The predictive value of transaminases at admission in patients hospitalized for heart failure: findings from the RO-AHFS registry

European Heart Journal: Acute Cardiovascular Care
2(2) 99–108

© The European Society of Cardiology 2013

Reprints and permissions:

sagepub.co.uk/journalsPermissions.nav

DOI: 10.1177/2048872612474906

acc.sagepub.com

**Andrew P Ambrosy¹, Mihai Gheorghiade², Serban Bubenek³,
Dragos Vinereanu⁴, Muthiah Vaduganathan⁵, Cezar Macarie³ and
Ovidiu Chioncel³; on behalf of the Romanian Acute Heart Failure
Syndromes (RO-AHFS) study investigators**

Abstract

Background: Transaminases are commonly elevated in both the inpatient and ambulatory settings in heart failure (HF).

Aims: To determine the prevalence and degree of elevated transaminase levels at admission and to evaluate the association between transaminase levels and in-hospital morbidity and mortality.

Methods: Over a 12-month period, the Romanian Acute Heart Failure Syndromes (RO-AHFS) registry enrolled consecutive patients hospitalized for HF at 13 medical centres. A post-hoc analysis of the 489 patients (15.2%) with alanine transaminase (ALT) and aspartate transaminase (AST) (upper limits of normal 31 IU/L and 32 IU/L, respectively) measured at baseline was performed. In-hospital mortality was compared across quartiles using multivariable Cox regression models.

Results: The prevalences of elevated ALT and AST were 28% and 24% and the medians (interquartile range) were 22 (16–47) and 23 (16–37 IU/L). Patients with elevated transaminases more commonly had right HF, cardiogenic shock, or an ejection fraction <45%. Patients with an ALT in the highest quartile were more likely to present with hypotension and a low pulse pressure, to have electrocardiographic evidence of left ventricular dyssynchrony and echocardiographic findings including increased left ventricular dimensions, reduced left ventricular ejection fraction, and valvular heart disease, to require inotropic or vasopressor support during hospitalization, and to report lower β -blocker and angiotensin-converting enzyme inhibitor utilization. After adjusting for potential confounders, ALT was directly associated with BUN increases ≥ 10 mg/dl, necessity for intensive care unit admission, and longer length of stay. Patients in the highest quartile of ALT experienced significantly higher rates of all-cause mortality.

Conclusions: In patients hospitalized for HF, there is a graded relationship between admission transaminase levels and surrogates for in-hospital morbidity, while more pronounced elevations of ALT predict in-hospital mortality independent of known prognostic indicators.

Keywords

Alanine transaminase, aspartate transaminase, hospitalization, mortality

Received: 28 September 2012; accepted: 24 December 2012

Introduction

Abnormal liver function tests (LFTs) are a common manifestation of heart failure (HF) in both hospitalized^{1–3} and ambulatory patients^{4–9} and are associated with worse outcomes. However, the pattern and prognostic value of LFTs are variable and dependent on the clinical setting (i.e. inpatient vs. outpatient) as well as the patient population (i.e. reduced vs. preserved ejection fraction) under

¹Stanford University School of Medicine, Stanford, CA, USA

²Northwestern University Feinberg School of Medicine, Chicago, IL, USA

³Institute of Emergency for Cardiovascular Diseases “C.C.Iliescu”,
Cardiology I, Bucharest, Romania

⁴Universitary Emergency Hospital, Bucharest, Romania

⁵Massachusetts General Hospital, Boston, MA, USA

Corresponding author:

Ovidiu Chioncel, Institute of Emergency for Cardiovascular Diseases
“C.C.Iliescu”, Cardiology I, Bucharest, Romania.

Email: ochioncel@yahoo.co.uk

consideration. Despite the fact that consensus guidelines in both the USA¹⁰ and Europe¹¹ recommend routinely assessing LFTs at admission, most of the data on the epidemiology of LFTs in HF are derived from large clinical trials with highly restrictive inclusion and exclusion criteria or smaller single-centre studies and may not be generalizable. Although anecdotal experience suggests mild/moderate transaminase elevations to be prevalent in patients hospitalized for HF requiring intensive care unit (ICU) or coronary care unit level of care, it is presently unclear whether there is an association between transaminase levels at admission and in-hospital morbidity and mortality.

