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Original article

Concomitant renal and hepatic dysfunctions in chronic heart failure: Clinical implications and prognostic significance☆

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ABSTRACT

Background: The cardio-renal syndrome is common and eGFR is an established biomarker in chronic heart failure (CHF). Recent findings also indicate a predictive role of liver function abnormalities such as GGT in CHF. We aimed to jointly investigate the characteristics and importance of renal and hepatic failure in CHF.
Methods: Clinical and laboratory parameters of 1290 ambulatory patients (NYHA class I 25%, II 47%, III/IV 27%; median LV-EF 29%) were evaluated. Hemodynamics was available in 253 patients. The endpoint was defined as death from any cause or heart transplantation.
Results: eGFR <60 mL/min and GGT elevations were highly prevalent (25% and 44%, respectively; 12.8% for both). Renal and hepatic dysfunctions were correlated with disease severity and independently associated with adverse outcome in univariate ($p<0.001$) and multivariate analyses ($p=0.012$ and $p<0.001$, respectively). Signs of congestion and elevated CVP but not CI were independent predictors of changes in eGFR and GGT. In patients with concurrent impairment of both organs estimated five-year event rate was 46% as compared to 25% in patients with eGFR and GGT in the normal ranges (HR 3.12, 95% CI 2.33–4.18; $p<0.001$).
Conclusions: Impairment of renal and hepatic function is related to functional status and a poor prognosis in patients with mild to moderate heart failure. Concurrent involvement of both organs indicates disease progression and further elevates the hazard for adverse outcomes. Moreover, our data suggest that venous congestion rather than forward failure accounts for the development of renal and hepatic dysfunctions in these patients.

1. Introduction

Chronic heart failure (CHF) is a systemic clinical syndrome characterized by the involvement of multiple organ systems. In recent years, the cardiorenal syndrome (CRS) has received increasing recognition [1,2]. Renal dysfunction is highly prevalent in HF and is one of the most important independent risk factors for poor outcome and all-cause mortality in these patients [3–6]. CRS type II comprises the complex and bidirectional nature of pathophysiological interactions between the failing heart and the kidneys in CHF [1]. By contrast, until recently perception of secondary liver dysfunction was basically restricted to acute and advanced heart failure (ischemic hepatitis, shock liver) [7]. This is remarkable since liver function abnormalities are frequently found in patients with chronic heart failure [8–11]. Recent studies indicate that liver dysfunction in this setting is characterized by a predominantly cholestatic enzyme pattern, whereas in acute heart failure elevation of transaminases prevails [7,11–13]. In particular, γ-glutamyltransferase (GGT) proved to be an independent predictor of transplant-free survival in CHF [14,15].

In many cases of CHF, coexisting renal and liver dysfunctions may complicate the treatment course. Also, recent findings indicate that both renal and liver dysfunctions in CHF may be attributed primarily to venous congestion rather than arterial blood flow [16–18].

Given the high frequency and the predictive potential of impaired glomerular filtration rate (GFR) and GGT elevation in CHF along with the inexpensive and easily accessible availability, both markers are clearly of interest as potential biomarkers in CHF. However, data on characteristics and adverse effects of concomitant organ dysfunction on patient outcome are not yet available.

The present study therefore aimed to jointly investigate the characteristics and importance of renal and hepatic failure in CHF.

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2. Methods

2.1. Study population

This retrospective analysis made use of a dataset consisting of 1325 consecutive Caucasian heart failure patients. Patients were recruited between April 2000 and December 2010 on occasion of first presentation at the specialized heart failure clinic of a tertiary referral center. Eligible patients were ≥18 years of age. The diagnosis of CHF was based on the presence of current or previous symptoms or characteristic clinical signs, and evidence of left ventricular systolic and/or diastolic 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 July 2011 (time point of data censoring) or to the occurrence of death or heart transplantation. Death events were retrieved from the local mortality registry and personal contacts with members of patient families. Thirty-five (2.6%) patients were excluded from the present study because of incomplete baseline data. Hence, the present analysis comprises 1290 participants. Of those, follow-up information was available in 1228 patients (95.2%).

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee.

2.2. Measurements

All laboratory variables were measured by a central laboratory that undergoes regular internal and external quality audits. Measurements were performed in fasting blood samples on the day of blood collection and are given as milliliters per minute per standardized body surface area (mL/min/1.73 m^2) for eGFR and as units per liter (U/L) for GGT. The upper laboratory reference limits differed by sex for GGT (65 U/L in men, 38 U/L in women). Glomerular filtration rate (GFR) was estimated by using the simplified modification of diet in renal disease equation (estimated glomerular filtration rate [eGFR] [mL/min/1.73 m^2] = $186.3 \times [\text{serum creatinine}]^{-1.154} \times \text{age}^{-0.203}$ [×0.742 if female]) [19]. Estimated GFR values >200 mL/min/1.73 m^2 were set equal to 200 mL/min/1.73 m^2, according to Coresh et al. [20].

Hemodynamic variables obtained during catheterization included cardiac output (thermodilution, L/min) and right atrial pressure as an indicator of central venous pressure (CVP, mm Hg). Cardiac index (CI) (L/min/m^2) was determined as cardiac output divided by the body surface area. Measurements were obtained from patients at rest.

2.3. Statistical analysis

Cross-sectional associations between eGFR and GGT and established heart failure variables were assessed for all patients and for a subgroup of patients with hemodynamic measurements available by univariate correlation and multiple linear regression analyses; Pearson's correlation coefficients and standardized beta coefficients are presented. Assessment of the prognostic relevance of eGFR and GGT for transplant-free survival was performed using sex-stratified Cox proportional hazards regression analyses, again in both univariate and multivariable manner. Selection of variables for Cox proportional hazards regression analyses was based on clinical relevance and data from the literature. All parametric analyses were performed on natural logarithm-transformed data for eGFR and GGT due to their skewed distribution. 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 18.0 for Windows, SPSS Corp.).

3. Results

Table 1a shows the baseline characteristics of the total population (n = 1290) and a subgroup of 253 patients for whom hemodynamic measurements were available. eGFR and GGT levels were skewed distributed for both sexes. Median estimates and serum levels, respectively, of eGFR and GGT were 72 mL/min (IQR 56–90) and 36 U/L (IQR 21–69) in women, and 78 mL/min (IQR 62–97) and 53 U/L (IQR 30–112) in men. Prevalence of reduced eGFR (≤60 mL/min) was 29.9% in women and 22.8% in men, overall 24.6%. Corresponding numbers for elevated GGT levels (>38 U/L, and >65 U/L, respectively) were 47% and 42%, overall 44%. Table 1b gives the characteristics of patients classified according to gender-specific cut-off values for eGFR (60 mL/min) and GGT. Prevalence of concurrent impairment of eGFR and GGT elevation (eGFR↓/GGT↑) was 12.8%.

3.1. Cross-sectional relations between eGFR/GGT and heart failure severity/duration

A weak but significant correlation was observed between eGFR and GGT (r = −0.11, p = 0.005). eGFR and GGT were significantly associated with NYHA class (r = −0.197, and r = 0.215; p<0.001). Also, in a subgroup of 764 patients with NT-proBNP available both

Table 1a
Baseline characteristics and medication for the entire cohort and a subgroup of 253 patients with hemodynamic measurements available.

	All patients		Patients with hemodynamics	
	n = 1290		n = 253	
	Median or %	IQR	Median or %	IQR
Demographic and clinical characteristics				
Age (years)	61	51–69	51	43–60
Gender (male)	74.3		76.6	
LV-EF (%)	29	22–38	25	19–32
Heart rate (bpm)	75	65–86	73	63–86
Systolic BP (mm Hg)	120	110–140	120	100–130
BMI	25.4	23.0–28.4	25.0	23.0–28.1
NYHA class I	25.4		18.0	
NYHA class II	47.2		49.8	
NYHA class III/IV	27.4		32.2	
Signs of congestion	26.6		27.0	
Duration of heart failure (>6 months)	64.4		50.7	
Ischemic etiology	29.3		18.1	
A-Fib	25.8		17.6	
Medical history				
Hypertension	48.1		32.0	
Diabetes	19.4		13.7	
Reported alcohol consumption	14.7		7.7	
Laboratory testing (serum)				
eGFR (mL/min/1.73 m^2)	**77.0**	**60.6–95.3**	**79.6**	**65.5–96.3**
GGT (U/L)	**48**	**27–95**	**50**	**31–100**
NT-proBNP (ng/L)	1181	377–2967	1254	372–3107
Hemodynamic measurements				
CVP (mm Hg)			**10**	**7–14**
CI (L/min per m^2)			**2.1**	**1.7–2.5**
Medication				
ACE inhibitor/ARB	81.6		86.0	
Beta-blocker	62.3		69.9	
Aldosterone antagonist	28.3		36.8	
Diuretic	70.5		68.9	

Data are reported as number (percentage) or median (interquartile range). Data for NT-proBNP were available in 764 patients. eGFR, GGT, CVP, and CI are presented in boldface.

LV-EF, left ventricular ejection fraction; SBP, systolic blood pressure; BMI, body mass index; NYHA, New York Heart Association class; signs of congestion, peripheral edema a/o jugular venous distension; A-Fib, atrial fibrillation; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; CVP, central venous pressure; CI, cardiac index; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.