Prevalence and clinical significance of liver function abnormalities in patients with acute heart failure

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Aims. Liver pathology caused by cardiac dysfunction is relatively well recognized, however, its clinical importance has not been fully evaluated. The aim of this study was to assess the prevalence of liver function tests (LFTs) abnormalities and to identify associated factors mediating hepatic impairment in patients with acute heart failure (AHF).
Methods. The AHEAD (Acute Heart Failure Database) registry is a database conducted in 9 university hospitals and 5 regional health care facilities in the Czech Republic. From December 2004 to October 2012, the data of 8818 patients were included. The inclusion criteria for the database followed the European guidelines for AHF. Serum activities of all LFTs and total bilirubin were available in 1473 patients at the baseline.
Results. In patients with AHF, abnormal LFTs were seen in 76% patients (total bilirubin in 34%, γ-glutamyltransferase in 44%, alkaline phosphatase in 20%, aspartate aminotransferase in 42%, alanine aminotransferase in 35%). Patients with cardiogenic shock were more likely to have LFTs abnormalities compared to mild AHF and pulmonary oedema. LFTs abnormalities were strongly associated with AHF severity (left ventricular ejection fraction and NYHA functional class) and clinical manifestation. While hepatocellular LFTs pattern predominated in left sided forward AHF, cholestatic profile occurred mainly in bilateral and right sided AHF. Additionally, patients with moderate to severe tricuspid regurgitation had significantly higher prevalence of abnormalities in cholestatic LFTs.
Conclusions. Defining the LFTs profile typical for AHF plays an important role in management of AHF patients, since it may avoid redundant hepatic investigations and diagnostic misinterpretations.

Key words: heart failure, liver function tests, bilirubin, congestive hepatopathy, ischemic hepatitis

Received: September 11, 2013; Accepted: March 4, 2014; Available online: March 13, 2014
http://dx.doi.org/10.5507/bp.2014.014

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INTRODUCTION

Cardiac failure has a negative impact on the function of all parenchymatous organs, based both on the low organ perfusion in the left-sided forward failure and on the venous congestion in the right-sided backward failure[1]. Most of the studies have been focused on cardiorenal syndromes, however, the impact of cardiac failure on liver function is also considerable[2,3].

Common histopatological findings of hepatic impairment caused by heart failure embrace inflammatory changes, sinusoidal dilatation, necrosis and fibrosis – all these features occur both in centrilobular and periportal location. While stage of fibrosis has been described mostly in chronic right-sided heart failure, centrilobular or periportal necrosis have mainly been seen in acute heart failure (AHF) patients (Fig. 1) (ref.[4,5]).

Current studies dealing with cardiac hepatopathy focus predominantly on the liver enzyme changes by analysing clinical and prognostic relevance of liver function tests (LFTs) abnormalities in patients with chronic heart failure. Strikingly, there are only few works investigating the liver involvement in AHF (Table 1) (ref.[6-14]).

The aim of this study was to evaluate the prevalence of LFTs abnormalities and to identify associated cardiac and noncardiac factors mediating hepatic impairment in AHF – new onset (*de novo*) heart failure as well as acute exacerbation of chronic.

Table 1. LFTs abnormalities in AHF patients.

Study	Patient population	Study character	Type of heart failure	Percentage of abnormal						
				↑ AST	↑ ALT	↑ ALP	↑ GGT	↑ T-BIL	↑ LD	↓ ALB
Allen, Eur J Heart Fail 2009	2679	retrospective, multicentric	chronic	4%	3%	14%	x	13%	x	18%
Nikolau, Eur Heart J 2012	1134	retrospective, monocentric	acute decompensation of chronic	33%	25%	21%	x	x	x	x
Poelzl, Eur J Clin Invest 2012	1032	retrospective, monocentric	chronic	13%	15%	12%	46%	15%	x	x
Batin, Eur Heart J 1995	552	retrospective, monocentric	chronic	9%	26%	44%	32%	36%	x	x
Van Deursen, J Card Fail 2010	323	retrospective, monocentric	chronic	18%	43%	x	x	x	65%	x
Shinagava, Circ J 2008	183	retrospective, monocentric	acute decompensation of chronic	x	x	x	x	64%	x	x
Felder, Circulation 1950	135	retrospective, monocentric	chronic	x	x	46%	x	52%	x	26%
Kubo, Arch Intern Med 1987	133	retrospective, monocentric	chronic	17%	16%	41%	48%	31%	36%	64%
Lau, Am J Cardiol 2002	110	retrospective, monocentric	acute	4%	7%	22%	41%	19%	x	42%

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; LD, lactate dehydrogenase; T-BIL, total bilirubin.