The RO-AHFS (Romanian Acute Heart Failure Syndromes) registry¹² is a prospective, hospital-based study including all consecutive patients hospitalized for HF. RO-AHFS provides a unique opportunity to investigate the epidemiology and predictive value of transaminases in a heterogeneous population including patients of all levels of acuity with both reduced and preserved ejection fraction. Specifically, the objectives of this post-hoc analysis of the RO-AHFS registry were to: (1) determine the prevalence and degree of transaminase elevation by clinical profile at presentation as well as ejection fraction; (2) describe the demographic and baseline clinical characteristics, electrocardiographic and echocardiographic findings, inpatient management, and admission and discharge medication utilization by transaminase levels; and (3) evaluate the association between transaminase levels at admission and in-hospital morbidity and mortality.

Methods

The study design and primary results of the RO-AHFS registry¹² have previously been reported. Briefly, RO-AHFS is a national, prospective, hospital-based study, which enrolled 3224 consecutive patients over a 12-month period at 13 medical centres, including academic and community hospitals, in Romania. The only inclusion criterion was a primary diagnosis of HF for the current hospital admission. This diagnosis required the presence of signs and symptoms of HF, documented objective evidence of cardiac dysfunction, and the need for intravenous therapy.¹¹ Patients with high-output HF were excluded.

The study protocol was approved by the Institutional Review Board of each participating site as well as the Executive Board of the Romanian Society of Cardiology and is in compliance with the Declaration of Helsinki. The present analysis includes only patients ($n=489$, 15.2%) with alanine transaminase (ALT) and aspartate transaminase (AST) measured at admission.

All data were collected by chart review and entered into a centrally managed online database using a web-based electronic case report form. Automated electronic data checks were performed to prevent out-of-range or duplicate

entries. Source verification was completed centrally for a random sample to ensure the validity of the data.

All laboratory testing was performed on site and was left to the discretion of the enrolling clinician-investigator. The upper limits of normal for ALT and AST, respectively, was 31 and 32 IU/L, based on centralized laboratory standards. The epidemiology of ALT and AST are both reported since they are typically measured together, but all subsequent descriptive and prognostic analyses were restricted to ALT since this enzyme is known to be a more sensitive and specific marker of liver disease than AST, which is also present in skeletal and cardiac muscle.

Patients were classified into the following five clinical profiles by the clinician investigators at the time of admission according to the 2008 European Society of Cardiology guidelines: acute decompensated HF, cardiogenic shock, pulmonary oedema, right HF, and hypertensive HF.^{11,13} Assignment to the pulmonary oedema clinical profile required radiographic evidence of pulmonary alveolar oedema at the time of admission.

All categorical variables are reported as a percentage and all continuous variables as a mean $\pm$ standard deviation (SD) and/or median (interquartile range). Clinical variables were compared using Fisher's Exact test or the chi-square test for categorical variables, as appropriate, and a one-way analysis of variance for continuous variables. For the end-point analyses, evidence of non-linear effects was observed by Kolmogorov-type supremum testing, thus ALT was divided into quartiles: Q1 10–20, Q2 21–30, Q3 31–64, and Q4 65–205 IU/l. The association between ALT at admission and event rates for in-hospital outcomes were assessed as a categorical variable using multivariate Cox regression models. The primary endpoint was in-hospital all-cause mortality (ACM). Secondary clinical endpoints included worsening renal function [i.e. defined as a >0.3 mg/dl increase in serum creatinine (sCr) or a >10 mg/dl increase in blood urea nitrogen (BUN)], ventricular tachycardia or fibrillation, utilization of intravenous (IV) inotropes, necessity for ICU admission and length of stay, which were selected a priori. All multivariable models were adjusted for age, gender, body mass index, ejection fraction, systolic blood pressure, serum Na, sCr, serum BUN, haemoglobin, QRS duration, atrial fibrillation/flutter on baseline EKG, and medication utilization [β -blockers, angiotensin-converting enzymes inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs)] except when the relevant covariate was also the clinical endpoint (i.e. sCr and BUN). Receiver operator characteristic curves were generated to determine the overall diagnostic accuracy of ALT to predict in-hospital ACM and necessity for ICU admission. Test performance was estimated by calculating the area under the curve (AUC) along with the 95% confidence interval (CI). All final analyses were conducted using SPSS version 16 (SPSS, Chicago, IL, USA).

