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Abstract

AIMS: The aim of this study was to assess the prevalence of abnormal liver function tests (LFTs) and the associated clinical profile and outcome(s) in acute decompensated heart failure (ADHF) patients. Alteration in LFTs is a recognized feature of ADHF, but prevalence and outcomes data from a broad contemporary cohort of ADHF are scarce and the mechanism(s) of ADHF-induced cholestasis is unknown. METHODS AND RESULTS: We conducted a post hoc analysis of SURVIVE, a large clinical trial including ADHF patients treated with levosimendan or dobutamine. All LFTs were available in 1134 patients at baseline. Abnormal LFTs were seen in 46% of ADHF patients: isolated abnormal alkaline phosphatase (AP) was noted in 11%, isolated abnormal transaminases in 26%, and a combination of abnormal AP and transaminases in 9%. Abnormal AP was associated with marked signs of systemic congestion and elevated right-sided filling pressure. Abnormal AP had no relationship with 31-day mortality but was associat...

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Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure

Maria Nikolaou[1,2,3], John Parissis[3], M. Birhan Yilmaz[1,15], Marie-France Seronde[1,2,4], Matti Kivikko[5,6], Said Laribi[1,2,7], Catherine Paugam-Burtz[2,8], Danlin Cai[9], Pasi Pohjanjousi[6], Pierre-François Laterre[10], Nicolas Deye[1,11], Pentti Poder[12], Alain Cohen-Solal[1,2,13], and Alexandre Mebazaa[1,2,14]*

[1]UMRS 942 Inserm, F-75010 Paris, France; [2]Univ Paris Diderot, Sorbonne Paris Cité, F-75205 Paris, France; [3]Heart Failure Unit, 2nd Cardiology Department, Attikon University Hospital, University of Athens, Athens, Greece; [4]Department of Cardiology, University Hospital Jean-Minjoz, Besançon, France; [5]Department of Cardiology, Helsinki University Central Hospital, Helsinki, Finland; [6]Orion Pharma, Kuopio, Finland; [7]AP-HP, Department of Emergency Medicine, Hôpital Lariboisière, F-75475 Paris Cedex 10, France; [8]AP-HP, Department of Anesthesiology and Critical Medicine, Hôpital Beaujon, F-92110 Clichy, France; [9]Abbott Laboratories, Abbott Park, IL, USA; [10]Department of Critical Care Medicine, Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium; [11]AP-HP, Medical ICU, Hôpital Lariboisière, F-75475 Paris Cedex 10, France; [12]First Department of Cardiology, North Estonia Medical Center, 12419 Tallinn, Estonia; [13]AP-HP, Department of Cardiology, Hôpital Lariboisière, F-75475 Paris Cedex 10, France; [14]AP-HP, Department of Anesthesiology and Critical Care Medicine, Hôpital Lariboisière, 2 Rue A Paré F-75475 Paris Cedex 10, France; and [15]Cumhuriyet University School of Medicine, Department of Cardiology, Sivas, Turkey

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Aims The aim of this study was to assess the prevalence of abnormal liver function tests (LFTs) and the associated clinical profile and outcome(s) in acute decompensated heart failure (ADHF) patients. Alteration in LFTs is a recognized feature of ADHF, but prevalence and outcomes data from a broad contemporary cohort of ADHF are scarce and the mechanism(s) of ADHF-induced cholestasis is unknown.

Methods and results We conducted a *post hoc* analysis of SURVIVE, a large clinical trial including ADHF patients treated with levosimendan or dobutamine. All LFTs were available in 1134 patients at baseline. Abnormal LFTs were seen in 46% of ADHF patients: isolated abnormal alkaline phosphatase (AP) was noted in 11%, isolated abnormal transaminases in 26%, and a combination of abnormal AP and transaminases in 9%. Abnormal AP was associated with marked signs of systemic congestion and elevated right-sided filling pressure. Abnormal AP had no relationship with 31-day mortality but was associated with worse 180-day mortality (23.5 vs. 34.9%, $P = 0.001$ vs. patients with normal AP). Abnormal transaminases were associated with clinical signs of hypoperfusion and with greater 31-day and 180-day mortality compared with normal transaminase profiles (17.6 vs. 8.4% and 31.6 vs. 22.4%, respectively; both $P < 0.001$). There was no additive value of abnormal AP plus abnormal transaminase on a long-term outcome.