MATERIALS AND METHODS

The AHEAD (Acute Heart Failure Database) registry is a Czech multi-centric database conducted in 9 university hospitals with a 24-h Catheterisation Laboratory service and 5 regional health care facilities. From December 2006 to October 2012, the data of 8818 patients with AHF were collected into the database prospectively. The inclusion criteria followed current European guidelines for AHF and patients were systematically classified according to type, clinical manifestation and aetiology of AHF (ref.[15-17]). The decision on inclusion in the registry and filling in the database was performed by experienced cardiologists through the Internet website http://www.ahead.registry.cz. There was no exclusion criterion and patients were enrolled only once during the study period. Written informed consent was obtained from all subjects and local ethics committees of involved centres approved the database protocol.

Serum activities of all LFTs – γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) – and total bilirubin (T-BIL) were available in 1473 patients (592 women) at the baseline. Laboratory samples were collected on admission or on the 2nd day of hospitalisation after overnight fasting. Abnormal levels of the laboratory values were set above the upper limit of reference range that was specific for each involved centre laboratory.

Statistical Analysis

Data analysis was performed by the Institute of Biostatistics and Analyses of Masaryk University (Brno, Czech Republic) using the Statistical Package for Social Sciences (Release 19.0.1, IBM Corporation 2010). Standard descriptive statistics was applied in the analysis: absolute and relative frequencies for categorical variables and median supplemented by 5th and 95th percentile for continuous variables. Statistical significance of differences between pairs of groups of patients was computed using maximum likelihood chi-square test for categorical variables, Mann-Whitney test for continuous variables. Logistic regression was used to estimate of relationships between liver function tests and heart failure-related variables (univariate and multivariate). The level of statistical significance was set at $\alpha = 0.05$.

RESULTS

Baseline characteristics

Of 1,473 patients with available LFTs serum levels, 724 (49%) had *de novo* (newly diagnosed) heart failure and 359 (24%) had acute coronary syndrome on admission. Mean age of the patients was 74 years and mean left ventricular ejection fraction was 35%.

Table 2 shows baseline clinical characteristics including medical history and medication on admission of patient cohort according to types of AHF – divided into AHF with mild signs, pulmonary oedema (associated with severe respiratory distress, rales over the lungs and

Table 2. Baseline characteristics of patients according to types of AHF.

