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ORIGINAL ARTICLE

Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance

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ABSTRACT

Background Although abnormal liver morphology and function have long been recognized, characterization and importance of liver dysfunction in heart failure are poorly defined. This study sought to investigate the relevance of circulating liver function tests (LFTs) in an unselected chronic heart failure (CHF) cohort.

Materials and methods A total of 1032 consecutive ambulatory patients with CHF were enrolled from 2000 to 2008. Clinical and laboratory variables including LFTs were collected at study entry. Follow-up (median 36 months) was available in 1002 (97·1%) patients. The endpoint was defined as death from any cause or heart transplantation. Hazard ratios (HR) for transplant-free survival were estimated per log unit using Cox proportional hazard regression models for sex-stratified data.

Results Sex-specific prevalence of cholestatic enzyme elevation was 19·2% as opposed to elevated transaminases in 8·3%. Cholestatic enzymes, but not transaminases, were significantly associated with severity of heart failure syndrome and backward failure. The endpoint was recorded in 339 patients (33·8%). T-Bil, γ-glutamyltransferase (GGT) and alkaline phosphatase (ALP) were associated with adverse outcome in bivariate models. Of these, GGT [HR 1·22 (1·06, 1·41); $P = 0·006$] and ALP [HR 1·52 (1·09, 2·12); $P = 0·014$] were independently associated with the endpoint after adjustment for a wide array of clinical and laboratory predictors.

Conclusions Liver dysfunction is frequent in CHF and characterized by a predominantly cholestatic enzyme profile that is associated with disease severity and prognosis. Thus, we propose a cardio-hepatic syndrome in CHF. Future studies are needed to clarify the exact mechanisms of organ interaction.

Keywords Cardio-hepatic syndrome, chronic heart failure, liver enzymes, prognosis.

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Introduction

Heart failure is a systemic clinical syndrome characterized by the involvement of multiple organ systems. Full appreciation of the syndrome's complexity demands exact characterization of interrelated organ derangements. However, whereas the cardio-renal syndrome has been studied extensively in recent years [1], data on characterization and significance of liver function abnormalities are sparse. This is remarkable because abnormal liver morphology and function in patients with heart failure have long been recognized. The first description of congested nutmeg liver in patients dying from heart failure dates back to the mid-19th century, and abnormal results of biochemical liver function tests (LFTs) were demonstrated early in the 20th century [2]. Whereas the histopathological pattern of impaired liver function is well characterized [3–5], the profile of abnormal LFTs in heart failure is not clearly defined. Historically, LFT abnormalities in heart failure have been attributed to hepatic congestion and/or impaired arterial perfusion [2,6,7]. Elevation of both transaminases and cholestatic enzymes was reported in several cohorts across the full spectrum of heart failure severity [3,4,8–13]. Also, transaminases and total bilirubin (T-Bil) as well as γ-glutamyltransferase (GGT) have been associated with poor outcome in heart failure [12–16].

Given the convenient availability and the frequently noted alterations in LFTs in heart failure patients, a better

understanding and characterization of liver dysfunction are of great interest. Thus, the purpose of the study was (i) to identify the characteristic pattern of LFT abnormalities in a large well-defined cohort of consecutive, nonselected patients with chronic heart failure (CHF) because of ischaemic and non-ischaemic cardiomyopathy and (ii) to evaluate the prognostic impact of elevated LFTs in CHF.

Methods

Study population

For this retrospective analysis, we made use of a data set consisting of 1053 consecutive Caucasian heart failure patients who were recruited between April 2000 and May 2008 at the *specialized* heart failure clinic of a university hospital in western Austria. Eligible patients were ≥ 18 years of age. CHF diagnosis was based on the presence of current or previous symptoms or characteristic clinical signs and on evidence of left ventricular dysfunction. Patients were included irrespective of the underlying cause of heart failure and were treated according to prevailing CHF guidelines. All patients were followed up to December 2008 (time of data censoring) or to the occurrence of death or heart transplantation. Death events were retrieved from the Tyrolean Mortality Register and personal contacts with members of patient families. Twenty-one (1·9%) patients were excluded from this study because of incomplete baseline data. Hence, this analysis comprises 1032 participants. Of these, follow-up information was available in 1004 (97·2%) patients. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Innsbruck Medical University.

Measurements

All laboratory variables were measured by a central laboratory that undergoes regular internal and external quality audits. Serum T-Bil, GGT, alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were measured at 25 °C with a Roche/Hitachi analyzer (Hitachi Corp.,Tokyo, Japan) until 2003 and thereafter at 37 °C with a Modular P800 analyzer (Hitachi Corp.) using reagents from Roche Diagnostics. Measurements were taken in fasting blood samples on the day of blood collection and are given as units per litre (GGT, ALP, AST and ALT) or micromoles per litre (T-Bil). The upper laboratory reference limits differed by sex. Values for GGT, ALP and AST/ALT in men were 65, 130 and 50 U/L, respectively. Respective values in women were 38, 105 and 35 U/L. T-Bil upper limit was 21·9 μM for both sexes. Laboratory results before 2003 were accordingly adjusted to results obtained at 37 °C using recommended multiplication factors (= GGT × 2, ALP × 0·7, AST × 2·5 and ALT × 1·7).