Conclusion Abnormal LFTs were present in about a half of patients presenting with ADHF treated with inotropes. Abnormal AP and abnormal transaminases were associated with specific clinical, biological, and prognostic features, including a short-term overmortality with increased transaminases but not with biological signs of cholestasis, in ADHF patients.

Keywords Heart failure • Liver • Prognosis • Inotropic agents

Introduction

Heart failure (HF) is a clinical syndrome associated with haemodynamic changes that may result in pressure-related damage to one or more organs.[1,2] Interactions between renal and cardiac dysfunction have been recently construed to be 'cardiorenal syndromes', including subtypes with specific pathophysiology, diagnostic and prognostic values, and management strategies.[3–5]

Liver involvement has been mostly described and investigated in patients with chronic HF.[6,7] Liver enzyme alterations are usually classified as relating predominantly to liver cell necrosis (signified

* Corresponding author. Tel: +33 1 49 95 80 71, Fax: +33 1 49 95 80 72, Email: alexandre.mebazaa @lrb.aphp.fr

by transaminase elevations) or predominantly to cholestasis [signified by elevated alkaline phosphatase (AP) levels].[8,9]

The prognostic importance of abnormalities in liver function tests (LFTs) has varied among published studies. The unfavourable predictive value of abnormal LFTs has been described in patients with chronic HF[10] or acute decompensated heart failure (ADHF).[11] Total bilirubin was among the most highly significant predictors of mortality in a *post hoc* analysis of a large cohort of chronic HF patients in a clinical trial.[12] However, a haemodynamic-independent prognostic value of liver function abnormalities was not found in a recent analysis of 323 patients with a history of HF.[13]

In the acute-care setting, hepatocyte necrosis has been the most frequently described histological finding associated with alteration in LFTs, in the cases of severe circulatory shock,[14] or severe ADHF.[15] However, the prevalence of altered LFTs (signifying hepatocellular lysis and/or cholestasis) in a large contemporary cohort of ADHF patients is unknown.

The purpose of this study was to prospectively characterize LFTs in a large, representative, well-treated cohort of ADHF patients. SURVIVE was a large clinical trial involving patients with ADHF in whom LFTs were performed before and after inotrope infusion.[16] The aims of this *post hoc* analysis of the SURVIVE trial were to assess: (i) the prevalence and the clinical profile of patients admitted for ADHF and abnormal LFTs; and (ii) the impact of abnormal LFTs on short- and long-term outcomes.

Methods

Study population

SURVIVE was a randomized, double-blind, international, multi-centre, parallel-group study of levosimendan vs. dobutamine in patients with severe ADHF. Participating patients had the left ventricular ejection fraction (LVEF) $<30\%$ and were hospitalized for ADHF requiring inotropic support.[16,17] In accordance with non-inclusion criteria, all enrolled patients had systolic blood pressure (SBP) >85 mm Hg; hence, cardiogenic shock patients were not enrolled. A great majority of patients (88%) had a known history of HF. Patients with severe hepatic failure (definition of which was at the discretion of the treating physicians) were not included from the main study because levosimendan is metabolized in the liver. In addition, patients with abnormal LFTs attributed to chronic hepatic inflammatory disease, substance abuse, or hepatotoxic medication were also not included in the SURVIVE trial. The main result of SURVIVE was that all-cause mortality at 180 days occurred in 26% patients in the levosimendan group and 28% patients in the dobutamine group (hazard ratio, 0.91; 95% confidence interval, 0.74–1.13; $P = 0.40$) and that the levosimendan group had greater decreases in the B-type natriuretic peptide level at 24 h that persisted through 5 days compared with the dobutamine group.[16] The population of the present substudy comprised patients included in the SURVIVE study who had all LFTs available at baseline ($n = 1134$) without taking into account any extra inclusion or exclusion criteria. Liver function tests were also performed at Days 1, 3, 5, and 31.

Biochemical measurements

Liver function tests were measured in a core laboratory (Roche, Modular-P chemical analyser, Icon clinical research, Ireland) and considered abnormal when levels exceeded 47 U/L for alanine transaminase (ALT), 37 U/L for aspartate transaminase (AST), and 135 U/L for AP. B-type natriuretic peptide (BNP) and creatinine levels were also recorded.

Statistical analyses

Baseline demographic and clinical characteristics are presented as means or medians for continuous variables, and as percentages for categorical variables. Comparisons between normal and abnormal liver enzyme groups for categorical variables were performed using Fisher's exact test. The analysis of variance or the Wilcoxon rank-sum test was used to explore differences between normal and abnormal liver enzyme groups for continuous variables. Treatment differences in changes from baseline to Days 1, 3, 5, and 31 since the start of study drug infusion were analysed using an analysis of covariance model with treatment and baseline value as covariates.