	Total[1] (N=1473)	AHF with mild symptoms (N=1067)	Pulmonary oedema (N=250)	Cardiogenic shock (N=156)	*P*-value
Demographic and clinical					
Age (years)	74 (65; 81)	74 (65; 82)	73 (67; 81)	69 (59;79)	<0.001
Gender (female)	592 (40.2%)	439 (41.1%)	105 (42.0%)	48 (30.8%)	**0.035**
Body mass index	28 (25; 32)	28 (25; 32)	28 (25; 31)	27 (24; 29)	**0.001**
Heart rate (bpm)	86 (72; 105)	84 (70; 103)	97 (80; 110)	90 (75; 110)	<0.001
Systolic BP (mm Hg)	134 (115; 152)	135 (120; 150)	145 (120; 180)	107 (90; 120)	<0.001
Diastolic BP (mm Hg)	80 (70; 90)	80 (70; 90)	80 (70; 100)	65 (55; 77)	<0.001
LV-EF (%)	35 (25; 45)	35 (25; 46)	35 (25; 45)	25 (20; 35)	<0.001
TR (moderate/severe)	517 (35.1%)	402 (37.7%)	60 (24.0%)	55 (35.3%)	<0.001
NYHA Class III/IV	821 (56.6%)	642 (60.3%)	118 (48.2%)	61 (43.0%)	<0.001
De novo HF	724 (49.2%)	462 (43.3%)	152 (60.8%)	110 (70.5%)	<0.001
Aetiology (ischaemic)	888 (60.3%)	609 (57.1%)	166 (66.4%)	113 (72.4%)	<0.001
ACS at admission	359 (24.4%)	188 (17.6%)	85 (34.0%)	86 (55.1%)	<0.001
Atrial fibrillation	501 (34.1%)	391 (36.7%)	74 (29.6%)	36 (23.4%)	**0.001**
Medical history					
Hypertension	1077 (74.0%)	796 (74.7%)	192 (78.0%)	89 (61.8%)	**0.002**
Diabetes mellitus	685 (47.1%)	489 (45.9%)	134 (54.5%)	62 (43.1%)	**0.032**
Dyslipidemia	235 (16.2%)	189 (17.7%)	34 (13.8%)	12 (8.3%)	**0.005**
Previous MI	445 (30.6%)	329 (30.9%)	76 (30.9%)	40 (27.8%)	0.740
Previous PCI or CABG	321 (22.1%)	240 (22.5%)	50 (20.3%)	31 (21.5%)	0.740
Device implanted (PM/ICD/CRT)	247 (17.0%)	205 (19.2%)	27 (11.0%)	15 (10.4%)	<0.001
COPD	370 (25.4%)	288 (27.0%)	53 (21.5%)	29 (20.1%)	0.058
Stroke or TIA in history	232 (15.9%)	168 (15.8%)	44 (17.9%)	20 (13.9%)	0.559
Medication at admission					
ACE-I/ARB	1071 (75.8%)	837 (79.7%)	188 (79.7%)	46 (36.5%)	<0.001
Beta-blocker	828 (58.6%)	636 (60.6%)	140 (59.3%)	52 (41.3%)	<0.001
Spironolactone	868 (61.5%)	678 (64.6%)	141 (59.7%)	49 (38.9%)	<0.001
Diuretic	830 (58.8%)	654 (62.3%)	121 (51.3%)	55 (43.7%)	<0.001
Statin	523 (37.0%)	374 (35.6%)	100 (42.4%)	49 (38.9%)	0.140
Calcium antagonist	283 (20.0%)	195 (18.6%)	66 (28.0%)	22 (17.5%)	**0.005**
Digoxin	271 (19.2%)	226 (21.5%)	26 (11.0%)	19 (15.1%)	<0.001
Other antiarrhytmic drug	249 (17.6%)	186 (17.7%)	34 (14.4%)	29 (23.0%)	0.127
Nitrate	207 (14.7%)	96 (9.1%)	101 (42.8%)	10 (7.9%)	<0.001
Antiaggregant	784 (55.5%)	582 (55.4%)	145 (61.4%)	57 (45.2%)	**0.013**
Anticoagulant	593 (42.0%)	442 (42.1%)	95 (40.3%)	56 (44.4%)	0.738

[1]Data from 1473 patients are reported as number (percentage) or median (interquartile range). Data on medical history were available in 1455 patients, data on medication at admission were available in 1412 patients. ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; ICD, implantable cardioverter-defibrillator, LV-EF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PM, pacemaker; TIA, transient ischaemic attack; TR, tricuspid regurgitation.

Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015 Sep; 159(3):429-436.

Table 3. Percentages of abnormal LFTs according to types of AHF.

	Total (N=1473)	AHF with mild symptoms (N=1067)	Pulmonary oedema (N=250)	Cardiogenic shock (N=156)	*P*
T-BIL (μmol/L)	498 (33.8%)	377 (35.3%)	59 (23.6%)	62 (39.7%)	<0.001
GGT (U/L)	653 (44.3%)	480 (45.0%)	97 (38.8%)	76 (48.7%)	0.104
ALP (U/L)	301 (20.4%)	219 (20.5%)	53 (21.2%)	29 (18.6%)	0.807
AST (U/L)	611 (41.5%)	363 (34.0%)	124 (49.6%)	124 (79.5%)	<0.001
ALT (U/L)	508 (34.5%)	320 (30.0%)	82 (32.8%)	106 (67.9%)	<0.001

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; T-BIL, total bilirubin.