Transthoracic echocardiography (TTE) was performed in all participants, and left ventricular ejection fraction (LV-EF) as measured by the biplane Simpson's rule and severity of tricuspid regurgitation were evaluated. Systolic pulmonary artery pressure was derived either from transthoracic Doppler echocardiography using the Bernoulli equation or from Swan-Ganz catheterization measurements. Clinical, laboratory and echocardiographic measurements were obtained on the same day in > 90% of the patients.

Statistical analysis

Cross-sectional associations between LFTs and established heart failure variables were assessed by means of bivariate correlation and multiple linear regression analyses; Pearson's correlation coefficients and standardized beta coefficients are presented. Additionally, sex-specific prevalence of elevated LFTs is given for the entire study group as well as for various patient subgroups. Kruskal–Wallis and chi-square tests were applied to test for differences in prevalence of elevated LFTs between patient groups. Assessment of the prognostic relevance of LFTs for transplant-free survival was performed using sex-stratified Cox proportional hazards regression analyses, again in bivariate and multivariable manner. Variables for the bivariate Cox proportional hazards regression analyses were selected based on clinical relevance and data from the existing literature. The variable entry criterion for multivariable models was set at $P < 0{\cdot}25$ in bivariate analyses. Because several covariates were highly correlated (e.g. correlation of regression coefficients was 0·61 for AST with ALT and 0·44 for GGT with ALP), two final multivariable, sex-stratified models were estimated. The prognostic significance of LFTs was further tested by calculating partial proportions of explained variation (PEV) according to the method of Heinze and Schemper [17]. Because of their skewed distribution, all parametric analyses were performed on natural logarithm-transformed LFTs. Results of endpoint and sex-stratified Kolmogorov–Smirnov testing for normality as well as inspection of Q–Q plots indicated approximately normal distribution for all log-transformed variables. *P*-values < 0·05 were considered to indicate statistical significance. Statistical analysis was performed using the SPSS software package (SPSS 17.0 for Windows; SPSS Corp., Munich, Germany).

Results

Clinical characteristics

Characteristics of study patients are shown in Table 1. Of 1032 patients, 333 (32·3%) had heart failure of ischaemic and 699 (67·7%) of nonischaemic origin. Patients had a median age of 61 (range 18–93) years and included 777 (75·3%) men and 255 (24·7%) women.

Table 1 Patient characteristics

			Death or heart transplantation			
	All subjects		**Subjects without event**		**Subjects with event**	
	***n* = 1032**		***n* = 665**		***n* = 339**	
Variable	**Median or %**	**IQR**	**Median or %**	**IQR**	**Median or %**	**IQR**
Demographic and clinical						
Age (years)	61	53–69	60	50–68	63	57–72
Gender (male)	75·3%		73·1%		79·6%	
LV-EF (%)	28	22–37	29	23–38	27	20–35
Heart rate (bpm)	75	64–86	73	63–85	77	68–88
BMI	25·6	23–28	26	23·6–28·4	25	22·5–27·8
NYHA Class I	25%		33·5%		8·5%	
NYHA Class II	46·1%		49·2%		40·4%	
NYHA Class III/IV	28·8%		17·3%		51%	
Previous hospitalization for heart failure	62·6%		58·5%		71·3%	
Ischemic aetiology	32·2%		25·6%		45·4%	
A-Fib	26·9%		23·4%		34·2%	
Medical history						
Hypertension	44·5%		46·2%		42·9%	
Diabetes	20%		16·6%		26·3%	
Alcohol consumption at study entry	14·5%		14·2%		15·1%	
Laboratory testing (serum)						
T-Bil (μM)	**12·5**	**8·9–17·1**	**11·8**	**8·6–16·4**	**13·6**	**9·7–19·3**
GGT (U/L)	**50**	**28–103**	**44**	**26–84**	**72**	**36–139**
SAP (U/L)	**74·6**	**58·3–96·7**	**69**	**57–89**	**81**	**64–112**
AST (GOT) (U/L)	**27·5**	**22·5–36·2**	**27**	**22·5–35**	**29**	**23–37·9**
ALT (GPT) (U/L)	**24**	**18–35·7**	**25**	**18–37**	**23**	**17–33**
NT-proBNP (ng/L)	1260	444–2930	961·5	376–2199	2775	1355–5523
GFR (mL/min/1·73 m^2)	73·2	57·4–91·7	75·9	61–95·6	66·9	51·2–83·4
Medication						
ACE inhibitor/ARB	83·5%		84·2%		81·8%	
Beta-blocker	60·7%		63·6%		53·3%	
Spironolactone	27·5%		22·6%		36%	
Diuretic	71·7%		63·5%		87·5%	