Stepwise logistic regression analysis was performed to determine the variables associated with abnormal baseline values for LFTs. Maximum likelihood parameter estimates of odds ratios with 95% Wald confidence intervals were calculated. The assessment of correlation was evaluated using the Spearman correlation coefficient.

Survival analysis was performed for the baseline normal/abnormal LFTs groups, which were defined by laboratory normal ranges. Cumulative survival curves for the normal/abnormal groups were constructed using the Kaplan–Meier methodology, and survival curves were compared using the log-rank test. As AST is also a marker of myocardial necrosis, we have repeated the analysis, excluding patients with acute coronary syndrome. Statistical analyses were performed using the SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA). A two-sided significant level of 5% was considered the level of statistical significance.

Results

Assessment of liver function tests

All LFTs were available in 1134 patients at baseline. *Table 1* shows that $>20\%$ of measured LFTs were abnormal and most of LFTs alterations were moderate elevations.

Following the initiation of inotropic support, AP decreased at Day 1 and thereafter showed a small rebound (*Figure 1*). Alanine transaminase and AST decreased progressively over the 31 days after inotrope therapy (*Figure 1*). Liver function tests response by treatment can be seen in Supplementary material online, *Figure S1*; treatment-specific decrements in AP levels paralleled greater changes in BNP levels in the levosimendan arm than in dobutamine arm during the initial days of treatment.

Table 1 Distribution of liver function tests elevations at baseline

	ALT (%)	AST (%)	AP (%)
Normal	847 (75)	759 (67)	894 (79)
1–2 times of UNL	168 (15)	206 (18)	205 (18)
≥2–5 times of UNL	66 (6)	102 (9)	32 (3)
≥5 times of UNL	53 (5)	67 (6)	3 (0.3)

UNL, upper normal limit defined as 135 U\L for AP, 47 U\L for ALT, 37 U\L for AS.

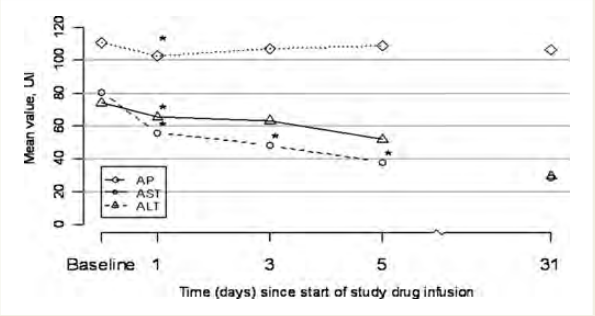

Figure 1 Time-course of liver enzymes in acute decompensated heart failure patients from the time of inotrope administration to 31 days. Absolute values of liver enzymes over time (*$P = 0.01$ vs. baseline values).

Factors associated with abnormal liver function tests at baseline

Tables 2 and *3* show that in this population of ADHF patients elevations in AP were associated with marked clinical and biochemical signs of systemic congestion and elevated right-sided filling pressure, whereas elevations in transaminases were associated with clinical signs of hypoperfusion.

Clinical signs coincident with abnormal AP levels included a greater incidence of peripheral oedema and tricuspid regurgitation, a two-fold increase in the incidence of ascites, a greater creatinine concentration, and a 1.5-fold increase in BNP concentrations compared with patients with normal AP, in uni- and multi-variate analysis (*Table 3*). The Spearman correlation coefficient between plasma levels of AP and BNP ranged from 0.21 to 0.26 at baseline, Day 1, Day 3, or Day 5 (all $P < 0.001$), and was greater than the Spearman correlation coefficient between plasma levels of transaminases and BNP (e.g. 0.04 for ALT and 0.06 for AST, at Day 5; both non-significant).

Tables 2 and *4* further show that abnormal ALT and/or AST levels at baseline were associated with various clinical signs of hypoperfusion: lower SBP, higher heart rate, and higher prevalence of cold extremities. Abnormal ALT and/or AST were also associated with a three-fold higher incidence of acute myocardial infarction, a lower incidence of a history of HF, and a lower incidence of worsening HF. Abnormalities of transaminases were further associated with a lower use of oral beta-blockers before admission compared with normal transaminases.

Factors associated with high AP or high transaminases were hardly affected by the occurrence of acute myocardial infraction (See Supplementary material online, *Table S1a* and *b*).