Figure 1. Boxplots including median, interquartile range, and minimum–maximum range of alanine transaminase (grey) and aspartate transaminase (black) at admission by ejection fraction and clinical profile at presentation. ADHF, acute decompensated heart failure; CS, cardiogenic shock; EF, ejection fraction; HT HF, hypertensive heart failure; PE, pulmonary oedema; RHF, right heart failure.

The RO-AHFS registry was funded through an unrestricted educational grant provided by Abbott Laboratories Romania. The sponsor had no involvement in study design, data collection, statistical analysis, results interpretation, or manuscript drafting. The authors had full access to the data, take responsibility for its integrity, and had complete control and authority over manuscript preparation and the decision to publish.

Results

A total of 489 patients (15.2% of registry enrollment) had ALT and AST measured at the time of admission and 80.7% and 19.2% of patients, respectively, were enrolled from academic centres and community hospitals. In contrast, the breakdown of enrollment in the RO-AHFS registry was 41% academic centres and 59% community hospitals.

The median (interquartile range) of ALT and AST were 22 (16–47) IU/L and 23 (16–37) IU/L, respectively, and the prevalences of elevated ALT and AST were 28% and 24% (Figures 1 and 2). The prevalence and degree of abnormal transaminases was highest in patients classified as cardiogenic shock and right HF and lowest in the hypertensive HF and pulmonary oedema clinical profiles. Transaminase elevations were also more pronounced in patients hospitalized for HF with reduced ejection fraction (i.e. <45%) compared to preserved ejection fraction (i.e. >45%).

The distribution of age and gender breakdown was comparable across ALT quartiles (Table 1). Although the prevalence of medical comorbidities (i.e. hypertension, dyslipidaemia, and diabetes) appeared to be inversely related to ALT quartile at admission, this trend approached but did not reach statistical significance. Similarly, for increasing ALT levels, there were signals towards more HF aetiologies attributable to ischaemia and valvular disease and less HF attributable to hypertension that did not reach the threshold for statistical significance. However, the incidence of de-novo HF and HF occurring in the setting of ACS was independent of admission ALT. In contrast, systolic blood pressure and pulse pressure were lower in patients with higher ALT levels.

Increasing ALT quartile was directly associated with the prevalence of atrial fibrillation, second or third degree AV block, evidence of permanent pacing, and prolonged QRS duration on baseline EKG (Table 2). In contrast, there was a trend towards less electrocardiographic evidence of left ventricular hypertrophy. Echocardiographic findings including increased left ventricular (LV) dimensions, decreased left ventricular ejection fraction, and valvular disease were also directly related to higher admission ALT, while the association between ALT and documented LV aneurysm and mechanical complications secondary to acute myocardial infarction only trended towards significance (Table 3).

Figure 2. Prevalence of elevated alanine transaminase (ALT) and aspartate transaminase (AST) at admission by ejection fraction and clinical profile at presentation.

ADHF, acute decompensated heart failure; CS, cardiogenic shock; EF, ejection fraction; HT HF, hypertensive heart failure; PE, pulmonary oedema; RHF, right heart failure.

Table 1. Demographics and baseline clinical characteristics by alanine transaminase quartile at admission.

	Overall	Q1 (10–20 IU/l)	Q2 (21–30 IU/l)	Q3 (31–64 IU/l)	Q4 (65–205 IU/l)	p-value
Age (years)	68.5±12.9	66.5±15.1	68±11.3	70.9±10.4	68.7±14.8	0.30
Sex (male)	60	57.6	58.1	61.3	63	0.80
Hypertension	61	64	62	59	58	0.07
Dyslipidaemia	37	40	39	36	35	0.08
Diabetes	35	35	37	33	34	0.10
Smoking	23	24	24	22	21	0.40
Previous MI	18	16	16	21	18	0.50
Aetiology						
Ischaemic	61	60	59	63	62	0.08
Valvular	39	36	38	40	42	0.05
Hypertensive	40	42	41	40	38	0.06
Congenital	2.0	1.7	1.9	2.6	2.0	0.30
Idiopathic	27	25	26	29	28	0.40
Other	12	11	10	12	13	0.40
De novo HF	18	19	18	17	17	0.80
ACS setting	12	10	12	14	12	0.90
SBP (mmHg)	138±27	151±20	147±25	133±31	121±34	<0.01
PP (mmHg)	53±23	57±21	54±20	52±30	50±22	0.02
HR (bpm)	97±28	91±24	96±28	101±26	99±35	0.04
BMI (kg/m ²)	28.2±5.4	29.5±6.1	29±5.8	26.9±4.4	27.2±5.2	0.09

Values are mean±SD or %.