Data from 1032 patients are reported as number (percentage) or median (interquartile range). Data on NT-proBNP were available in 485 patients. For all other variables, < 5% of data were missing. LFT variables are presented in boldface.
LV-EF, left ventricular ejection fraction; BMI, body mass index; A-Fib, atrial fibrillation; T-Bil, total bilirubin; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; GFR, glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

LFT levels in heart failure

Prevalence of sex-specific elevated LFTs was high in the overall cohort (T-Bil 15·2%, GGT 46%, ALP 12%, AST 13% and AST 13·3%). A cholestatic profile (i.e. at least two cholestatic enzymes elevated) was found in 19·2% of patients. Transaminases were elevated in 8·3%. A mixed profile of elevated LFTs was observed in 3·5% of patients. The relevant LFT differences in various subgroups are shown in Appendix 1. Of note, the proportion of patients with elevated LFTs was higher in women with the exception of T-Bil, which occurred more often in men (17·8% vs. 7·7%; $P < 0·001$). Also, elevations in T-Bil (17·2% vs. 14·1%), GGT (49·1% vs. 42·9%) and ALP (14·6% vs. 7·7%) were more frequently observed in patients with a history of heart failure of ≥ 6 months duration ($P < 0·05$ for all parameters). As expected, prevalence of GGT elevation was greater in patients with a history of alcohol consumption (58·9% vs. 43·6%; $P < 0·001$) although the corresponding percentage in non-alcohol consumers with CHF was still higher than that reported in healthy subjects (18·6% in men, 19·2% in women) [18].

Associations between LFTs and severity of heart failure and right ventricular dysfunction

Because in this outpatient study population, only a minority of patients were classified as NYHA Class IV ($n = 13$; 1·3%), patients in NYHA Classes III and IV were pooled for further analysis (NYHA I 25%, II 46·2%, III/IV 28·8%). Median levels of T-Bil, GGT and ALP clearly increased with every NYHA Class (Fig. 1). The differences between groups were significant for both women and men. A significant stepwise increase in median serum levels according to decreasing LV-EF category (> 35%, 26–35%, ≤ 25%) and decreasing quartile for pulse pressure was seen for T-Bil ($P < 0·001$ and $P < 0·001$, respectively) and GGT ($P = 0·002$ and $P = 0·014$, respectively; Appendix 2). Moreover, in a subgroup of 486 patients with measurements available for NT-proBNP, T-Bil, GGT and ALP levels were closely related to increasing quartiles for NT-proBNP ($P = 0·001$). Of note, neither AST nor ALT levels were associated with severity of heart failure.

A stepwise increase in median levels of T-Bil, GGT and ALP was also seen with increasing categories of pulmonary artery pressure (< 35, 35–45, 46–60 and > 60 mmHg) ($P < 0·001$ for all parameters) and severity of tricuspid regurgitation (none, mild, moderate and severe) ($P < 0·001$ for all parameters). T-Bil, GGT and ALP levels were also elevated in patients with jugular vein (JV) distension and peripheral oedema ($P < 0·001$, respectively; Appendix 2).

LFT correlates

Age- and sex-adjusted associations among liver enzymes were high for AST and ALT ($r = 0·70$), and GGT and ALP ($r = 0·49$), moderate for GGT and AST ($r = 0·39$), GGT and ALT ($r = 0·32$), T-Bil and GGT ($r = 0·32$), ALP and AST ($r = 0·27$), ALP and ALT ($r = 0·18$), T-Bil and ALP ($r = 0·18$), and T-Bil and AST ($r = 0·22$; all $P < 0·001$), but weak for T-Bil and ALT ($r = 0·08$; $P = 0·033$).