No difference was also seen between factors associated with abnormal AST and those associated with abnormal ALT (data not shown).

Abnormal liver function tests and outcome

All-cause mortality rates of the SURVIVE population were 13% at 31 days and 27% at 180 days[16]. *Table 2* shows that abnormal AP was not associated with an overmortality at 31 days, but was at 180 days (23.5 vs. 33.8%, normal vs. abnormal AP, respectively, $P = 0.001$). Abnormal elevations in levels of at least one transaminase was associated with an immediate and persistent overmortality, with an almost two-fold greater 31-day mortality compared with patients with normal transaminases (17.7 vs. 8.3%; $P < 0.001$) and a greater 180-day mortality (31.8 vs. 22.1%, $P < 0.001$) (*Table 2*).

Kaplan–Meier curves over 180 days were drawn based on normal vs. abnormal values of baseline LFTs. Kaplan–Meier analysis found log-rank *P*-values <0.001 for both abnormal AP and abnormal transaminases. *Figure 2* illustrates the immediate negative effect of abnormal transaminases and the lack of effect of abnormal AP on the short-term outcome. *Figure 2* also illustrates similar long-term overmortality in abnormal AP or transaminases.

Of note, *Figure 3* shows that results remained unchanged for AP and ALT when patients with acute myocardial infarction were excluded ($n = 941$; log-rank $P < 0.001$ for AP and $P = 0.035$ for ALT); overmortality was also present although not statistically significant for abnormal AST (log-rank $P = 0.07$).

Data in *Table 5* affirm a lack of additive values of abnormal transaminases and abnormal AP on the long-term outcome. Abnormal transaminases alone, abnormal AP alone, or combined transaminases and AP abnormalities were characterized by similar 180-day mortality (30.0, 31.0, and 36.9%, respectively), all of which were greater than the mortality rate among patients with normal LFTs (20.1%). Likewise, multi-variate analysis identified AP as a factor independently associated with 180-day mortality (Supplementary material online, *Table S2*).

Of note, though the absolute values of LFTs at baseline were associated with outcome, changes of LFTs during the initial 5 days (decrease or increase) were not associated with the outcome except a worse mortality (at both 30 and 180 days) in patients that decreased AP (*Table 6* and Supplementary material online, *Table S3*); the decrease in AP during the initial 5 days is even associated with a worse 31-day (Supplementary material online, *Table S3*) and 180-day mortality than the increase in AP (*Table 6*).

Discussion

This analysis of the SURVIVE database identified that (i) cardiohepatic dysfunction is present in about a half of this cohort of patients with severe ADHF and (ii) LFTs can be used as surrogates of haemodynamics. Biochemical signs of cholestasis were associated with marked signs of systemic congestion and elevated right-sided filling pressure, while biochemical signs of liver cytolysis were associated with clinical signs of hypoperfusion. Cardiohepatic dysfunction was associated with increased long-term mortality.

Heart failure-induced cholestasis

In the present study, abnormal plasma AP (alone or in conjunction with abnormal transaminase levels) was seen in 20% of ADHF patients at baseline. High levels of AP at baseline were associated with clinical and biochemical signs of marked systemic congestion and elevated right-sided filling pressure, including peripheral oedema, ascites, tricuspid regurgitation, and high plasma levels of

Table 2 Demographic characteristics, medical history, signs, and symptoms at admission, drugs before admission and mortality depending on normal/abnormal values of liver function tests

	Normal AP	Abnormal AP	*P*-value	Normal ALT and AST	Abnormal ALT and/or AST	*P*-value
n	894	240		716	418	
Age (years)	66.8	66.2	0.450	66.9	66.2	0.297
Weight (kg)	79.2	79.3	0.943	79.7	78.4	0.206
Height (cm)	169	170	0.020	169	169	0.445
Male (%)	70.8	75.8	0.145	71.7	72.2	0.838
Caucasian (%)	94.6	94.6	>0.999	93.7	96.2	0.101
Clinical signs at baseline						
SBP (mmHg)	117	114	0.015	117	114	0.010
DBP (mmHg)	71	70	0.196	71	70	0.446
HR (b.p.m.)	83	83	0.955	81	87	<0.001
Peripheral oedema (%)	65.4	78.8	<0.001	71.2	63.2	0.005
Ascites (%)	17.3	31.7	<0.001	22.2	17.1	0.047
Cold extremities (%)	20.7	25.8	0.094	19.6	25.6	0.021
Biochemical parameters at baseline (median)						
ALT (IU/L)	26.0	31.5	<0.001	21.0	59.0	<0.001
AST (IU/L)	28.0	83.0	<0.001	23.0	60.0	<0.001
AP (IU/L)	83.0	173.5	0.001	90.0	101.0	<0.001
Creatinine (μM/L)	120.0	143.2	<0.001	123.4	127.4	0.289
BNP (pg/mL)	1027	1606	<0.001	1070	1341	<0.001
Cardiovascular history (%)						
Previous CHF	88.7	89.2	0.909	92.9	81.8	<0.001
Previous MI	68.9	67.9	0.814	68.2	69.6	0.642
Hypertension	64.1	59.2	0.175	62.9	63.4	0.899
Atrial fibrillation/flutter	46.5	53.3	0.069	50.1	44.3	0.057
Diabetes mellitus	33.1	40.0	0.047	34.1	35.4	0.651
Initial hospitalization characteristics (%)						
Worsening HF	79.3	81.3	0.528	88.3	65.1	<0.001
AMI	18.6	11.3	0.002	8.8	31.1	<0.001
LVEF	24.0	23.3	0.054	24.1	23.5	0.070
Tricuspid regurgitation	46.0	53.3	0.049	51.7	40.4	<0.001
Cardiovascular medications at admission (%)						
ACE-I/ARB use	72.2	65.4	0.046	73.5	66.0	0.008
BB use	51.8	44.2	0.006	53.6	44.3	0.003
All-cause mortality (%)						
At 31 days	11.1	14.2	0.213	8.3	17.7	<0.001
At 180 days	23.5	33.8	0.002	22.1	31.8	<0.001

n, 1134; ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine transaminase; AMI, acute myocardial infarction during current admission; AP, alkaline phosphatase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; BB, beta-blocker; BNP, B-type natriuretic peptide; CHF, chronic heart failure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NS, not significant; SBP, systolic blood pressure.
Abnormal LFTs are defined in *Table 1*.

creatinine and BNP. Our results are in line with studies showing that biochemical markers of cholestasis, including bilirubin, γ-glutamyl transpeptidase, or AP, are increased in the plasma of patients with elevated central venous pressure[13] or severe tricuspid regurgitation.[7]

The mechanism by which systemic congestion and elevated right-sided filling pressure may alter biochemical markers of cholestasis remains uncertain. In ADHF patients, the marked increase in the vena cava and centrilobular pressure is transmitted back to liver sinusoids (*Figure 3*).[18–20] It is highly likely that congestion in

Table 3 Multi-variate analysis of factors that predicted abnormal alkaline phosphatase

	OR	Lower CI	Upper CI	*P*-value
Ascites (yes/no)	1.808	1.276	2.561	0.002
Peripheral oedema (yes/no)	1.724	1.276	2.561	0.001
Diabetes mellitus (yes/no)	1.460	1.067	1.998	0.018
BNP (pg/mL per 100)	1.026	1.014	1.032	<0.0001
Creatinine (μM/L)	1.004	1.001	1.006	0.002
SBP (mmHg)	0.989	0.980	0.997	0.008

AP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BNP, B-type natriuretic peptide; CI, confidence interval; MI, myocardial infarction; OR, odds ratio; SBP, systolic blood pressure.
Of note, AST and ALT were excluded from this analysis.

Table 4 Multi-variate analysis of factors that predicted abnormal alanine transaminase and/or abnormal aspartate transaminase

	OR	Lower CI	Upper CI	*P*-value
Acute MI during current admission (yes/no)	3.138	2.010	4.899	<0.0001
BNP (pg/mL per 100)	1.020	1.011	1.028	<0.0001
HR (b.p.m.)	1.018	1.010	1.026	<0.0001
SBP (mmHg)	0.990	0.983	0.998	0.010
Beta-blocker at admission (yes/no)	0.690	0.526	0.905	0.007
Worsening heart failure during current admission (yes/no)	0.395	0.263	0.595	<0.0001

HR, heart rate; MI, myocardial infarction.
Of note, AP was excluded from this analysis.

liver sinusoids would compress any collapsible structure within the lobule, including bile canaliculi and ductules. Raised hydrostatic pressure in liver sinusoids has been shown to increase the size of liver cells;[19] the latter might further compress bile canaliculi. Those phenomena, named the 'starling resistor'[21] in various organs such the lung and the brain, are suggested, in the present study to also apply in the liver. Compression of bile ducts in the way described might compromise bile flow and direct bile production (including AP) towards the blood. The deterioration of creatinine in our patients with elevated AP (and not in patients with elevated transaminase) is in line with an increased venous congestion.[22,23] Hence, our study strongly suggests that AP is a biological marker of liver congestion and of the extent of right-sided filling pressure in ADHF patients.