ACS, acute coronary syndrome; BMI, body mass index; HF, heart failure; HR, heart rate; MI, myocardial infarction; PP, pulse pressure; SBP, systolic blood pressure.

Patients with an admission ALT in the highest quartile were much more likely to receive IV therapies including loop diuretics (i.e. furosemide), inotropes,

and vasopressors and far less likely to be treated with nitroglycerin (Figure 3). Increasing ALT levels was also associated with higher utilization of temporary

Table 2. EKG findings by alanine transaminase quartile at admission.

	Overall	Q1 (10–20 IU/l)	Q2 (21–30 IU/l)	Q3 (31–64 IU/l)	Q4 (65–205 IU/l)	p-value
QRS >120 ms	38.2	31.9	34.2	43.1	45.5	<0.01
PPM	5.0	3.7	4.4	5.1	6.8	0.01
LVH	21.6	24.1	20.6	21.2	20.4	0.10
Atrial fibrillation	48.5	41.2	44.2	51.4	57.2	0.02
Second or third degree AV block	5.9	2.6	3.1	9.2	8.8	<0.01

Values are %.

AV, atrioventricular; LVH, left ventricular hypertrophy; PPM, permanent pacemaker.

Table 3. Echocardiographic findings by alanine transaminase quartile at admission.

	Overall	Q1 (10–20 IU/l)	Q2 (21–30 IU/l)	Q3 (31–64 IU/l)	Q4 (65–205 IU/l)	p-value
LVEDD (mm)	61±11	59±14	60±11	63±10	64±9	0.02
LVESD (mm)	47±12	45±11	46±12	49±13	47±10	0.04
LVEF (%)	39±12	42±11	40±12	37±13	36±13	0.04
LVEF <45%	66.3	60.8	64.2	68.7	71.4	<0.01
Significant MVD ^a	34.9	28.7	33.3	37.2	40.2	<0.01
Significant AVD ^a	18.3	17.3	18.0	19.2	18.8	0.06
LV aneurism	8.1	7.1	8.5	8.4	8.2	0.10
Mechanical complications secondary to AMI ^b	1.3	0	0.9	1.6	2.8	0.20

Values are mean±SD or %. Echocardiographic data were only available for 397 patients.

^aStenosis and regurgitation.

^bPapillary muscle and interventricular septum rupture.

AMI, acute myocardial infarction; AVD, aortic valve disease; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MVD, mitral valve disease.

Figure 3. Percentage of patients receiving intravenous therapies by alanine transaminase quartile at admission.

p-value <0.05 for all comparisons.

Table 4. Procedural interventions by alanine transaminase quartile at admission.

	Overall	Q1 (10–20 IU/l)	Q2 (21–30 IU/l)	Q3 (31–64 IU/l)	Q4 (65–205 IU/l)	p-value
Coronary angiography	5.45	6.1	8.3	5.4	2	0.20
PCI	1.6	2.2	2.7	1.2	0.4	0.20
CABG	0.3	0.5	0.5	0.3	0.0	0.70
Cardioversion	4.5	5.3	5.5	3.8	3.2	0.03
Pacing	3.35	1.2	2.2	4.1	5.9	0.01
CRT/ICD	0.3	0.7	0.3	0.0	0.0	0.50
Swann-Ganz	0.3	0.0	0.8	0.3	0.0	0.60
IABP	0.2	0.3	0.3	0.1	0.0	0.70
Mechanical ventilation	4.0	1.8	2.2	6.8	5.2	0.04
Ultrafiltration	1.4	0.0	0.9	1.9	2.6	0.02

Values are %.

CABG, coronary artery bypass graft; CRT/ICD, cardiac resynchronization therapy/implantable cardioverter-defibrillator; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention.

Table 5. Medication utilization at admission and discharge by alanine transaminase quartile at admission.