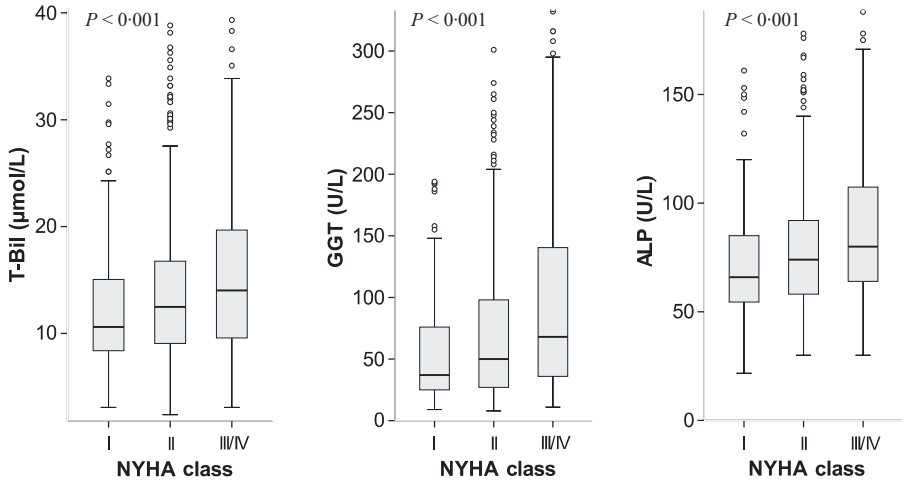


Figure 1 T-Bil, GGT and ALP levels are presented as box (25th percentile, median, 75th percentile) and whisker plots together with *P*-values as assessed with the Kruskal–Wallis test. Median (IQR) values for progressing NYHA Classes for T-Bil (µM) were 10·6 (6·9), 12·7 (7·3) and 14·0 (10·1), for GGT (U/L) 38 (56·5), 49 (73) and 69 (105), and for ALP (U/L) 66 (31·0), 74 (34·0) and 80 (43·4), respectively. T-Bil, bilirubin; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase.

Cross-sectional correlates of LFTs with various heart failure-related variables as assessed in bivariate and multivariable analyses are given in Table 2. Cholestatic variables were strongly correlated with most of the signs and indices of right heart failure as studied in this cohort. Of these, only the presence of JV distension, peripheral oedema and tricuspid regurgitation remained independently predictive of cholestatic enzyme elevation. By contrast, none of the associations between cholestatic enzymes and LV-EF and pulse pressure as indirect measures of forward failure were independent correlates in multiple linear regression analyses with the exception of T-Bil, which was correlated with LV-EF.

Alcohol consumption at study entry, as expected, was strongly correlated with GGT. Interestingly, an independent association was also observed between alcohol and ALP and AST.

LFTs predict transplantation-free survival in patients with heart failure

Median follow-up time was 36 (IQR 16, 63) months. A total of 256 (25·5%) patients died, and 83 (8·3%) underwent heart transplantation as their first event. The median transplant-free survival time estimated from the Kaplan–Meier function was 60 months.

In bivariate sex-stratified Cox regression analysis, T-Bil, GGT and ALP, but not AST or ALT, were predictors of death or heart transplantation (Table 3). Considering the high level of collinearity between GGT and ALP and between AST and ALT, two final multivariable, sex-stratified models were constructed that included relevant clinical and laboratory predictors; the first model showed GGT [HR 1·22 (1·06–1·41); $P = 0·006$] and the other model ALP [HR 1·52 (1·09–2·12); $P = 0·014$] to be an independent predictor of death or heart transplantation (Table 3). Neither T-Bil nor AST was seen to be independent predictors of adverse events in the multivariable models. In a subgroup of 485 patients, the predictive accuracy of GGT [HR 1·23 (1·01–1·5); $P = 0·037$] and ALP [HR 1·86 (1·1–3·1); $P = 0·018$] was also independent of NT-proBNP.

Partial PEVs for prediction of death or heart transplantation were significantly lower for T-Bil (0·09%) than for GGT (1·03%, $P = 0·0009$) or ALP (1·06%, $P = 0·001$), and comparable for GGT and ALP ($P = 0·838$). This was further supported by unadjusted ROC analysis. The area under the curve generated for GGT was 0·64 (95% CI 0·60–0·67), and for ALP 0·61 (95% CI 0·57–0·65); ($P < 0·001$, respectively). In bivariate sex-stratified Cox regression analysis based on either sex-specific cut-off values as derived from the ROC analysis (36 U/L in women and 69 U/L in men for GGT; 111 U/L in women and 68 U/L in men for ALP) or as suggested by the manufacturer, elevations of GGT [HR 1·82 (1·48–2·25); $P < 0·001$, and HR 1·74 (1·42–2·15); $P < 0·001$, respectively] as well as ALP [HR 2·06 (1·65–2·59); $P < 0·001$, and HR 1·9 (1·48–2·6); $P < 0·001$] were significantly associated with adverse outcome.

When patients were classified into four groups (GGT−/ALP−, GGT+/ALP−, GGT−/ALP+ and GGT+/ALP+) according to sex-specific cut-off levels as derived from the ROC analysis, an additive value of GGT and ALP in the prediction of transplant-free survival was evident (Fig. 2).