Our data suggest that abnormal AP did not affect the short-term outcome. This is consistent with various studies showing that the extent of systemic congestion, including the increase in body weight[24] or elevated levels of central venous pressure,[25] at admission for ADHF, did not affect in-hospital mortality but rather the rate of rehospitalization. Our study found that decreased AP paralleled a decrease in BNP. This may be interpreted as an indication that improvement in heart function and in liver congestion might lead to reopening of the biliary tract and to reductions in AP plasma levels. Extending that reasoning, our new data suggest that plasma AP levels in ADHF patients mostly reflect bile duct compression or decompression and not cell death. It is therefore understandable that AP levels had no influence on short-term survival.

Heart failure-induced liver cytolysis

In accordance with previous reports, our study shows that elevated levels of transaminases resolve rapidly in response to intensive medical therapy based on inotropes.[15] Elevated plasma levels of transaminases typically result from a leak of ALT and/or AST from damaged hepatocytes into the bloodstream. In the present study, AST and ALT showed a rapid normalization within the first 5 days, with a more rapid plasma reduction for AST than for ALT, as previously described.[8] However, as shown in *Table 6*, the decline in transaminases is not always indicative of liver recovery and good outcome.

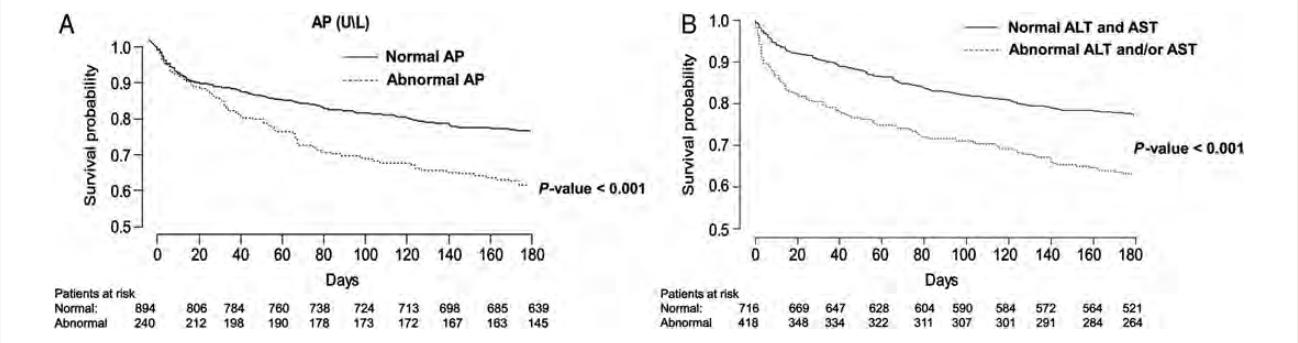

Figure 2 Kaplan–Meier curves of mortality based on (*A*) abnormal or normal alkaline phosphate at baseline, or (*B*) abnormal or normal transaminases. ALT, alanine transaminase; AST, aspartate transaminase.

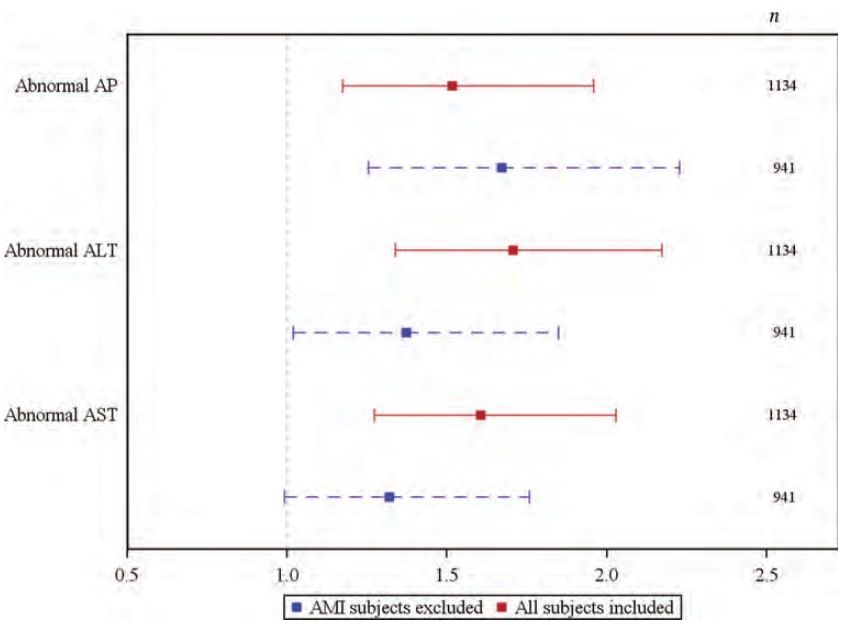

Figure 3 Log-rank analysis of 180-day mortality, acute myocardial infarction excluded or not. $P < 0.001$ for AP, $P = 0.035$ for ALT, $P = 0.07$ for AST.

Table 5 Additive values of abnormal transaminases and abnormal alkaline phosphatase on a short- and long-term outcome

	AST and ALT normal	AST and/or ALT abnormal
30-day mortality		
AP (%)		
Normal	46/587 (7.8)	53/307 (17.3)
Abnormal	13/129(10.0)	21/111 (18.9)
180-day mortality		
AP (%)		
Normal	118/587 (20.1)	92/307 (30.0)
Abnormal	40/129 (31.0)	41/111 (36.9)

Table 6 Effect of change of liver function tests from baseline to Day 5 on 180-day mortality

	Alive	Died
AP ($n = 883$) (%)		
Decrease	319 (73.8)	113 (26.2)
Increase	373 (82.7)	78 (17.3)
Log-rank $P = 0.001$		
ALT ($n = 883$) (%)		
Decrease	350 (76.3)	109 (23.8)
Increase	342 (80.7)	82 (19.3)
Log-rank $P = 0.111$		
AST ($n = 883$) (%)		
Decrease	362 (78.7)	98 (21.3)
Increase	330 (78.0)	93 (22.0)
Log-rank $P = 0.792$		

ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase. Subjects who have Day 5 ALT, AST, and AP assessment are included to the analysis.

In our study, a profile of abnormal transaminase elevation was associated with signs of hypoperfusion, including hypotension, tachycardia, and cold extremities. This is consistent with previous reports[9,26] showing that hepatic cytolysis is related to hypoperfusion and/or hypooxygenation of the liver cells of the centrilobular region ('nutmeg liver') that are the more distant from the dual circulatory supply of the hepatic artery and portal veins (*Figure 4*). We think it likely therefore that elevated levels of transaminases reflected liver ischaemia secondary to hypoperfusion caused by rapid deterioration in cardiovascular function. This conjecture is supported by the unfavourable short-term prognosis associated with abnormal transaminases in the present study.

Liver function tests and long-term prognosis

Acute decompensated heart failure patients requiring inotrope treatment represent a critically ill group of patients with high short- and long-term mortality rates. Many predictive factors

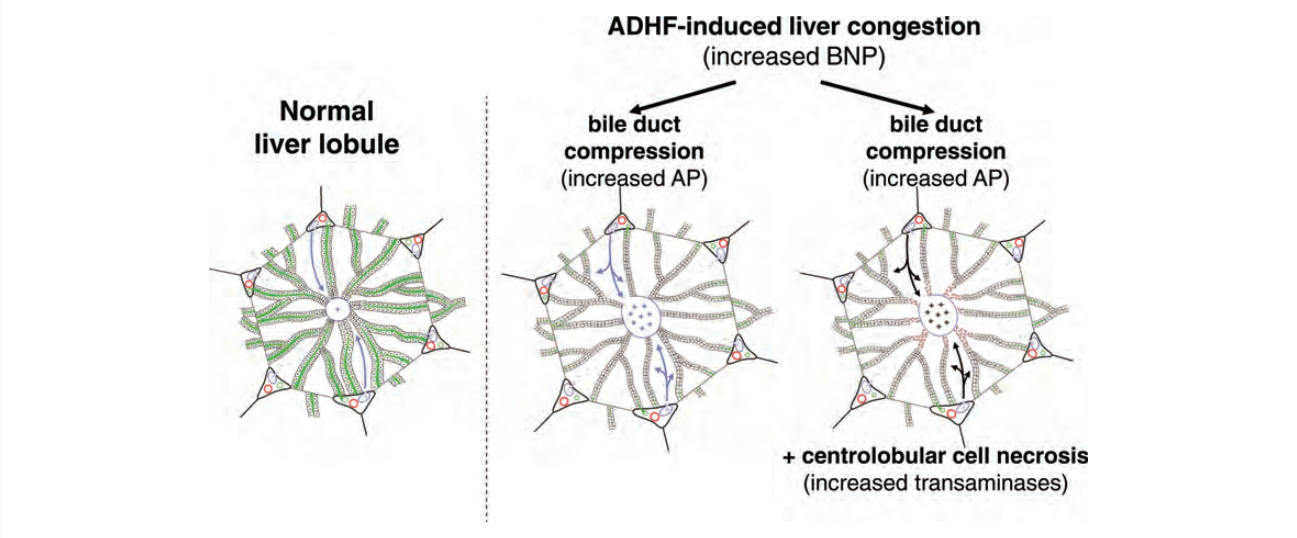

Figure 4 Suggested mechanism of acute decompensated heart failure-induced cholestasis and/or liver cell necrosis. Within each normal liver lobule, blood easily flows from portal veins (or hepatic artery) through the sinusoids into the centrilobular vein, vena cava, and right atrium. In the other hand, bile is secreted into a network of minute bile canaliculi situated between adjacent hepatocyte. Bile canaliculi originate close to the centrilobular region and join to form bile ductules and ducts at the periphery of the lobule. In ADHF patients, congestive liver sinusoids would likely compress bile canaliculi and ductules by increased hydrostatic pressure and increase in the size of liver cells; this phenomenon is named 'Starling resistor'. Hepatic cytolysis is related to hypoperfusion and/or hypooxygenation of the liver cells of the centrilobular region ('nutmeg liver') that are the more distant from the dual circulatory supply of the hepatic artery and portal veins. AHF, acute heart failure; AP, alkaline phosphatase; BNP, B-type natriuretic peptide.

have been described that aid risk stratification of patients and decision-making for 'invasive' treatment options (cardiac resynchronization therapy, left ventricular assist devices, transplantation, etc.). The present study shows that impaired hepatic biochemistry was associated with a 50% increase in the 180-day mortality rate (~30% absolute mortality in ADHF patients with altered LFTs compared with 20% absolute mortality in patients with normal LFTs) and should be tested as an additional risk factor of poor outcome. High levels of AP and/or transaminases likely reflected the severity of the underlying right-sided and/or left-sided HF. Acute myocardial infarction—more prevalent in the group of patients with elevated transaminases—may have interacted with those results. In our examination of this matter, the prognostic value of abnormal ALT—but not abnormal AST—persisted independently of the acute myocardial infarction status.

Whether the severity of liver damage influences by itself the prognosis, or only reflects the severity of the HF remains still unclear.

Limitations

This is a retrospective analysis based on a cohort of patients that did not represent the entire ADHF population.[27] Patients with severe liver injury were excluded from SURVIVE. Furthermore, invasive haemodynamic data and liver imaging tests were not available. Concerning the panel of LFTs, unfortunately other markers of liver function, such as bilirubin, albumin, or prothrombin time were not measured. Cholestasis, though, is followed by the increase in bilirubin or AP as well. Measuring prothrombin time may also be confusing in patients receiving anticoagulants. This trial may boost future prospective trials to compare the changes in all LFTs along with haemodynamic and imaging techniques in AHF patients.

Clinical implications

Measurements of LFTs should be recommended in the early phase of ADHF management. Abnormal LFTs signify the presence of cardiohepatic syndromes and, most importantly, indicate the mechanism of liver injury and of its related heart dysfunction: liver congestion related to 'backward' HF in case of elevated AP and/or liver ischaemia related to 'forward' HF in case of elevated transaminases. Abnormal LFTs may therefore offer a guide to the most appropriate management of ADHF patients. Priority should therefore be directed towards reducing congestion in cases of increased AP and/or towards improving perfusion in cases of increased transaminases. Abnormal LFTs are also indicative of an unfavourable long-term outcome and this knowledge may inform future treatment strategies.

In summary, the present study describes cardiohepatic dysfunction in about half of patients presenting with ADHF that required inotrope treatment. Cardiohepatic syndromes share some common pathophysiological mechanisms with cardiorenal syndromes, such as the increase in venous congestion and/or reduced cardiac output leading to the worsening of renal function.[3] Our study further shows that high levels of transaminases were associated with a short-term overmortality that was not seen with increased AP. Future studies should give attention to the

place of cardiohepatic syndromes, including the use of liver biomarkers, in the diagnosis and the management of ADHF.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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