	Overall	Q1 (10–20 IU/l)	Q2 (21–30 IU/l)	Q3 (31–64 IU/l)	Q4 (65–205 IU/l)	p-value
β -blockers						
Admission	43	49	43	41	40	0.06
Discharge	51	59	55	46	42	0.02
ACEIs						
Admission	49	52	53	46	45	0.05
Discharge	54	58	57	54	47	0.06
ARBs						
Admission	7	8	7	8	6	0.80
Discharge	8	11	9	7	7	0.21
MRAs						
Admission	33	37	39	29	29	0.10
Discharge	51	46	48	48	61	0.12
Digoxin						
Admission	35	31	35	40	33	0.60
Discharge	38	34	35	42	41	0.07
Diuretics						
Admission	72	73	75	69	70	0.05
Discharge	81	77	76	83	85	0.02
Amiodarone						
Admission	9	7	11	11	7	0.90
Discharge	10	10	12	9	8	0.31
Antithrombotics						
Admission	40	47	43	36	33	0.01
Discharge	53	64	65	46	39	<0.01
Statins						
Admission	20	26	22	22	8	0.02
Discharge	27	37	29	27	14	<0.01

Values are %.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

transcutaneous pacing, mechanical ventilation, and ultrafiltration (Table 4).

The utilization of β -blockers and ACEIs at admission was inversely associated with higher baseline ALT and the disparity in the use of these evidence-based

therapies was even more prominent at the time of discharge (Table 5). However, there was a trend towards greater use of MRAs at discharge among patients with an ALT measurement in the highest quartile. Finally, patients in the highest ALT quartile were substantially

Table 6. Outcomes of interest by alanine transaminase quartile at admission.

	Overall	Q1 (10–20 IU/l)		Q2 (21–30 IU/l)		Q3 (31–64 IU/l)		Q4 (65–205 IU/l)		p-value
	%	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)	
↑sCr (≥ 0.3 mg/dl)	7	8	REF	6	0.8, 0.5–1.2	12	1.51, 1.0–2.1	15	1.8, 1.2–3.3	0.20
↑BUN (≥ 10 mg/dl)	7.3	2.0	REF	5.0	2.6, 1.3–4.8	10.0	4.7, 2.8–6.5	11.0	5.1, 4.9–5.2	0.01
VT or VF	4.1	3.9	REF	4.8	1.2, 1.0–1.3	3.5	0.9, 0.8–1.0	4.0	1.0, 1.0–1.1	0.50
IV inotropes	19.3	3.0	REF	8.0	2.6, 1.0–4.2	28.0	9.2, 3.2–14.8	38.0	12.4, 6.2–17.0	0.05
ICU admission	10.5	2.0	REF	7.0	3.4, 1.2–5.5	14.0	4.8, 1.9–8.1	19.0	6.9, 2.5–10.3	0.02
LOS	9.5	7.2	REF	7.4	1.04, 1.0–1.1	10.6	1.4, 1.2–1.6	12.9	1.8, 1.3–2.1	0.01
ACM	8.3	6.4	REF	7.2	1.1, 0.9–1.3	8.2	1.3, 1.0–1.4	11.3	1.7, 1.3–3.0	0.07

Multivariate Cox regression models adjusted for age, gender, body mass index, ejection fraction, systolic blood pressure, serum Na, serum BUN, sCr, haemoglobin, QRS duration, atrial fibrillation/flutter on baseline EKG, and medication utilization (β -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists).

ACM, all-cause mortality; BUN, blood urea nitrogen; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; IV, intravenous; LOS, length of stay; sCr, serum creatinine; VF, ventricular fibrillation; VT, ventricular tachycardia.

less likely to be taking an antithrombotic or statin at admission or discharge.

After adjusting for clinically relevant covariates, admission ALT was directly associated with in-hospital BUN increases, necessity for ICU admission, and longer length of stay across quartiles (Table 6). In addition, the highest quartile of ALT at admission was associated with greater utilization of IV inotropes. The overall ACM rate in this analysis was 8.3%, ranging from 6.4% in quartile 1 to 11.3% in quartile 4 of ALT in a non-linear fashion ($p=0.07$ for trend). The highest quartile of admission ALT was independently associated with higher in-hospital ACM compared to patients in the lowest quartile (HR 1.7, 95% CI 1.3–3.0).

Receiver operator characteristic curves for ALT as a predictor of ACM and ICU admission are depicted in Figure 4. For ACM an ALT cutoff of 31 IU/l, the upper limit of normal, had a sensitivity of 0.76 and a specificity of 0.51, while for ICU admission the same cutoff had a sensitivity of 0.80 and a specificity of 0.74. The AUC for ALT as a predictor of ACM and ICU admission, respectively, were 0.686 (95% CI 0.564–0.769, $p=0.02$) and 0.798 (95% CI 0.718–0.897, $p=0.01$).

Discussion

Approximately 25% of patients enrolled in the RO-AHFS registry with transaminase measurements at admission were found to have abnormally high ALT and/or AST levels.

Elevated transaminases were most prevalent in the patients classified as right HF or cardiogenic shock at initial presentation or found to have a reduced ejection fraction (i.e. $<45\%$) and least prevalent in the patients classified as hypertensive HF or pulmonary oedema or found to have a preserved ejection fraction (i.e. $>45\%$). High ALT was associated with relative hypotension and a low pulse pressure at

presentation, LV dyssynchrony on baseline EKG, echocardiographic evidence of increased LV dimensions and valvular heart disease, inotropic and/or vasopressor support during hospitalization, and lower rates of utilization of evidence-based therapies (i.e. β -blockers and ACEIs). After adjusting for potential confounders, increasing ALT was independently predictive of in-hospital outcomes including worsening renal function, necessity for ICU admission, and longer length of stay as well as significantly higher rates of ACM at extremes of ALT (i.e. highest quartile).

More than a quarter of the patients in the present analysis were found to have elevated ALT and/or AST at the time of admission, while cross-sectional studies have estimated the prevalence of asymptomatic transaminase elevations to range from 0.5–4% in the general population.^{14,15} Notably, the prevalence of elevated transaminase levels in the present analysis was also significantly higher than the $<5\%$ reported in CHARM⁵ (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Program) and the $\sim 20\%$ reported in EVEREST³ (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan). It is well established that ambulatory HF patients (i.e. CHARM) tend to exhibit a predominantly cholestatic LFT pattern (i.e. bilirubin, alkaline phosphatase, and gamma glutamyl transferase), while patients hospitalized for HF manifest a mixed LFT pattern with features of both cholestasis and hepatocellular injury (i.e. ALT and AST). In addition, although both RO-AHFS and EVEREST enrolled patients hospitalized for HF, the EVEREST trial^{16–18} employed very specific exclusion criteria (e.g. supine systolic blood pressure <90 mmHg, haemodynamically significant uncorrected valvular heart disease, candidates for ventricular assist devices or continuous positive intravenous inotropic therapy, life expectancy <6 months) designed to exclude patients with refractory or end-stage HF, at least partially explaining the lower reported prevalence of abnormal transaminase levels.

Figure 4. Receiver operator characteristic curves for alanine transaminase as a predictor of all-cause mortality (A) and ICU admission (B).

In interpreting these data it is important to note that alternative sources of transaminases cannot be definitively excluded as information regarding alcohol consumption and co-existing primary liver disease was not collected. Romania is well known as having one of the highest prevalences of chronic viral hepatitis in Europe.^{19,20} Similarly, nonalcoholic fatty liver disease is also a plausible causative aetiology of elevated transaminase levels, though body mass index was found to be unrelated to ALT concentration. Although higher ALT was inversely associated

with statin therapy, it is uncertain whether this life-saving therapy was intentionally not initiated because of preexisting elevated transaminases or stopped early due to increasing transaminases. However, the incidence of asymptomatic transaminase abnormalities in patients on statin therapy has generally not been found to exceed 3%.^{21,22} Finally, more than 10% of the study population was hospitalized for HF in the setting of ACS, suggesting a cardiac source may have contributed to the high prevalence of elevated transaminases.

Although age, gender, and past medical history were comparable across quartiles of ALT, higher ALT at admission was definitively associated with a constellation of clinical findings suggestive of abnormal haemodynamics and poor end-organ perfusion. Compared to the bottom quartile, patients with an ALT in the top quartile were 50% more likely to have evidence of LV dyssynchrony on baseline EKG, a known independent predictor of post-discharge morbidity and mortality.²³ Similarly, close to 40% of patients in the top quartile required inotropic support for a median duration >48 hours at some point during hospitalization, a notable finding since even short-term use of inotropes has been associated with increased in-hospital and post-discharge mortality.²⁴ Finally, β -blocker and ACEI utilization was inversely associated with ALT, suggesting a potential risk-treatment mismatch. However, initiation and dose titration of these medications was likely limited by low blood pressure, at least partially explaining this finding.²⁵

To the best of our knowledge, this is the first study to find an association between admission ALT and short-term (i.e. days) mortality in patients hospitalized for HF. Previous studies conducted in patients hospitalized for HF^{1–3} have found the association between transaminases and post-discharge outcomes (i.e. rehospitalization and mortality) to not be statistically significant after adjusting for natriuretic peptide concentrations or invasive haemodynamic measurements (i.e. central venous pressure and cardiac index). In Romania, natriuretic peptides are only routinely measured at academic medical centres and as a result were not available for a large proportion of the patients enrolled in RO-AHFS and thus could not be included in the multivariate model. However, the higher level of acuity and the focus on short-term outcomes may have both contributed to detecting a discernible independent prognostic value of admission ALT on morbidity and mortality.

It has been previously hypothesized that the deleterious effects of HF on the liver are a consequence of two mechanisms: (1) hepatic congestion secondary to volume and pressure overload; and (2) reduced cardiac output and compromised liver perfusion causing hypoxic injury.¹ ALT and AST are primarily cytosolic enzymes and these two mechanisms likely result in hepatocellular injury and immediate release into the bloodstream. However, the liver's complex dual blood supply (i.e. portal vein and hepatic artery) make it more resistant to hypoxic injury, which may explain why the present analysis found the AUC for ALT as a predictor of ACM to be relatively modest and only more pronounced elevations of ALT to be independently predictive of in-hospital mortality (i.e. a threshold effect). Notably, the mode of death in patients with markedly elevated transaminases is likely due to progressive pump failure, a hypothesis which is supported by the high rate of inotropic and/or vasopressor support in this subset of

patients and the absence of an association between ALT and fatal arrhythmias (i.e. pulseless ventricular tachycardia and fibrillation).

There are several limitations of the data that should be acknowledged. First, in contrast to the primary results of the RO-AHFS registry, this post-hoc analysis did not include all consecutive patients due to availability of transaminase data in only a subset. Although the utilization of this Romanian-based registry provides a relatively homogenous population for analysis, this may limit the overall generalizability of the study findings. However, the study population included patients of all levels of acuity with both reduced and preserved ejection fraction and no multicentre, cross-sectional studies of LFTs in HF have been conducted to date. Second, this study provides only a partial description of liver function in HF at a single point in time as laboratory markers of cholestasis (i.e. bilirubin, alkaline phosphatase, and gamma glutamyl transferase) and synthetic function (i.e. albumin and coagulation studies) were either not collected or not interpretable (i.e. coagulation times in patients on anticoagulants). Third, this study cannot exclude primary liver disease or cardiac ischaemia as a source of transaminases. Fourth, natriuretic peptides were not measured and correcting for this well-studied surrogate of haemodynamic congestion may have partially attenuated the association between admission ALT and in-hospital morbidity and mortality. Finally, long-term follow-up data were not collected as part of the RO-AHFS registry, limiting the present analysis to the association between ALT and in-hospital events.

Abnormal transaminase levels may occur in more than a quarter of patients admitted with a primary diagnosis of HF. High transaminases are part of a clinical profile suggestive of low cardiac output, frequently require inotropic and/or vasopressor support at some point during hospitalization, and are associated with in-hospital morbidity including worsening renal function, ICU admission, and longer length of stay. Most importantly, more pronounced elevations in transaminases are suggestive of progressive pump failure and independently associated with increased short-term mortality in patients hospitalized for HF.

Disclosures

Mihai Gheorghiade is a consultant for and/or has received research support from Abbott Labs, Astellas, AstraZeneca, Bayer Schering PharmaAG, CorThera Inc, Cytokinetics Inc, DebioPharm SA, ErrekappaTerapeutici (Milan, Italy), Glaxo Smith Kline, JNJ, Medtronic, Novartis Pharma AG, Otsuka, Sigma Tau, Solvay Pharmaceuticals, and Pericor Therapeutics. The other authors declare no conflicts of interest.

Acknowledgements

We would like to thank all of the physicians and nurses who participated in the RO-AHFS registry.

Appendix A: Co-ordinators and Study Investigators

Alina Giuca, Ionut Donoiu si Dan Dominic Ionescu (Centrul de Cardiologie Craiova); Ruxandra Cristodorescu and Dan Darabantiu (ASCAR Timisoara); Lucica Grigoric and Eugenia Nechita (Spitalul Judetean Galati); Valentin Ochean and Monica Bengus (Spitalul Judetean Focsani); Dragos Ott (Spitalul Sfantul Ioan Bucuresti); Mircea Vladoianu (Spitalul Judetean Targoviste); Adela Serban, Radu Capalneau (Institutul Inimii Cluj Napoca); Gabriela Bicescu, Dragos Vinereanu (Spitalul Universitar Bucuresti); Cati Istrate, Oana Mihailescu, and Anca Florian, Cezar Macarie, Ovidiu Chioncel (Institutul de Urgente pentru Boli Cardiovasculare C.C. Iliescu Bucuresti); Ana Fruntelata, Maria Dorobantu (Spitalul De Urgenta Floreasca Bucuresti); Viviana Aursulesei, Antoniu Petris, Daniela Crisu, Mihai Datcu (Spitalul Sfantul Spiridon Iasi); Adriana Gurghean, Ioan Bruckner (Spitalul Clinic Coltea); Marius Vintila and Liliana Protopopescu (Spitalul Sfantul Pantelimon Bucuresti)

Presentation

Data were presented in part at the European Society of Cardiology Congress 2012 in Munich, Germany.

Funding

This work was supported by an unrestricted educational grant, (grant number R11/2007) provided by Abbott Laboratories Romania.

References

1. van Deursen VM, Damman K, Hillege HL, et al. Abnormal liver function in relation to hemodynamic profile in heart failure patients. *J Card Fail* 2010; 16: 84–90.
2. Shinagawa H, Inomata T, Koitabashi T, et al. Prognostic significance of increased serum bilirubin levels coincident with cardiac decompensation in chronic heart failure. *Circ J* 2008; 72: 364–369.
3. Ambrosy AP, Vaduganathan M, Huffman MD, et al. Clinical course and predictive value of liver function tests in patients hospitalized for worsening heart failure with reduced ejection fraction: an analysis of the EVEREST trial. *Eur J Heart Fail* 2012; 14: 302–311.
4. Batin P, Wickens M, McEntegart D, et al. The importance of abnormalities of liver function tests in predicting mortality in chronic heart failure. *Eur Heart J* 1995; 16: 1613–1618.
5. Allen LA, Felker GM, Pocock S, et al. 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: 170–177.
6. Felder L, Mund A and Parker JG. Liver function tests in chronic congestive heart failure. *Circulation* 1950; 2: 286–297.
7. Jolliffe N. Liver function in congestive heart failure. *J Clin Invest* 1930; 8: 419–433.
8. Richman SM, Delman AJ and Grob D. Alterations in indices of liver function in congestive heart failure with particular reference to serum enzymes. *Am J Med* 1961; 30: 211–225.
9. Sherlock S. The liver in heart failure; relation of anatomical, functional, and circulatory changes. *Br Heart J* 1951; 13: 273–293.
10. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; 119: 1977–2016.
11. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; 29: 2388–2442.
12. Chioncel O, Vinereanu D, Datcu M, et al. The Romanian Acute Heart Failure Syndromes (RO-AHFS) registry. *Am Heart J* 2011; 162: 142–453, e1.
13. Nieminen MS, Bohm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; 26: 384–416.
14. Pratt DS and Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Eng J Med* 2000; 342: 1266–1271.
15. Giboney PT. Mildly elevated liver transaminase levels in the asymptomatic patient. *Am Fam Physician* 2005; 71: 1105–1110.
16. Gheorghiade M, Orlandi C, Burnett JC, et al. Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the Efficacy of Vasopressin antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST). *J Card Fail* 2005; 11: 260–269.
17. Gheorghiade M, Konstam MA, Burnett JC Jr, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST clinical status trials. *JAMA* 2007; 297: 1332–1343.
18. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. *JAMA* 2007; 297: 1319–1331.
19. Nardone A, Anastassopoulou CG, Theeten H, et al. A comparison of hepatitis B seroepidemiology in ten European countries. *Epidemiol Infect* 2009; 137: 961–969.
20. Gheorghe L, Iacob S and Csiki IE. Prevalence of hepatitis C in Romania: different from European rates? *J Hepatol* 2008; 49: 661–662, author reply.
21. McKenney JM, Davidson MH, Jacobson TA, et al. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol* 2006; 97: 89C–94C.
22. Cohen DE, Anania FA and Chalasani N. An assessment of statin safety by hepatologists. *Am J Cardiol* 2006; 97: 77C–81C.
23. Wang NC, Maggioni AP, Konstam MA, et al. Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction. *JAMA* 2008; 299: 2656–2666.
24. Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; 46: 57–64.
25. Gheorghiade M, Abraham WT, Albert NM, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006; 296: 2217–2226.