Table 2 Cross-sectional correlates of LFTs: bivariate and multivariate associations with heart failure-related variables

	T-Bil ($\log_e$) ($r^2 = 0·146$)		GGT ($\log_e$) ($r^2 = 0·175$)		ALP ($\log_e$) ($r^2 = 0·121$)		AST ($\log_e$) ($r^2 = 0·040$)		ALT ($\log_e$) ($r^2 = 0·043$)	
	R	β	*r*	β	*R*	β	*r*	β	*r*	β
JV distended	0·190***	0·085*	0·193***	0·096**	0·128***	0·001	0·038		−0·013	
Oedema	0·214***	0·147***	0·204***	0·107**	0·251***	0·200***	0·033		−0·068*	−0·056
TR mod./severe	0·240***	0·142**	0·242***	0·160***	0·218***	0·128**	0·078*	0·074	−0·003	
PAP > 45 mmHg	0·226***	0·063	0·205***	0·050	0·171***	0·049	0·083*	0·040	0·013	
LV-EF (%)	−0·175***	−0·094*	−0·144***	−0·054	−0·011		−0·018		−0·059	−0·011
PP (mmHg)	−0·158***	−0·067	−0·111***	−0·017	−0·051*	−0·008	−0·034	0·028	−0·068*	−0·006
NYHA Class III/IV	0·126***	−0·034	0·160***	0·083*	0·160***	0·042	0·051	0·021	−0·012	
HF duration > 6 months	0·113**	0·024	0·111***	0·064	0·058	0·007	0·023		−0·057	−0·067
Alcohol	0·020		0·172***	0·144***	0·070*	0·115**	0·119***	0·094*	0·064	0·006

Age- and sex-adjusted Pearson's correlation coefficients and standardized beta coefficients are presented (*$P < 0·05$; **$P < 0·01$; ***$P < 0·001$).
JV, jugular vein; TR, tricuspid regurgitation; PAP, pulmonary artery pressure; LV-EF, left ventricular ejection fraction; LFTs, liver function tests; PP, pulse pressure; HF, heart failure.

Table 3 Crude and adjusted sex-stratified Cox regression analyses for heart transplant-free survival

			Multivariable Cox models			
	Bivariate Cox model		T-Bil, GGT, AST adjusted		T-Bil, ALP, AST adjusted	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
T-Bil (per log unit)	**1·28 (1·05–1·56)**	**0·016**	**1·00 (0·80–1·25)**	**0·99**	**0·99 (0·78–1·26)**	**0·95**
GGT (per log unit)	**1·46 (1·30–1·65)**	**< 0·001**	**1·22 (1·06–1·41)**	**0·006**		
ALP (per log unit)	**2·50 (1·89–3·31)**	**< 0·001**			**1·52 (1·09–2·12)**	**0·014**
AST (per log unit)	**1·25 (0·97–1·61)**	**0·083**	**1·09 (0·81–1·46)**	**0·57**	**1·16 (0·86–1·55)**	**0·33**
ALT (per log unit)	**0·89 (0·73–1·09)**	**0·253**				
Age (per year)	1·03 (1·03–1·04)	< 0·001	1·01 (1·00–1·02)	0·044	1·01 (0·99–1·02)	0·092
BMI (per kg/m^2)	0·94 (0·92–0·97)	< 0·001	0·95 (0·92–0·98)	0·001	0·95 (0·92–0·98)	0·004
Diabetes (no/yes)	1·59 (1·25–2·03)	< 0·001	1·11 (0·84–1·46)	0·47	1·09 (0·82–1·47)	0·54
Alcohol (no/yes)	0·85(0·67–1·07)	0·17	1·04 (0·74–1·46)	0·82	1·03 (0·72–1·47)	0·89
Ischemic aetiology	2·07 (1·67–2·57)	< 0·001	1·46 (1·15–1·87)	0·002	1·50 (1·16–1·93)	0·002
LV–EF (per %)	0·99 (0·98–1·00)	0·057	1·00 (0·99–1·01)	0·47	1·00 (0·99–1·01)	0·70
NYHA Class (II vs. I)	3·03 (2·03–4·52)	< 0·001	2·86 (1·77–4·63)	< 0·0001	2·68 (1·61–4·44)	< 0·001
NYHA Class (III/IV vs. I)	8·01 (5·4–11·88)	< 0·001	5·63 (3·46–9·17)	< 0·0001	5·28 (3·16–8·80)	< 0·001
GFR (per log unit)	0·44 (0·36–0·54)	< 0·001	0·68 (0·53–0·88)	0·003	0·69 (0·53–0·90)	0·006

Multivariable Cox proportional hazards regression models were estimated with either T-Bil, GGT and AST or T-Bil, ALP and AST entered plus potential confounders (adjustment). Liver function test variables are presented in boldface.
T-Bil, total bilirubin; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; LV-EF, left ventricular ejection fraction; GFR, glomerular filtration rate.