Table 4. Distribution of LFTs elevations according to presence of ACS.

	Total[1] (N=1473)	AHF with ACS (N=359)	AHF without ACS (N=1114)	*P*
T-BIL (xULN)	0.8 (0.3; 2.2)	0.7 (0.3; 1.7)	0.8 (0.3; 2.3)	<0.001
GGT (xULN)	0.9 (0.2; 5.0)	0.7 (0.2; 3.1)	1.0 (0.2; 5.2)	<0.001
ALP (xULN)	0.7 (0.4; 1.7)	0.6 (0.3; 1.3)	0.7 (0.4; 1.8)	<0.001
AST (xULN)	0.9 (0.4; 13.0)	2.1 (0.4; 24.0)	0.7 (0.4; 5.1)	<0.001
ALT (xULN)	0.7 (0.3; 5.5)	1.1 (0.3; 7.0)	0.7 (0.3; 5.0)	<0.001

[1]Data are reported as median (5^{th}; 95^{th} percentil).
ACS, acute coronary syndrome; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; T-BIL, total bilirubin; ULN, upper limit of normal.

oxygen hyposaturation prior treatment) and cardiogenic shock (defined as tissue hypoperfusion despite adequate intravascular volume induced by cardiac failure)(ref.[15]). Patients with cardiogenic shock were significantly younger and more likely to have ischemic aetiology of AHF (both *P*<0.001). They were in significantly better NYHA functional class (*P*<0.001). that can be explained by higher prevalence of *de novo* onset of AHF and acute coronary syndromes in the shock group compared to pulmonary oedema and group with mild AHF symptoms (both *P*<0.001).

Prevalence of LFTs abnormalities in AHF

In patients with AHF, abnormal LFTs were seen in 76% patients (T-BIL in 34%, GGT in 44%, ALP in 20%, AST in 42%, ALT in 35%). Percentage of LFT abnormalities differed according to type of AHF. Patients with cardiogenic shock were more likely to have LFTs abnormalities (*P*<0.001 for T-BIL, AST, ALT, *P=NS* for GGT, ALP) compared to AHF with mild symptoms and pulmonary oedema (Table 3).

Clinical correlations of abnormal LFTs in AHF

Concerning the distribution of LFTs elevations, the highest levels were seen in patients with acute coronary syndromes that had significantly higher transaminases (AST and ALT), while AHF patients without acute coronary syndromes had significantly higher cholestatic enzymes (T-BIL, GGT and ALP) – all *P*<0.001 (Table 4).

LFTs abnormalities were strongly associated with AHF severity and clinical manifestation. While bilateral and right sided AHF were mainly presented mainly by cholestatic LFT profile, for left sided forward AHF hepatocellular pattern (elevation of transaminases) was typical (Fig. 2).

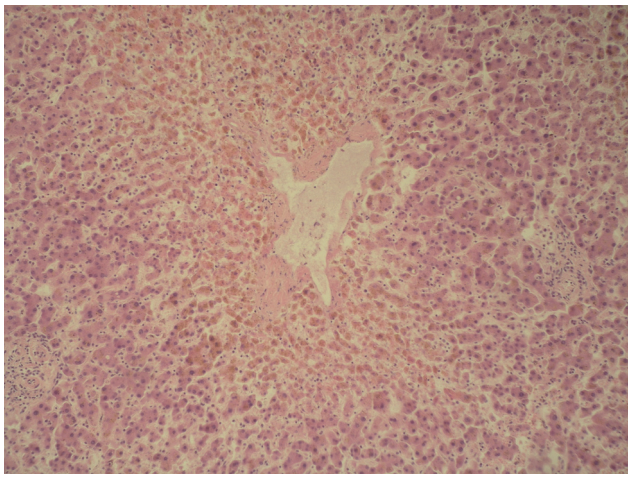

Fig. 1. Central necrosis in AHF (liver autopsy). Original magnification x400, hematoxylin-eosin stain (Courtesy of Dr. Lenz, St. Anne's Faculty Hospital, Brno, Czech Republic).

