS presence on long-term mortality in ambulatory patients with HFrEF.

ABBREVIATIONS

ALP	Alkaline phosphatase
CHS	Cardiohepatic syndrome
CI	Confidence interval
GGT	Gamma-glutamyl transferase
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
LVEF	Left ventricular ejection fraction
MELD-XI	Model for end-stage liver disease excluding international normalized ratio
NYHA	New York Heart Association
TB	Total bilirubin

Materials and Methods

Patients followed at the outpatient HF clinic of our hospital with HFrEF (left ventricular ejection fraction, LVEF ≤40%) between 01.2010 and 01.2018 were retrospectively analyzed. Patients that were ≥18 years of age and receiving guideline-recommended optimal treatment were included in the study. Patients hospitalized for HF in the last 3 months, patients with chronic liver diseases, bone diseases, malignancies and end-stage renal disease (estimated glomerular filtration <15 mL/min/1.73 m^2), and patients with missing laboratory data to assess CHS were excluded (Figure 1). Four hundred and sixty-nine patients constituted the final study cohort. Ethics Committee approval was obtained from Haydarpaşa Numune Training and Research Hospital (Approval Number: HNEAH-KAEK 2022/KK/118, Date: 30.05.2022) and the study conformed to the Declaration of Helsinki.

Clinical, medical, biochemical, echocardiographic, and mortality data were obtained from the medical records. The primary endpoint of the study was all-cause mortality. Patients were followed until January 2022 or to the occurrence of death.

Assessment of Cardiohepatic Syndrome

TB, GGT, and ALP levels were measured with a commercially available device. TB, GGT, and ALP were considered abnormal if >1.2 mg/dL; >39 U/L (female) and >59 U/L (male); and >105 U/L (female) and >130 U/L (male), respectively.

In line with pre-existing studies, CHS was defined as the elevation of at least two of three laboratory cholestasis parameters.[14] Patients were classified according to the presence of CHS.

The Model for End-Stage Liver Disease excluding international normalized ratio (MELD-XI) was also evaluated using the following formula: 5.11 × ln (TB [mg/dL]) + 11.76 × ln (creatinine [mg/dL]) + 9.44.[15]

Statistical Analysis

R 4.01 software (R Foundation for Statistical Computing, Vienna, Austria) with "ipw," "ggplot," "rms" packages was used for statistical analysis. Two-sided $P < 0.05$ was considered significant. Categorical data were presented as numbers (percentages) and continuous data were reported as mean ± standard deviation or median (25^{th}–75^{th} percentile). Pearson's Chi-square test was performed to compare categorical data. Continuous data were compared with Student's *t*-test or Mann–Whitney *U* test. Survival rates of the groups were compared using the log-rank test. Kaplan–Meier curves were used to display the survival probabilities of the groups. Cox regression analysis was used to define predictors of all-cause mortality and results are presented as hazard ratios (HR), 95% confidence intervals (CI), and *p* values. CHS was included in the Cox model as a dichotomic variable. All predictors were kept in the model, and no predictors were removed based on statistical significance. Variables with a missing value of more than 5% were excluded from the model. The predictive performances of models were evaluated using likelihood ratio, adjusted R^2 value, and Akaike information criterion.

Results

Table 1 presents the characteristics of the study group. The mean age was 52.2 ± 11.9 years and 75.5% (*n* = 354) of the patients were males. The mean LVEF of the group was 26.2 ± 7.5%. Coronary artery disease was present in 45.6% (*n* = 214) of the patients.

Abnormality in at least one cholestatic liver parameter was present in 47.3% (*n* = 222) of the study group. One hundred and five patients (22.4%) had CHS. Elevations in all cholestatic liver parameters were present in 27 (12.2%) patients. The most common parameters with simultaneous elevations in serum levels leading to the diagnosis of CHS were ALP and GGT (44 patients, 19.8%).

CHS (+) patients were significantly older and had more comorbidities except atrial fibrillation than patients without CHS. New York Heart Association (NYHA) functional class at enrollment showed no difference between groups. Although groups were similar regarding medical treatment, utilization of device therapy (implantable cardioverter defibrillator and cardiac resynchronization therapy) was significantly more frequent in the CHS (+) group.

In terms of laboratory parameters, all three cholestatic liver parameters were significantly higher and serum albumin level was significantly lower in CHS (+) group. No difference was observed in the other laboratory parameters among group.

Echocardiographic variables of the groups differed significantly. Patients with CHS had significantly lower LVEF, tricuspid annular plane systolic excursion, and tricuspid lateral annular systolic velocity than patients without CHS. Severe tricuspid regurgitation was more common in CHS (+) group. Significantly higher systolic pulmonary artery pressure and inferior vena cava diameter were observed in patients with CHS.

One hundred and thirty-six patients (29%) died during a median follow-up period of 4.4 (3.3–5.9) years. Mortality rate was significantly higher in CHS (+) group (61.9% vs. 19.5%, $P < 0.001$). Survival curves of the groups are illustrated in the Figure 2. The presence of CHS was identified as an independent predictor of long-term all-cause mortality (HR: 2.92, 95% CI: 2.09–4.07, $P < 0.001$) besides age, LVEF, TAPSE, and MELD-XI score in multivariate analysis (Table 2). Performance comparison of models including CHS and MELD-XI revealed that CHS outperformed MELD-XI with increased likelihood ratio and adjusted R^2 value without an increase in Akaike information criterion (Table 3). Furthermore, it can be observed in Table 3 that reduced model with age, LVEF, TAPSE, and CHS is comparable in performance to full model. We also studied the additive effect of cholestatic liver parameters on mortality and the analysis revealed that predicted mortality increases as the number of elevated cholestatic parameters increases (Figure 3).

Discussion

The present study demonstrated that CHS was common in HFrEF and its presence was an independent predictor of all-cause long-term mortality in this patient group.

HF is a syndrome with multi-system involvement and the patients with HFrEF encounter various organ dysfunctions (e.g., renal, hepatic, gastrointestinal system) throughout their life span that result in impaired quality of life and increased mortality.[16,17] Liver dysfunction is quite common in HF and has been known for a long time, yet the data about its clinical importance is sparse. Hypoperfusion and hepatic congestion lead to CHS, or cardiac hepatopathy, in HF. The latter is thought to be the primary pathology in chronic HF patients and characterized by predominant elevations in cholestatic liver parameters rather than liver transaminases.[18,19] With a prevalence of 22.4% in the present study group, CHS was common in ambulatory patients with HFrEF. Poelzl et al.[11] studied 1032 ambulatory patients with chronic HF and reported that cholestatic profile (i.e., defined as in our study) was present in 19.2% of the patients, in line with our findings.

The previous literature reports prognostic importance of isolated elevations of cholestatic liver parameters with inconsistent results. TB, not ALP, was found as one of the most significant predictors of prognosis in a *post hoc* analysis of a large cohort of chronic HF patients in which 59.5% of the group had HFrEF.[13] Furthermore, a *post hoc* analysis of PARADIGM-HF trial reported TB as the strongest predictor of cardiovascular death and HF hospitalizations among liver function parameters (where ALP and liver transaminases were available, GGT was not evaluated).[20] On the other hand, in a study of 1087 patients with stable HF,

Table 1. Baseline Characteristics of the Study Group

	Total Population (*n* = 469)	CHS (-) Group (*n* = 364)	CHS (+) Group (*n* = 105)	*P*
Age, Years	52.2 ± 11.9	51.6 ± 12	54.2 ± 11.7	**0.04**
Male	354 (75.5)	279 (76.6)	75 (71.4)	0.27
NYHA Class I/II III/IV	366 (78) 103 (22)	285 (78.3) 79 (21.7)	81 (77.1) 24 (22.9)	0.33
CAD	214 (45.6)	149 (40.9)	65 (61.9)	**<0.001**
ICD/CRT	188 (40.1)	134 (36.8)	54 (51.4)	**<0.01**
Hypertension	208 (44.3)	134 (36.8)	74 (70.5)	**<0.001**
Diabetes Mellitus	187 (39.9)	128 (35.2)	59 (56.2)	**<0.001**
CKD	130 (27.7)	75 (20.6)	55 (52.4)	**<0.001**
Atrial Fibrillation	83 (17.7)	59 (16.2)	24 (22.9)	0.12
Medications				
ACEI/ARB	372 (79.3)	295 (81)	77 (73.3)	0.09
Beta-blocker	446 (95.1)	344 (94.5)	102 (97.1)	0.27
MRA	367 (78.3)	279 (76.6)	88 (83.8)	0.12
Ivabradine	137 (29.2)	107 (29.4)	30 (28.6)	0.87
Digoxin	105 (22.4)	77 (21.2)	28 (26.7)	0.23
Loop Diuretics	390 (83.2)	299 (82.1)	91 (86.7)	0.27
Thiazide	210 (44.8)	163 (44.8)	47 (44.8)	0.99
Laboratory Parameters				
WBC (×10^3/μL)	8.8 ± 2.8	8.9 ± 2.7	8.4 ± 3	0.07
Hemoglobin (g/dL)	13.6 ± 1.7	13.6 ± 1.7	13.4 ± 1.7	0.20
Creatinine (mg/dL)	1.0 ± 0.4	1.0 ± 0.5	1.0 ± 0.2	0.71
AST (IU/L)	41.1 ± 41.1	42.8 ± 44.6	35.5 ± 24.8	0.11
ALT (IU/L)	30.2 ± 32.7	30.1 ± 35.2	30.7 ± 22	0.87
TB (mg/dL)	0.9 ± 0.8	0.7 ± 0.6	1.5 ± 1.0	**<0.001**
ALP (IU/L)	86.1 ± 37.8	72.1 ± 21.6	134.7 ± 41.3	**<0.001**
GGT (IU/L)	67.8 ± 70.9	47.6 ± 43.3	137.8 ± 98.3	**<0.001**
Albumin (g/dL)	4.0 ± 0.5	4.1 ± 0.5	3.9 ± 0.6	**<0.001**
Echocardiographic Parameters				
LVEF (%)	26.2 ± 7.5	26.9 ± 7.5	23.7 ± 7.1	**<0.001**
LVEDD (mm)	62.3 ± 8.6	62.1 ± 8.5	62.9 ± 9.0	0.41
LVESD (mm)	50.9 ± 10.3	50.7 ± 10	51.4 ± 11.3	0.50
LAAP (mm)	43.9 ± 7.1	43.4 ± 7.1	45.7 ± 6.5	**<0.01**
RVD (mm)	37.1 ± 7.5	36.5 ± 7.3	39.2 ± 8.0	**0.001**
TAPSE (mm)	18.6 ± 4.8	19.1 ± 4.8	16.8 ± 4.3	**<0.001**
RV S' Velocity (cm/s)	10.4 ± 3.0	10.7 ± 3.0	9.5 ± 2.6	**<0.001**
Severe MR	89 (19)	63 (17.3)	26 (24.8)	0.08
Severe TR	50 (10.7)	28 (7.7)	22 (21)	**<0.001**
sPAP (mmHg)	35.6 ± 22.6	33.6 ± 20.2	42.8 ± 28.5	**<0.001**
IVC (mm)	17.7 ± 5.5	17.3 ± 5.3	19.2 ± 5.7	**<0.01**
All-cause Mortality	136 (29)	71 (19.5)	65 (61.9)	**<0.001**

Categorical data are presented as numbers (percentages) and continuous data are presented as mean±standart deviation.
ACEI/ARB, Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CAD, Coronary artery disesase; CKD, Chronic kidney disease; CRT, Cardiac resynchronization therapy; GGT, Gamma-glutamyl transferase; ICD, Implantable cardioverter defibrilator; IVC, Inferior vena cava; LAAP, Left atrium anteroposterior diameter; LVEDD, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; LVESD, Left ventricular end-systolic diameter; MR, Mitral regurgitation; MRA, Mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RVD, Right ventricular basal diameter; RVS', Tricuspid lateral annular systolic velocity; sPAP, Systolic pulmonary artery pressure; TAPSE, Tricuspid annular plane systolic excursion; TB, Total bilirubin; TR, Tricuspid regurgitation; WBC, White blood cell. Bold *p* values indicate statistical significance.

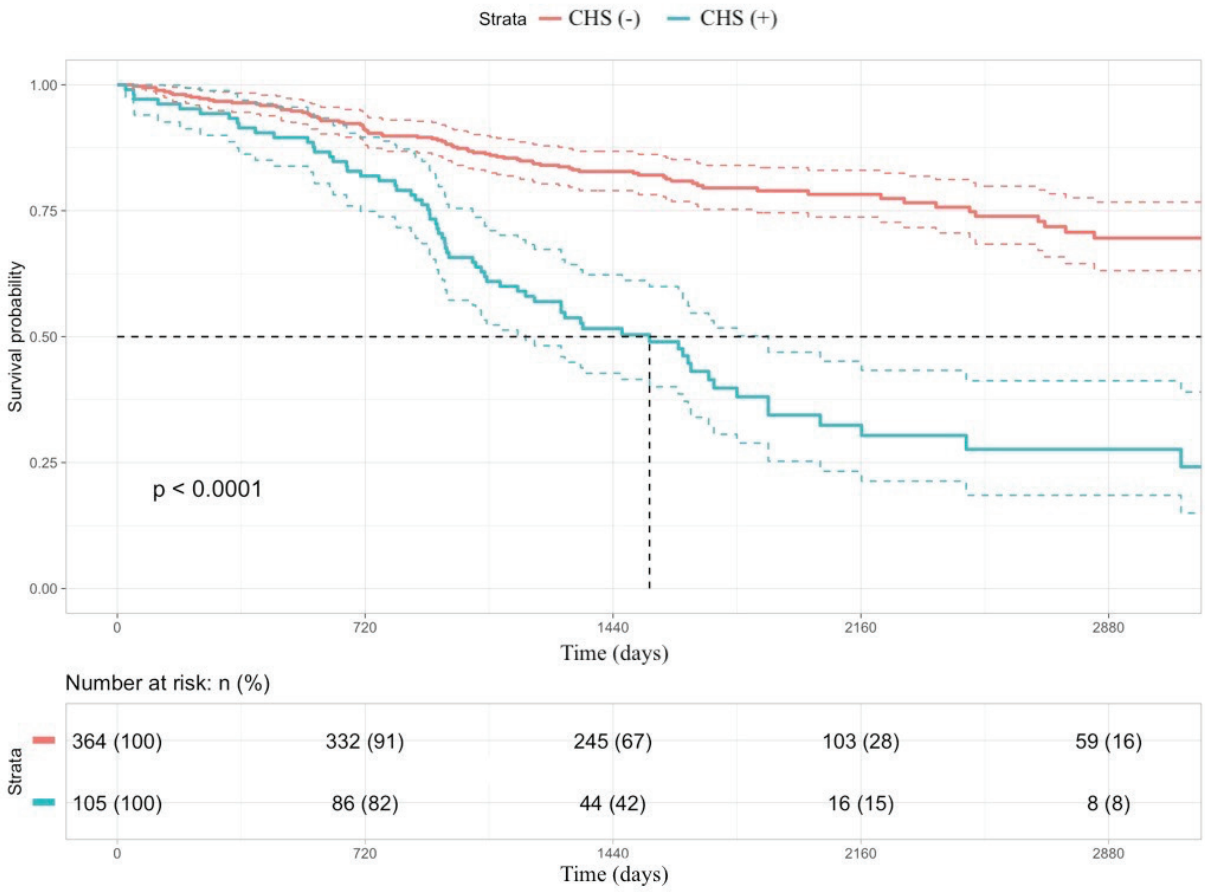


Figure 2. Kaplan–Meier curve demonstrating increased mortality in the presence of cardiohepatic syndrome (CHS).

Table 2. Cox Regression Analysis for Long-term All-cause Mortality Prediction

Variables	Full Model		Reduced Model	
	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Age	1.24 (0.99–1.56)	**0.06**	1.25 (1.01–1.56)	**0.04**
Male Gender	0.69 (0.44–1.29)	0.11		
NYHA Class III-IV	1.19 (0.77–1.85)	0.43		
Coronary Artery Disease	1.42 (0.99–2.05)	0.07		
Hypertension	0.87 (0.59–1.29)	0.50		
Diabetes Mellitus	0.84 (0.58–1.21)	0.35		
Atrial Fibrillation	0.67 (0.43–1.04)	0.07		
Hemoglobin	0.99 (0.77–1.27)	0.94		
Creatinine	1.04 (0.91–1.19)	0.55		
Albumin	1.0 (0.81–1.25)	0.94		
MELD-XI	1.79 (1.49–2.15)	**<0.001**	1.60 (1.32–1.94)	**<0.001**
CHS	3.25 (2.25–4.72)	**<0.001**	2.92 (2.09–4.07)	**<0.001**
LVEF	0.65 (0.50–0.85)	**<0.001**	0.65 (0.52–0.82)	**<0.001**
TAPSE	0.63 (0.51–0.78)	**<0.001**	0.60 (0.49–0.73)	**<0.001**

Bold *P* values indicate statistical significance.
CHS, Cardiohepatic syndrome; CI, Confidence interval; LVEF, Left ventricular ejection fraction; MELD-XI, Model for End-stage Liver Disease excluding international normalized ratio; NYHA, New York Heart Association; TAPSE, Tricuspid annular plane systolic excursion.

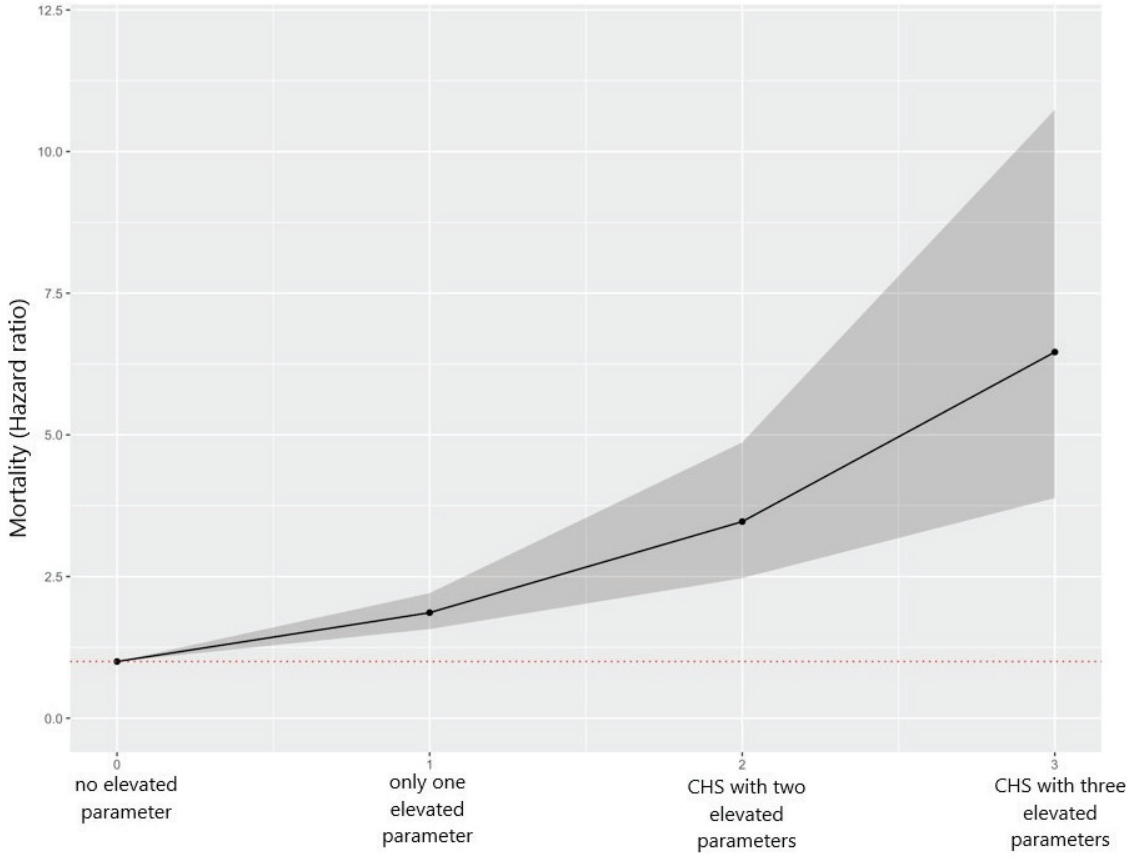


Figure 3. Hazard ratio plot displaying the additive effect of cholestatic liver parameters on mortality prediction with cubic spline regression. CHS, Cardiohepatic syndrome.

Table 3. Performance Comparison of Full and Reduced Models

	Likelihood Ratio	R^2	AIC
Full Model	128	0.246	1660
Reduced Model 1	114	0.222	1650
Reduced Model 2	98.2	0.193	1666

Full model= Age, gender, NewYork Heart Association functional class, coronary artery disease, hypertension, diabetes mellitus, atrial fibrillation, hemoglobin, creatinine, albumin, cardiohepatic syndrome, Model for End-stage Liver Disease excluding international normalized ratio (MELD-XI), left ventricular ejection fraction, tricuspid annular plane systolic excursion. Reduced model 1= Age, left ventricular ejection fraction, tricuspid annular plane systolic excursion, cardiohepatic syndrome. Reduced model 2= Age, left ventricular ejection fraction, tricuspid annular plane systolic excursion, MELD-XI. AIC, Akaike information criterion.

GGT and TB were found to be associated with disease severity but only GGT was found to be an independent predictor of prognosis. However, they also mentioned that addition of TB to GGT improves the risk stratification of these patients.[21] Poelzl et al. [11] reported that ALP and GGT, not TB, were significantly related to mortality in chronic HF with better prediction of survival if used together. ALP and GGT were also the most common combination leading to CHS diagnosis in our study. None of these studies evaluated the combined effect of these three parameters in different combinations. Our study revealed that elevation in at least two of these three parameters, that is, CHS, predicts all-cause long-term mortality in ambulatory HFrEF patients. It also showed that CHS outperforms MELD-XI score in prognostic predictive ability which is also a common parameter used to evaluate liver function.

Patients with CHS in our study had lower left and right ventricular systolic function which are well-known parameters associated with poor prognosis in HFrEF.[16] They also had higher estimated systolic pulmonary artery pressure and inferior vena cava diameter. Severe tricuspid regurgitation was more common in CHS (+) group, all of which are indirect measures of increased right-sided pressures. Although no association was found between CHS and NYHA functional class, these findings may reflect more severe disease in patients with CHS and support the literature that hepatic congestion is the main pathophysiological mechanism causing liver dysfunction in chronic HF. While CHS might develop

due to low cardiac output and increased hepatic congestion, this study showed that its effect on long-term mortality after its occurrence is independent from these parameters.

This study has several limitations. Inherent biases exist and causality cannot be established due to its retrospective observational design. Although patients with known liver diseases before enrollment were excluded from the study, some patients might have been missed. Furthermore, medications that might affect liver enzymes were not evaluated in this study. Liver function tests were assessed only once at the recruitment. N-terminal pro-brain natriuretic peptide levels of the patients were not evaluated. Furthermore, changes in medical and device therapy were not tracked during follow-up which might have impact on survival.

Conclusion

Liver dysfunction evaluated with CHS is common in stable HFrEF patients and the presence of CHS is associated with long-term all-cause mortality in this patient group. As a cost-effective and easily available parameter from three routine laboratory tests without any formula, the presence of CHS can be used to identify high-risk patients followed with HFrEF in daily clinical practice.

Ethics Committee Approval: Ethics committee approval was obtained from Haydarpaşa Numune Training and Research Hospital (Approval Number: HNEAH-KAEK 2022/KK/118, Date: 30.05.22).

Author Contributions: Concept – M.A.S., A.S., A.E.Z.; Design – M.A.S., A.S., A.E.Z.; Supervision – M.A.S., A.E.Z.; Resource – M.A.S., A.S., A.E.Z.; Materials – M.A.S., A.S.; Data Collection and/or Processing – M.A.S., A.S.; Analysis and/or Interpretation – A.E.Z.; Writing – M.A.S., A.S.; Critical Review – M.A.S., A.S., A.E.Z.

Peer-review: Externally peer-reviewed.

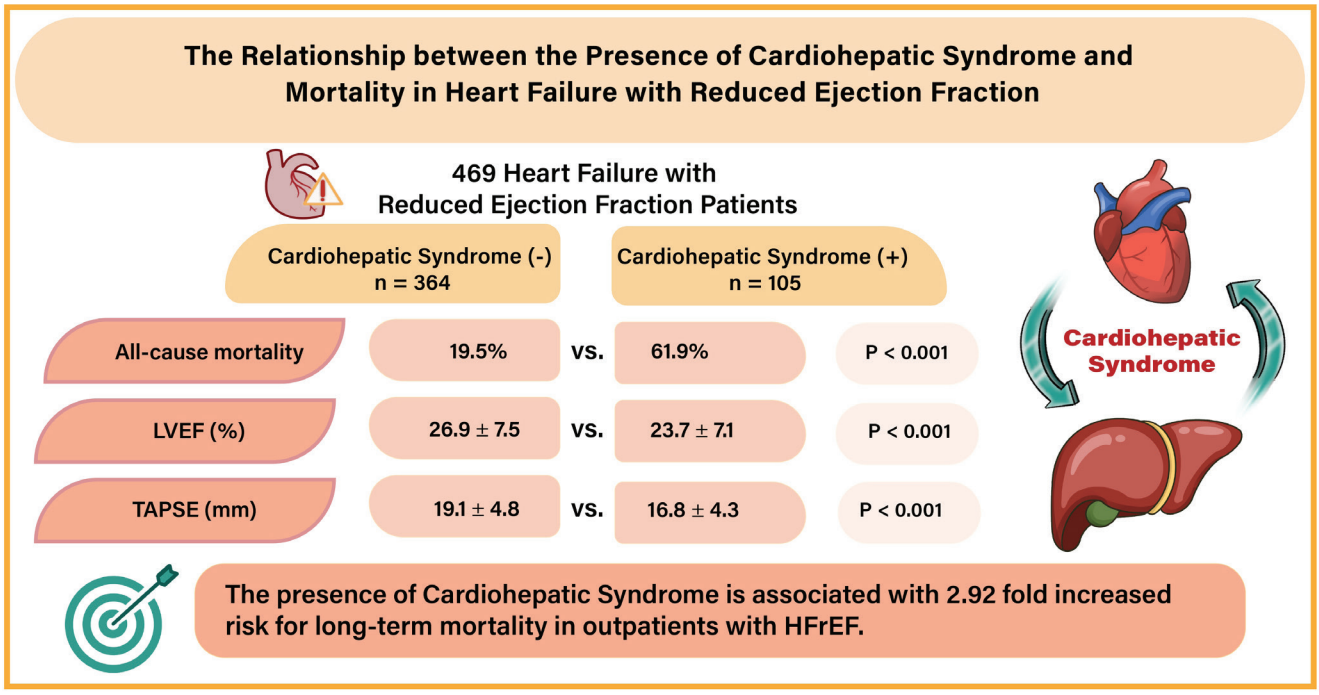
Use of AI for Writing Assistance: No artificial intelligence applications were used in the development of the article.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study received no financial support.

References

1. Meyer S, Brouwers FP, Voors AA, et al. Sex differences in new-onset heart failure. *Clin Res Cardiol.* 2015;104(4):342-350. [CrossRef]
2. Brouwers FP, de Boer RA, van der Harst P, et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J.* 2013;34(19):1424-1431. [CrossRef]
3. van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. *Eur J Heart Fail*. 2014;16(7):772-777. [CrossRef]
4. Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J*. 2004;25(18):1614-1619. [CrossRef]
5. Koh AS, Tay WT, Teng THK, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail*. 2017;19(12):1624-1634. [CrossRef]
6. Fouad YM, Yehia R. Hepato-cardiac disorders. *World J Hepatol*. 2014;6(1):41-54. [CrossRef]
7. Alvarez AM, Mukherjee D. Liver abnormalities in cardiac diseases and heart failure. *Int J Angiol*. 2011;20(3):135-142. [CrossRef]
8. Lautt WW, Greenway CV. Conceptual review of the hepatic vascular bed. *Hepatology*. 1987;7(5):952-963. [CrossRef]
9. Hilscher M, Sanchez W. Congestive hepatopathy. *Clin Liver Dis (Hoboken)*. 2016;8(3):68-71. [CrossRef]
10. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. *Am J Cardiol*. 2002;90(12):1405-1409. [CrossRef]
11. Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. *Eur J Clin Invest*. 2012;42(2):153-163. [CrossRef]
12. Poelzl G, Eberl C, Achrainer H, et al. Prevalence and prognostic significance of elevated gamma-glutamyltransferase in chronic heart failure. *Circ Heart Fail*. 2009;2(4):294-302. [CrossRef]
13. Allen LA, Felker GM, Pocock S, et al.; CHARM Investigators. Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Eur J Heart Fail*. 2009;11(2):170-177. [CrossRef]
14. Stolz L, Orban M, Besler C, et al. Cardiohepatic syndrome is associated with poor prognosis in patients undergoing tricuspid transcatheter edge-to-edge valve repair. *JACC Cardiovasc Interv*. 2022;15(2):179-189. [CrossRef]
15. Heuman DM, Mihas AA, Habib A, et al. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. *Liver Transpl*. 2007;13(1):30–37. [CrossRef]
16. McDonagh TA, Metra M, Adamo M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42(36):3599-3726. Erratum in: *Eur Heart J.* 2021.
17. Ciccarelli M, Dawson D, Falcao-Pires I, et al. Reciprocal organ interactions during heart failure: a position paper from the ESC Working Group on Myocardial Function. *Cardiovasc Res.* 2021;117(12):2416-2433. [CrossRef]
18. Poelzl G, Auer J. Cardiohepatic syndrome. *Curr Heart Fail Rep*. 2015;12(1):68-78. [CrossRef]
19. Xanthopoulos A, Starling RC, Kitai T, Triposkiadis F. Heart failure and liver disease: Cardiohepatic interactions. *JACC Heart Fail*. 2019;7(2):87-97. [CrossRef]
20. Suzuki K, Claggett B, Minamisawa M, Packer M, Zile MR, Rouleau J, et al. Liver function and prognosis, and influence of sacubitril/valsartan in patients with heart failure with reduced ejection fraction. *Eur J Heart Fail*. 2020;22(9):1662-1671. [CrossRef]
21. Ess M, Mussner-Seeber C, Mariacher S, et al. γ-Glutamyltransferase rather than total bilirubin predicts outcome in chronic heart failure. *J Card Fail*. 2011;17(7):577-584. [CrossRef]



@PAY 2024 Sungur MA et al. Turk Kardiyol Dern Ars. 2024;52(3):167-173.