Discussion

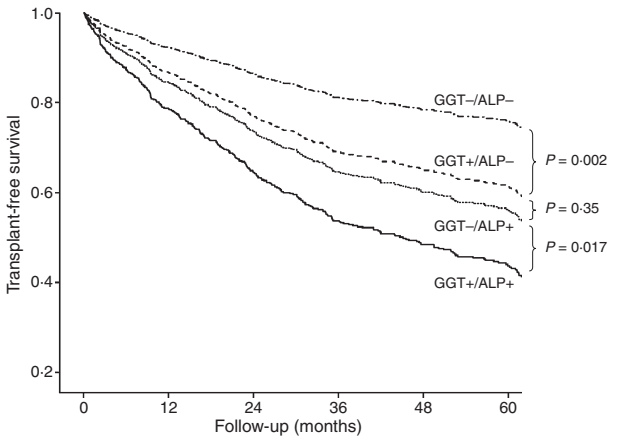
The present study clearly characterizes components and correlates of liver dysfunction in a well-defined cohort of patients with CHF. We demonstrate a high prevalence of elevated cholestatic liver enzymes and a direct association with disease severity. GGT and ALP also provide prognostic information independently of established clinical and biochemical risk factors. Thus, we propose a cardio-hepatic syndrome in CHF that shares features with the cardio-renal syndrome. These findings emphasize the importance of heart failure as a syndrome of multiple failing organs and underscore a holistic approach to its understanding.

Role of LFTs in heart failure

In this study, the percentage of sex-specific elevations of cholestatic LFTs above the upper limit of normal was clearly higher than in healthy subjects. Prevalence of GGT, which was most frequently seen to be elevated, was more than twice that in a large, age-matched healthy Austrian population (46% vs. 19%) [12,18]. Also, elevations in T-Bil (15·2% vs. 3·2%) and ALP (12% vs. 9·1%) were more prevalent in this cohort of patients with stable heart failure than in healthy subjects, whereas elevations in aminotransferases (8·3%) were within the range of those seen in a general US population (7·9%) [19–21]. Prevalence data on LFT abnormalities compare well with data from previous studies in stable CHF [9,10,13].

The relatively common predominantly cholestatic enzyme pattern (19·2%) observed in this study is consistent with previous data reported in patients with stable heart failure [2,10,11,13,22]. By contrast, acute heart failure and cardiogenic shock were repeatedly associated with a predominant rise in transaminases [4,9,23–25]. Consequently, it can be postulated that in CHF, the cardio-hepatic syndrome is characterized by a predominant cholestatic enzyme pattern, whereas in acute heart failure, a rise in transaminases prevails.

Elevations in cholestatic enzymes were associated with severity of the heart failure syndrome as assessed by NYHA classification and, in a subgroup of patients, with NT-proBNP levels. Furthermore, T-Bil, GGT and ALP correlated with signs of congestion and right heart failure. By contrast, only a weak association was seen with markers of forward failure, such as LV-EF and pulse pressure.



Number of patients at risk (events)

GGT–/ALP+	277	225 (26)	175 (17)	133 (8)	98 (3)	44 (3)
GGT+/ALP–	140	116 (18)	91 (15)	76 (7)	60 (7)	29 (4)
GGT–/ALP+	158	122 (25)	94 (14)	68 (14)	53 (4)	27 (3)
GGT+/ALP+	227	169 (45)	130 (27)	94 (23)	71 (9)	40 (7)

Figure 2 Kaplan–Meier transplant-free survival curves for patients stratified according to sex-specific cut-off levels of γ-glutamyltransferase (GGT) and alkaline phosphatase (ALP) as derived from ROC analysis are shown and compared with the log-rank test. Cut-off level for GGT = 69 U/L in men and 36 U/L in women; cut-off level for ALP = 68 U/L for men and 111 U/L for women.

The relation with right-side heart failure is supported by previous findings that indicated a correlation between cholestatic enzymes and the severity of tricuspid regurgitation [22]. Also, recent data show an independent relationship of direct bilirubin, ALP and GGT with central venous pressure but not with cardiac index in 323 patients with CHF [26]. Therefore, backward rather than forward failure appears to be the predominant cause of LFT elevation in CHF. Hyperaemia and congestion of the central zone of the hepatic lobule are the histopathological substrates of nonischaemic cardiac hepatopathy [4,6]. GGT and ALP are localized in the biliary epithelium and elevated in conditions involving bile canaliculus damage [27]. By contrast, transaminases are released after hepatocellular injury or death. The liver's complex dual blood supply, however, makes it relatively resistant to hepatocyte necrosis resulting from haemodynamic perturbations alone.