Fig. 3 shows multivariate analysis of factors predicting abnormal LFTs. As expected, patients with newly diagnosed acute coronary syndromes on admission and also hypotensive patients (with systolic blood pressure less than 100 mmHg) had significantly higher prevalence of abnormal AST and ALT. Patients with left ventricular ejection fraction less than 30 had significantly greater likelihood to have abnormal T-BIL, GGT and AST. In

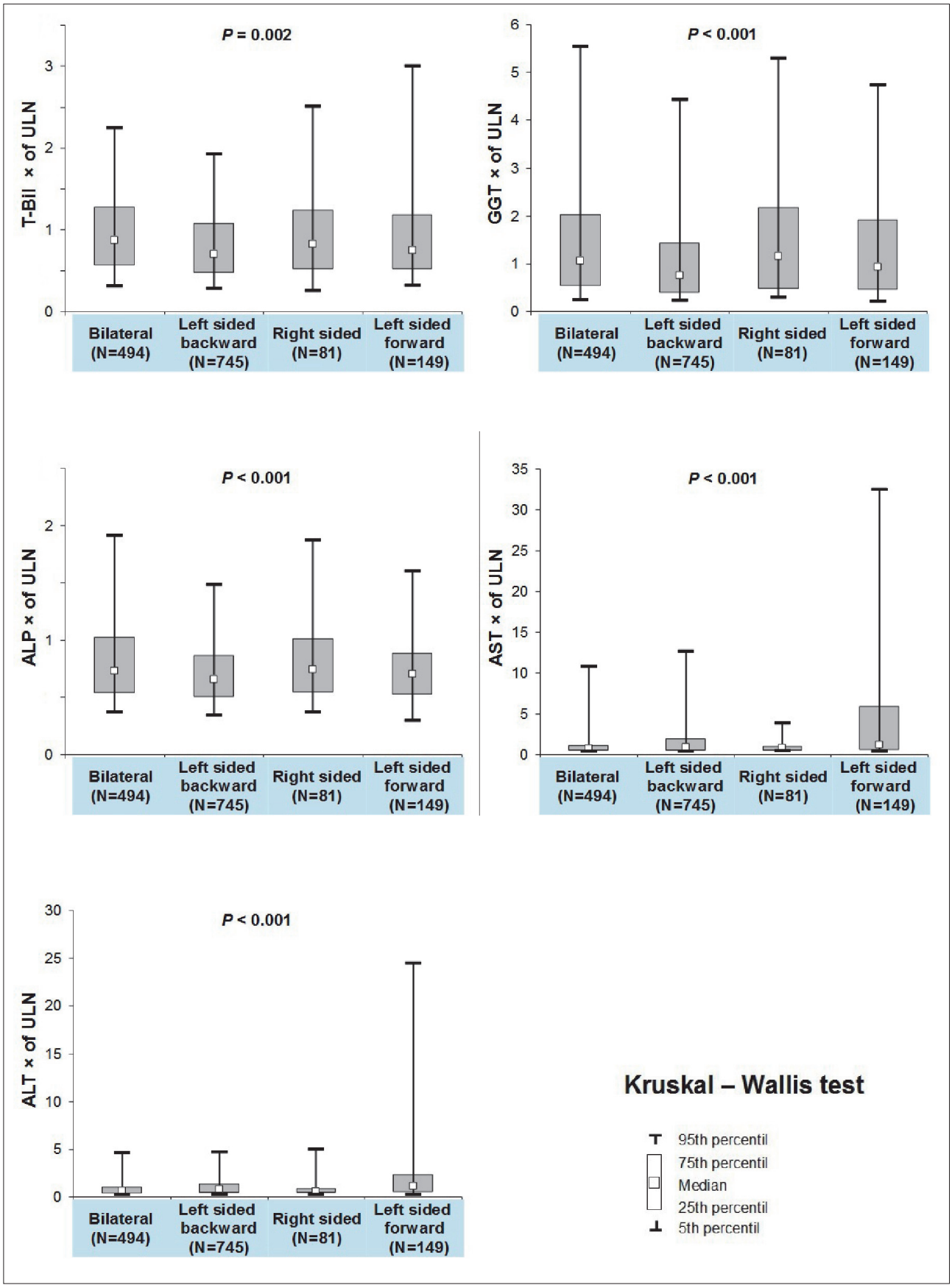

Fig. 2. Distribution of LFTs elevations according to clinical manifestation of AHF.