LFTs as potential biomarkers in heart failure

This study demonstrates that in patients with stable heart failure and predominant left ventricular dysfunction, T-Bil, GGT and ALP, but not transaminases, predicted transplant-free survival. Of these variables, GGT and ALP retained their prognostic power after adjustment for a representative array of clinical and laboratory predictors. Furthermore, GGT and ALP are of additive prognostic value if both enzymes are considered concomitantly. These findings from an unselected heart failure cohort clearly extend data from the literature. In a recently published analysis of the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) programme that enrolled 2579 selected patients with CHF, T-Bil was a strong predictor of adverse outcome both for the composite outcome of cardiovascular death or heart failure hospitalization and for all-cause mortality [13]. However, that analysis did not include GGT. Similarly, two smaller studies suggesting T-Bil as an independent predictor of long-term prognosis in patients with acute and CHF also omitted the role of GGT [15,16]. In a prior study in CHF, all LFTs including GGT were significantly related to mortality. AST, which was elevated in only 9% of the patients, accounted for the greatest variance, followed by T-Bil [14]. It must be noted, however, that that study enrolled patients well before contemporary heart failure therapy became established, and no correlation between LFT abnormalities and severity of heart failure was documented.

The prognostic significance of cholestatic enzymes in heart failure can be attributed to some extent to their relation to disease severity and right heart failure, both of which have been associated with adverse prognosis [28,29]. Differences in LFTs in predicting outcome may possibly be explained by the enzymes' associations with cardiovascular risk factors and diseases. Bilirubin has been suggested as an antioxidant and is inversely associated with the risk for myocardial infarction and the prevalence and outcome of stroke [30–33]. Contrarily, GGT, which is less specific for hepatobiliary injury, has been found to be consistently associated with most cardiovascular risk factors and cardiovascular mortality risk [18,34–38]. Thus, GGT, unlike bilirubin, may not only mirror disease severity and haemodynamic perturbations, but may also act as an indicator of comorbidities that definitely contribute to disease progression and poor outcome.

Strengths and limitations

We investigated a large cohort of well-defined patients with CHF using a longitudinal design with a long follow-up time and comprehensive adjustment for covariates at baseline. However, several limitations must be noted. The observational character of the study does not permit conclusions on causal relationships. Also, we did not measure surrogates of neurohumoral or inflammatory activation, which are most likely to influence the mutual interaction between the heart and liver. Other than a thorough medical history and baseline LFTs, no information on liver pathology such as hepatitis serology or

liver imaging was available. Patients were not monitored for changes in medication and/or device implantation during follow-up. This may constitute a potential source for confounding the study results, even though medication was well balanced at baseline.

Summary

In conclusion, in patients with stable heart failure, liver dysfunction is characterized by a predominantly cholestatic enzyme profile, which is positively associated with disease severity and signs and indices of congestion and backward failure. Of these, GGT and ALP as single markers are strongly associated with adverse prognosis in both men and women. Thus, we propose a cardio-hepatic syndrome that merits intensified appreciation in pathophysiologic and prognostic considerations in CHF. Further studies are needed to identify the exact mechanisms of interrelated derangements between heart and liver.

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Conflict of interest

None declared.

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Appendix 1 Cross-sectional correlates of LFTs: prevalence in various subgroups is given as percentage

	% of patients	T-Bil	GGT	ALP	AST	ALT
Overall *n* = 1032		15·2	46	12	13·3	14·9
Age						
< 65 years	61·7	15·3	46·3	11	13·7	17·7**
≥ 65 years	38·3	15·2	45·5	13·7	12·5	10·4
Gender						
Male	75·3	17·8***	44·2	8·8	9·4	12·6
Female	24·7	7·7	51·6*	22***	25***	22***
Duration of HF†						
< 6 months	35·2	14·1	42·9	7·7	10·2	16·9
≥ 6 months	64·8	17·2*	49·1*	14·6*	14·9	13·1
LV-EF						
≥ 40%	18·0	9·3	38·8	15·9	15·3	16·4
< 40%	82·0	16·3*	47·5*	11·3	12·9	14·5
NYHA Class						
I/II	71·1	12·8	40·6	8·9	13·2	14·9
III/IV	28·8	21·2**	59·7***	19·1***	13·4	14·8

Appendix 1 *Continued*

	% of patients	T-Bil	GGT	ALP	AST	ALT
JV distended						
No	77·8	12·6	42·4	10	12·2	14·0
Yes	22·2	24·8***	59·9***	19·1**	13·7	15·3
Oedema						
No	90·8	13·5	44·3	9·6	13·1	15·4
Yes	9·2	32·6***	66***	34·5***	15·4	11
TR[‡]						
Mild/none	77·5	10·5	38·3	8·2	12·8	15·2
Moderate/severe	23·3	29·6***	67·8***	24·7***	15·9	15·4
PAP[§]						
< 45 mmHg	76·8	11·9	38·7	10	13·3	14·4
> 45 mmHg	23·2	25***	66·3***	20·8***	14·8	16·3
Ischemic aetiology						
No	67·8	14·7	45·6	10·6	13·4	15·4
Yes	32·2	16·3	46·9	15*	12·9	13·8
Diabetes						
No	80·0	14·2	44·4	11·2	14·2	15·9
Yes	20·0	18·8	52·7*	14·2	9·9	10·9*
GFR						
> 60 mL/min/1·73 m^2	71·8	14·9	44·1	9·3	14	15·5
< 60 mL/min/1·73 m^2	28·2	15·7	51·9**	18·8***	11·2	13·1
Alcohol						
No	85·5	15·1	43·6	11·4	13·6	14·3
Yes	14·5	16·8	58·9***	13·9	14·9	18·4