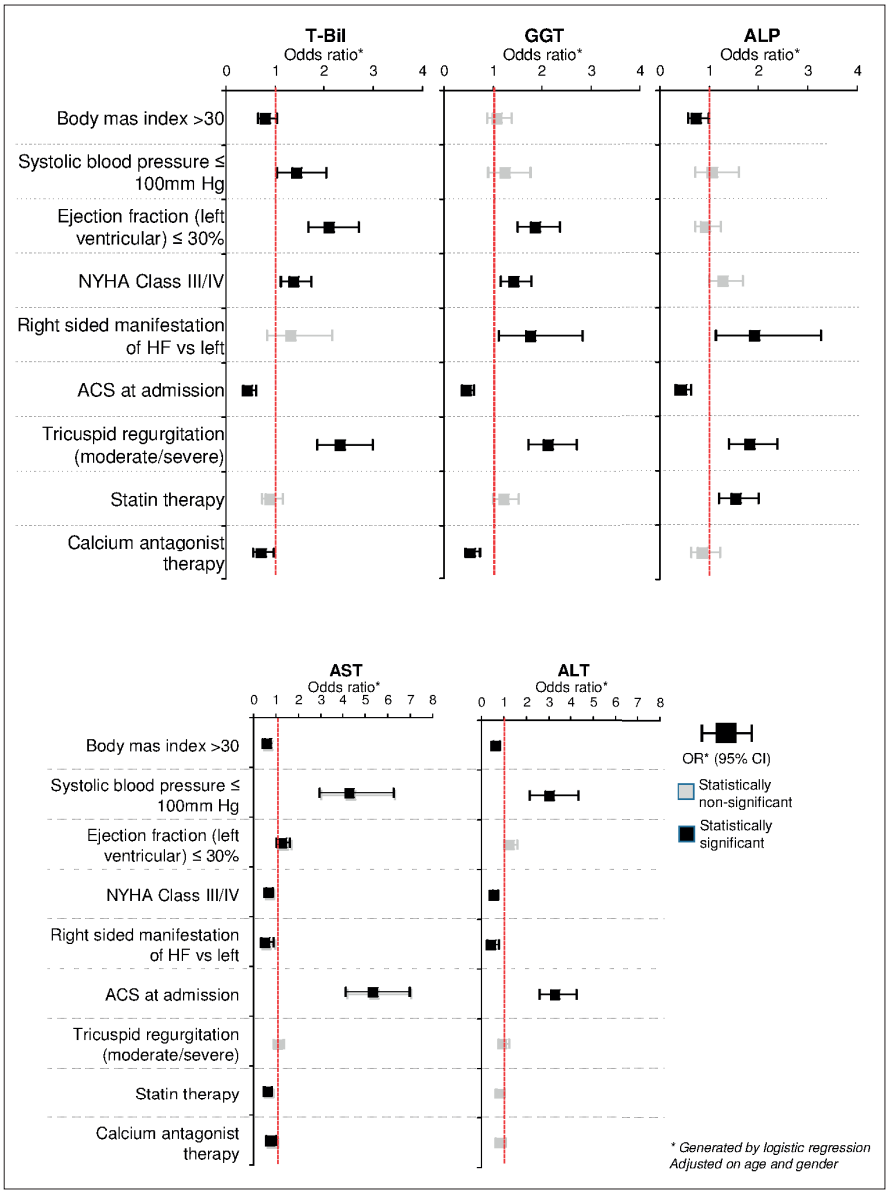

Fig. 3. Multivariate analysis of factors predicting abnormal LFTs.

addition, patients with moderate to severe tricuspid regurgitation had significantly higher prevalence of abnormalities in cholestatic LFTs (T-BIL, GGT, ALP). Patients with worse NYHA class had significantly higher abnormalities among all LFTs except ALP. Of noncardiac factors, surprisingly, higher body mass index predicts better liver condition concerning all LFTs in AHF. While potential harmful effect of statin therapy is not convincing from our results, there may be a protective effect of calcium antagonist therapy (statistically significant for T-BIL, GGT, AST).

DISCUSSION

In our study, prevalence of LFTs abnormalities was relatively high, however, it did not differ markedly from other similar studies with AHF patients when taking into account some important patients characteristics – see Table 1 (ref.[6-14]). Concerning T-BIL, according Shinigava et al the prevalence of abnormal serum levels was much higher (64%) compared to work of Lau et al (19%) and this study (34%). Nevertheless, Shinigava did not include *de novo* AHF and that can explain such high prevalence of T-BIL abnormalities, associated mostly with chronic (predominantly right-sided) cardiac failure. Regarding abnormal ALP and GGT, results were almost identical compared to other relevant studies (for ALP - 21% and 22% vs 20% found in our study, for GGT – 41% vs 44% found in our study). Of transaminases, prevalence of abnormal levels of AST and ALT in our study was higher than previously reported (42% and 35%, respectively – compared to 33% and 25% in study of Nikolau et al and 4% and 7% in study of Lau et al, respectively) (ref.[7,11,14]). Lower prevalence of abnormal transaminases in Lau's work was caused by exclusion of acute myocardial infarction patients from the study. In our study, percentage of acute coronary syndromes was high (24% - in comparison

with 15% reported in Nikolau's work) and that explains high prevalence of transaminase abnormalities in our patient cohort[7,14].

Similarly as described in previous studies, we have also proven that there are certain clinical features associated with specific LFTs profile – whereas elevation of cholestatic enzymes occurs mainly in right-sided heart failure (based on the systemic congestion), elevation of transaminases is mainly connected with the clinical signs of hypoperfusion (systemic hypotension) (ref.[7,8,14]). Concerning the right-sided heart failure, the role of the tricuspid regurgitation in elevation of cholestatic LFTs is convincing from our study. Furthermore, our data suggest that LFTs abnormalities are strongly associated with AHF severity – lower left ventricular ejection fraction predicts higher prevalence of all LFTs abnormalities, moreover, worse NYHA functional class (grade III and IV) is associated with cholestatic LFTs pattern – see Fig. 3. Considerable is better clinical stage (NYHA functional class grade I and II) of patients with elevated transminases - we are convinced that this patient group embraces *de novo* AHF and also acute coronary syndromes with no or lower previous evidence of heart failure symptoms.

By evaluation of noncardiac features, role of the body mass index in predicting abnormal LFTs is questionable – patients with body mass index more than 30 had less frequent all LFTs abnormalities in our study. We assume that patients with cardiac cachexia and so lower body mass index were in worse clinical stage of AHF that contributed to higher occurrence of LFTs abnormalities.

We also investigated the potential harmful effect of statin therapy in AHF patients. Statins have wide spectrum of liver side effects, the most common is an asymptomatic elevation of transaminases without histopatological changes of the liver parenchyma. This phenomenon occurs mostly during the first three months after starting the therapy and is described as "transaminitis" (ref.[18]). Our data correspond with the prevailing opinion in current literature that elevation of transaminases in patients taking statins is not much clinically relevant[19-21]. However, rare case reports when statin therapy led to autoimmune hepatitis or liver cirrhosis must be taken into consideration in the AHF patients management[22-23].

The surprising potential protective effect of calcium antagonist therapy (statistically significant for T-BIL, GGT, AST in our study) may be explained by less severe ventricular dysfunction in patients using calcium channel antagonists. Still, there are some results from animal studies indicating that calcium antagonists can reduce the increase of LFTs and development of liver fibrosis[24-25].

CONCLUSIONS

In patients with AHF, abnormal LFTs were seen in 76% patients (T-BIL in 34%, GGT in 44%, ALP in 20%, AST in 42%, ALT in 35%). Percentage of LFTs abnormalities varied according to type of AHF. Patients with cardiogenic shock were more likely to have LFTs abnormalities compared to ADHF with mild symptoms and pulmonary oedema. Concerning the distribution of LFTs elevations, the highest levels were seen in patients with acute coronary syndromes that had significantly higher transaminases, particularly AST, while AHF patients without acute coronary syndromes presented more likely with cholestatic LFTs profile.

LFTs abnormalities were strongly associated with AHF severity (left ventricular ejection fraction and NYHA functional class) and clinical manifestation. Left sided forward AHF was presented predominantly by hepatocelullar pattern whereas cholestatic LFTs profile occurred mainly in bilateral and right sided AHF. Additionally, patients with moderate to severe tricuspid regurgitation had significantly higher prevalence of abnormalities in cholestatic LFTs.

In summary, defining the LFTs profile typical for AHF plays an important role in management of AHF patients, since it may avoid redundant hepatic investigations and diagnostic misinterpretations. Furthermore, early recognition of hepatic impairment may warrant more intensive treatment of AHF and therapy optimisation.

Limitations

We do acknowledge limitations of this study. The study had an observational character – patient inclusion depended on the personal decision of the physician and therefore data filled in the database may be biased. Invasive haemodynamic data and information on liver pathology such as hepatitis serology or immunology tests or liver imaging were not available.

Concerning the panel of LFTs, albumin and prothrombin time were not recorded in the database. We did not investigate LFTs and T-BIL changes during hospitalisation. Patients with alcohol consumption were not excluded and potential hepatotoxic medications such as amiodarone or antibiotics were not followed. Moreover, echocardiographic measurements were performed by different cardiologists that may lead to data inconsistencies.

ABBREVIATIONS

ACE-I, Angiotensin-converting enzyme inhibitor; ACS, Acute coronary syndrome; AHF, Acute heart failure; ALB, Albumin; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; ARB, Angiotensin receptor blocker; AST, Aspartate aminotransferase; BP, Blood pressure; CABG, Coronary artery bypass graft; COPD, Chronic obstructive pulmonary disease; CRT, Cardiac resynchronisation therapy; GGT, γ-glutamyltransferase; ICD, Implantable cardioverter-defibrillator; LD, Lactate dehydrogenase; LFTs, Liver function tests; LV-EF, Left ventricular ejection fraction; MI, Myocardial infarction; PCI, Percutaneous coronary intervention; PM, Pacemaker; TIA, Transient ischaemic attack; T-BIL, Total bilirubin; TR, Tricuspid regurgitation; ULN, Upper limit of normal.

ACKNOWLEDGEMENT

We thank the study investigators for their contribution to the study.

Participating centres and investigators: University Hospital Brno, Brno: Roman Miklik, Marian Felsoci, Kateřina Horakova, Ondrej Ludka; General University Hospital, Prague: Jan Belohlávek; University Hospital Kralovske Vinohrady, Prague: Filip Rohac, Richard Fojt; University Hospital, Olomouc: Jan Vaclavik, David Vindis; T. Bata Regional Hospital, Zlin: Zdenek Coufal, Petr Hrdy, Stanislava Penasova, Miroslav Bambuch; Hospital Havlickuv Brod, Havlickuv Brod: Ladislava Malkova; Hospital in Frydek-Mistek, Frydek-Mistek: Pohludova L., Zeman K.

The project was supported by grant IGA 9880-3 of the Czech Ministry of Health, grant MSM0021622402 of the Czech Ministry of Education, Youth and Sports and by European Regional Development Fund - Project FNUSA-ICRC (No.CZ.1.05/1.1.00/02.0123).

Author contributions: KV: manuscript writing and data collection, LS: data interpretation and manuscript writing, JS and JP: study design, TM, JV, JM, FM, AL, MF, PW, CC: data collection; SL and JJ: data analysis, statistical analysis, figures.

Conflicts of interests statement: None declared.

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