Data available from [†]930, [‡]901 and [§]899 patients. Missing data amounted to < 5% for all remaining variables. Percentages were calculated from the available data set. Differences between groups were assessed with Pearson's chi-square test (*P < 0·05; **P < 0·01; ***P < 0·001).
LV-EF, left ventricular ejection fraction; JV, jugular vein; TR, tricuspid regurgitation; PAP, pulmonary artery pressure; T-Bil, total bilirubin; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase;

Appendix 2 Cross-sectional correlates of LFTs: median values (IQR) in markers of forward and backward heart failure

	T-Bil (μM) Median (IQR)	GGT (U/L) Median (IQR)	ALP (U/L) Median (IQR)
LV-EF (%)			
> 35 (n = 322)	10·7 (8–15·4)	43·0 (24–92)	76·0 (60·9–98)
26–35 (n = 353)	12·3 (8·9–17)	53·0 (28–96)	72·0 (58–87·5)
≤ 25 (n = 352)	14·2 (10–14·2)***	54·0 (30·2–120·7)**	76·0 (58–102·1)

Appendix 2 *Continued*

	T-Bil (μM) Median (IQR)	GGT (U/L) Median (IQR)	ALP (U/L) Median (IQR)
PP (mmHg)			
> 55 (*n* = 250)	10·8 (8·4–15·3)	47·0 (28–90·5)	72·9 (56·8–93·4)
46–55 (*n* = 211)	12·0 (8·6–15·6)	44·0 (27·7–84·2)	68·0 (58–89)
36–45 (*n* = 301)	13·0 (8·8–18·3)	51·0 (28–113)	74·5 (58·6–97)
≤ 35 (*n* = 255)	13·7 (9·9–22·4)***	57·0 (31–128)*	76·5 (61–103·7)
NT-proBNP (ng/L)			
< 450 (*n* = 121)	9·4 (7·4–13)	32·0 (21–54)	66·0 (54–86)
452–1260 (*n* = 121)	10·1 (8·2–14)	41·0 (26·2–69·7)	66·0 (55–84·5)
1261–2911 (*n* = 122)	11·5 (8·5–15·6)	47·5 (27·7–102·5)	76·0 (61–94·7)
> 2912 (*n* = 121)	13·4 (10·3–18·1)***	60·0 (37–126·5)***	82·0 (65–110)***
PAP (mmHg)			
< 35 (*n* = 507)	10·6 (7·9–15·6)	40·0 (25–80·7)	68·3 (55·3–89·7)
35–40 (*n* = 183)	13·0 (9·1–18·1)	55·0 (30–121)	78·0 (62–115)
45–60 (*n* = 152)	14·7 (10·9–20·6)	72·0 (36–116)	79·1 (62–115)
> 60 (*n* = 57)	16·3 (12·2–22·8)***	93·0 (44·5–174)***	82·4 (67·2–108·9)***
TR			
None (*n* = 198)	9·8 (7·7–14·8)	41·0 (24–80·2)	67·0 (55·3–91·3)
Mild (*n* = 500)	12·3 (8·7–16·2)	45·0 (27–86·5)	72·0 (57–91)
Moderate (*n* = 163)	14·9 (10·3–23·5)	77·5 (39–149)	86 (64·4–122)
Severe (*n* = 40)	17·1 (12·1–23·9)***	100·5 (68·7–195)***	80·5 (72·8–115)***
JV distension			
No (*n* = 796)	11·8 (8·6–16·4)	47·0 (27–90)	72·0 (58–92)
Yes (*n* = 227)	14·4 (10·4–21·9)***	81·0 (38–158)***	80·0 (64–109·2)***
Oedema			
No (*n* = 929)	12·1 (8·6–16·4)	48·0 (28–94)	72·0 (58–91)
Yes (*n* = 94)	17·1 (12·1–29·8)***	111·0 (44–251)***	100·5 (79·3–143)***

Differences between groups were assessed with the Kruskal–Wallis and the Mann–Whitney tests, respectively (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).
LV-EF, left ventricular ejection fraction; PP, pulse pressure; PAP, pulmonary artery pressure; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; TR, tricuspid regurgitation; JV, jugular vein; T-Bil, total bilirubin; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase.