ORIGINAL ARTICLE

Liver function tests in patients with acute heart failure

Jan Biegus[1], Robert Zymliński[1], Mateusz Sokolski[1,2], Sylwia Nawrocka[1], Paweł Siwołowski[1], Joanna Szachniewicz[1], Ewa A. Jankowska[1,2], Waldemar Banasiak[1], Piotr Ponikowski[1,2]

1 Centre for Heart Diseases, 4th Military Hospital, Wrocław, Poland
2 Department of Heart Diseases, Faculty of Health Science, Wroclaw Medical University, Wrocław, Poland

KEY WORDS

acute heart failure, liver dysfunction, liver function tests, prognosis

ABSTRACT

INTRODUCTION Acute heart failure (AHF) is associated with multiorgan dysfunction, which may unfavorably affect prognosis.

OBJECTIVES We investigated the prevalence, clinical determinants, and prognostic consequences of abnormal liver function tests (LFTs) in population with AHF.

PATIENTS AND METHODS We conducted a retrospective analysis of patients with AHF, in whom the following LFTs were performed on admission: serum bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), and albumin. Abnormal LFTs were defined as the elevation above the upper normal limit of bilirubin, AST, and ALT, or reduction below the lower normal limit of albumin.

RESULTS The study involved 189 patients (age, 68 ±11 years; men, 68%; *de novo* AHF, 25%). On admission, abnormal LFTs were observed in 46% of the patients for AST, 31% for ALT, 33% for bilirubin, and 44% for albumin. Only 29% of the patients had all LFTs within the normal ranges. The following variables were independently related to abnormal LFTs: high hemoglobin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels for AST; high hemoglobin, bilirubin, and NT-proBNP levels for ALT; high hemoglobin, low sodium levels, and dilated right ventricle for bilirubin; and high NT-proBNP levels for albumin (all $P < 0.05$). In 21 patients, hemodynamic monitoring was performed, which revealed that among LFTs only elevated bilirubin independently correlated with higher right atrial pressure ($P < 0.005$). In a univariate Cox model, among LFTs, low albumin and markedly elevated AST and ALT (>3 times above the upper normal limit) were associated with increased mortality during 180-day follow-up.

CONCLUSIONS Abnormal LFTs are common in patients with AHF and may have prognostic relevance. Among them, only elevated bilirubin was correlated with impaired hemodynamic parameters.

INTRODUCTION The pathophysiology of acute heart failure (AHF) is complex and not fully understood.[1] Only recently, it has been hypothesized that an episode of acute decompensation affects not only the cardiovascular system itself, but may also deteriorate the function of other organs, causing serious clinical consequences. Traditionally, this phenomenon has been investigated on the cardiorenal axis and the term "cardiorenal syndrome" has been proposed to link cardiac dysfunction with the subsequent deterioration in renal function.[2] The interactions between impaired hemodynamics, characterizing the early stage of AHF, with other key organs, have been rather poorly described.

Liver function abnormalities have been well characterized mainly in patients with chronic heart failure (CHF).[3-8] The available data show that organ hypoperfusion as a consequence of low cardiac output and tissue congestion may lead to liver dysfunction.[9] Additionally, several reports have linked abnormal liver function tests (LFTs) with poor outcome in the chronic setting.[3,6-8] Surprisingly, there are only few reports comprehensively assessing liver function in AHF.[10] Thus, we designed a study to detect the prevalence of liver dysfunction in well-characterized, typical, contemporary population of patients admitted to the hospital due to AHF.

Correspondence to:
Jan Biegus, MD, Ośrodek Chorób Serca, 4. Wojskowy Szpital Kliniczny, ul. Weigla 5, 50-981 Wrocław, Poland, phone/fax: +48-71-766-02-50, e-mail: janbiegus@o2.pl
Received: July 25, 2012.
Revision accepted: October 3, 2012.
Published online: October 4, 2012.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2012; 122 (10): 471-479

TABLE 1 Baseline clinical and laboratory characteristics of patients with acute heart failure

Parameter		
male sex		129 (68)
age, y		68 ±11
SBP, mmHg		127 ±31
LVEF, %		35 ±14
LVEDD, mm		61 ±10
de novo AHF		47 (25)
etiology of HF	ischemic	107 (57)
	hypertension	35 (18)
	other	47 (25)
comorbidities	myocardial infarction	64 (34)
	hypertension	110 (58)
	atrial fibrillation	90 (48)
	diabetes	77 (41)
medications (prior to hospitalization)	ACEI/ARB	126 (67)
	β-blockers	130 (69)
	aldosterone antagonists	78 (41)
	diuretics	140 (74)
	digoxin	42 (22)
	VKA/ASA	120 (63)
liver function tests	AST, IU/l	29 (21–45)
	ALT, IU/l	25 (17–47)
	bilirubin, mg/dl	1.2 (0.8–1.9)
	albumin, mg/dl	3.8 (3.5–4.1)
hemoglobin, g/dl		13 ±1.8
sodium, mmol/l		139 ±4
creatinine, mg/dl		1.35 ±0.5
BUN, mg/dl		24 (19; 33)
NT-proBNP, pg/ml		5468 (3158–11846)
troponin I, ng/ml		0.05 (0.03–0.16)

Data are shown as number (%), mean ± SD or median (IQR).

Abbreviations: ACEI – angiotensin-converting enzyme inhibitor, AHF – acute heart failure, ALT – alanine transaminase, ARB – angiotensin receptor blocker, ASA – acetylsalicylic acid, AST – aspartate transaminase, BUN – blood urea nitrogen, HF – heart failure, IQR – interquartile range, LVEDD – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction, NT-proBNP – N-terminal pro-B-type natriuretic peptide, SBP – systolic blood pressure, SD – standard deviation, VKA – vitamin K antagonist

We also aimed to establish potential determinants of abnormal LFTs and their impact on the patient's outcome.

PATIENTS AND METHODS

Study population

We performed a retrospective analysis of all patients who were hospitalized at the Centre of Heart Diseases, 4th Military Hospital, Wrocław, Poland, with primary diagnosis of AHF between January 2009 and October 2010, in whom the following LFTs were available on admission: serum bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), and albumin. Patients with known liver disease or with clinical diagnosis of acute coronary syndrome on admission were excluded from the analysis.

During recruitment, there were 242 hospitalized patients with the diagnosis of AHF, of whom 189 (78%) had all LFTs available at baseline and this group constituted the study population. They were predominantly men (68%), with the mean age of 68 ±11 years; 25% of the patients had *de novo* AHF and 57% had ischemic heart failure. The baseline clinical and laboratory characteristics of the study population are presented in **TABLE 1**.

Every patient underwent standard clinical evaluation and transthoracic echocardiography with the measurements of the left ventricular ejection fraction (LVEF, Simpson method) and the right and left ventricular end-diastolic dimensions (RVEDD, LVEDD).

Patients were treated in accordance with the recommendations of the European Society of Cardiology.[11] The study protocol was approved by the local ethics committee, and the study was conducted in accordance with the Helsinki Declaration.

Laboratory measurements

On admission, the following laboratory parameters were assessed in all patients using standard methods: 1) LFTs: AST, ALT, bilirubin, and albumin; in order to assess the prevalence of liver dysfunction we defined abnormal LFTs as the values above the upper normal limit for AST, ALT, bilirubin (38 IU/l, 35 IU/l, and 1.3 mg/dl, respectively) or below the lower normal limit for albumin (3.8 mg/dl); additionally, we defined a marked elevation of AST and ALT as exceeding 3 times the upper normal limit; 2) blood count: hemoglobin, leukocytes, platelets; 3) renal function: creatinine and blood urea nitrogen (BUN); 4) electrolytes: sodium (NA^+), potassium (K^+); 4) peripheral blood gases: pH, sO_2, pCO_2, serum osmolarity, lactate; 5) plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) by an immunoenzymatic method (Siemens, Marburg, Germany); 6) cardiac troponin I (TnI) by an immunoenzymatic method (single Dimension RxLMax, Siemens).

Hemodynamic assessment

In patients who required hemodynamic monitoring on the basis of clinical evaluation, pulmonary artery catheterization using the Swan-Ganz catheter was performed. Hemodynamic variables obtained during catheterization included: heart rate, blood pressure (systolic and diastolic), right atrial pressure (RAP), pulmonary artery pressure (PAP) (systolic, diastolic, mean), pulmonary capillary wedge pressure (PCWP), cardiac output (thermodilution method). Each invasive assessment included from 3 to 5 separate injections of cold saline (10 ml), and the cardiac output was calculated as the mean value of all injections. The cardiac index (CI) was determined as the cardiac output divided by the body surface area.

Clinical follow-up

Data on survival was obtained directly from patients or their relatives (telephone contact), from the heart failure clinic database, or from the hospital system. No patient was lost to follow-up. The primary endpoint was all-cause death at 180 days. The length of follow-up of survivors and patients in whom the events occurred after 180 days were censored at 180 days.

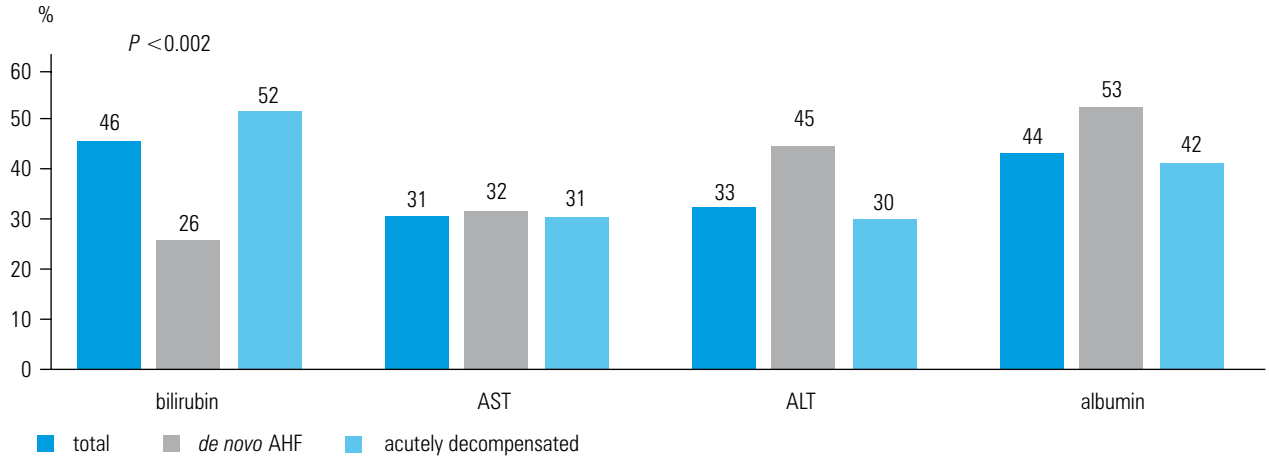


FIGURE 1 Prevalence of abnormal liver function tests in acute heart failure
Abbreviations: see TABLE 1

Statistical analysis Continuous variables with normal distribution were described using means ± standard deviation; variables with skewed distribution were described by medians with upper and lower quartiles; categorized variables were presented as numbers and percentage. Variables with skewed distribution were normalized by a logarithm. The statistical significance of differences between the groups were assessed using *t* test, Mann-Whitney *U* test, or χ^2 test, where appropriate.

Survival analyses were made using Cox proportional univariate hazard models, and the Kaplan-Meier survival curves were demonstrated.

The associations between clinical/laboratory variables (age, sex, etiology of heart failure, systolic blood pressure on admission, hemoglobin, Na^+, creatinine, BUN, LFTs, NT-proBNP, pH, serum osmolarity, lactate, LVEF, LVEDD, and RVEDD) and abnormal LFTs were assessed by univariate logistic regression analyses. All variables that were significantly associated with abnormal LFTs in a univariate model were used to build a multivariate model.

The relationships between variables were assessed using the Spearman rank coefficients. A *P*-value below 0.05 was considered statistically significant.

RESULTS

Prevalence of abnormal liver function tests On admission, median [Q1; Q4] levels of AST, ALT, bilirubin, and albumin were 29 [21; 45] IU/l, 25 [17; 47] IU/l, 1.2 [0.8; 1.9] mg/dl, and 3.8 [3.5; 4.1] mg/dl, respectively. Abnormal LFTs were common in the study population, with the prevalence of 46% for AST, 31% for ALT, 33% for bilirubin, and 44% for albumin (FIGURE 1). Only 54 patients (29%) had all LFTs within the normal range.

The percentage of patients with elevated baseline bilirubin was higher in patients with decompensated CHF compared with *de novo* AHF (52% vs. 26%, $P < 0.01$) (FIGURE 1). We did not find any difference in the prevalence of other abnormal LFTs between decompensated CHF and *de novo* AHF.

Comparison of patients with normal vs. abnormal liver tests Patients with abnormal transaminases had higher hemoglobin, bilirubin, and NT-proBNP levels and patients with elevated ALT had also lower albumin levels compared with patients with normal transaminases (TABLE 2).

Patients with elevated bilirubin had lower LVEF along with more dilated LVEDD and RVEDD (all $P < 0.05$). This group had lower systolic blood pressure and Na^+ concentration, and higher hemoglobin, BUN, AST, and NT-proBNP levels compared with patients with normal bilirubin (all $P < 0.05$) (TABLE 2).

Compared with patients with normal albumin, patients with low albumin had ischemic etiology of heart failure less often, lower Na^+, and higher NT-proBNP concentration (all $P < 0.05$) (TABLE 2).

Associations of abnormal liver function tests with other variables A multivariate regression model revealed that the following variables independently predicted abnormal LFTs (TABLE 3): high hemoglobin and NT-proBNP levels for AST; high hemoglobin, bilirubin, and NT-proBNP levels for ALT; high hemoglobin, low sodium levels, and dilated RVEDD for bilirubin; and high NT-proBNP levels for albumin (all $P < 0.05$).

Effect of liver dysfunction on mortality During 180-day follow-up, there were 40 deaths (21%). In a univariate Cox model, among abnormal LFTs, only low albumin and markedly elevated transaminases affected prognosis (hazard ratio [95% confidence interval]: for albumin, 2.13 [1.13–4.0]; for AST, 2.53 [1.06–6.03]; for ALT, 2.4 [1.06–5.44]; all $P < 0.05$). Patients with abnormal albumin as well as those with markedly elevated AST and ALT had significantly higher mortality compared with patients without these abnormalities: 29% vs. 15%, 39% vs. 19%, and 38% vs. 19%, respectively; all $P < 0.05$. (FIGURE 2ABC). A multivariable Cox model of LFTs (adjusted for age, NT-proBNP, and creatinine / estimated glomerular filtration rate [eGFR]) revealed that markedly elevated ALT and low albumin were significant prognosticators of adverse outcome (TABLE 4).

TABLE 2 Comparison of clinical and laboratory characteristics in patients with acute heart failure with normal vs. abnormal liver function tests

Parameter		Normal AST, n = 130	Elevated AST, n = 59	Normal ALT, n = 126
male sex		90 (69)	39 (66)	88 (70)
age, y		69 ±10	67 ±14	69 ±10
SBP, mmHg		129 ±32	123 ±28	129 ±34
LVEF, %		36 ±14	32 ±14	36 ±14
LVEDD, mm		61 ±10	63 ±11	61 ±10
de novo AHF		34 (26)	14 (24)	28 (22)
etiology of HF	ischemic	77 (59)	30 (51)	74 (59)
	hypertension	27 (21)	8 (14)	26 (21)
	other	25 (19)	23 (39)	25 (20)
comorbidities	myocardial infarction	49 (38)	15 (25)	49 (39)
	hypertension	82 (63)	28 (47)	77 (61)
	atrial fibrillation	57 (44)	33 (56)	58 (46)
	diabetes	56 (43)	41 (69)	57 (45)
medications (before hospitalization)	ACEI/ARB	84 (65)	42 (71)	88 (70)
	β-blockers	88 (68)	42 (71)	89 (71)
	aldosterone antagonists	51 (39)	27 (46)	54 (43)
	diuretics	96 (74)	44 (75)	99 (79)
	digoxin	29 (22)	13 (22)	30 (24)
	VKA/ASA	82 (63)	38 (64)	84 (67)
liver function tests	AST, IU/l	23 (19–29)	64 (48–113)[c]	23 (18–29)
	ALT, IU/l	20 (15–28)	73 (45–114)[c]	19 (15–25)
	bilirubin, mg/dl	1 (0.8–1.7)	1.5 (1.1–2.5)[c]	1 (0.8–1.7)
	albumin, mg/dl	3.9 (3.6–4.1)	3.8 (3.4–4)	3.9 (3.6–4.1)
hemoglobin, g/dl		12.9 ±1.8	13.6 ±1.7[b]	12.9 ±1.9
sodium, mmol/l		139 ±4	139 ±5	139 ±4
creatinine, mg/dl		1.4 ±0.6	1.3 ±0.4	1.4 ±0.6
BUN, mg/dl		25 (19–33)	24 (18–32)	25 (19–33)
NT-proBNP, pg/ml		4951 (2927–9536)	7273 (3626–15,858)[a]	4763 (2785–9515)
troponin I, ng/ml		0.05 (0.03–0.16)	0.06 (0.02–0.15)	0.05 (0.03–0.2)
hemodynamic parameters (n=21)	cardiac output, l/min	4.0 ±1	4.2 ±1	3.8 ±1
	cardiac index, l/min/m^2	2.1 ±0.5	2.2 ±0.5	2.0 ±0.5
	MAP, mmHg	80 ±15	81 ±20	80 ±15
	PAP, mmHg	34 ±10	34 ±15	35 ±10
	RAP, mmHg	10 ±5	10 ±8	11 ±6
	PCWP, mmHg	17 ±5	18 ±6	17 ±5

Data are shown as number (%), mean ± SD, or median (IQR).

a $P < 0.05$, **b** $P < 0.01$, **c** $P < 0.001$

Abbreviations: MAP – mean arterial pressure, PAP – pulmonary artery pressure, PCWP – pulmonary capillary wedge pressure, RAP – right atrial pressure, others – see **TABLE 1**

Relationship between hemodynamic indices and liver function tests Based on clinical indications, 21 patients (11%) underwent hemodynamic assessment. There were no differences in the hemodynamic profile of patients with normal vs. elevated transaminases. Patients with elevated bilirubin when compared with patients with normal bilirubin had lower CI (2.0 ±0.3 vs. 2.4 ±0.6 l/min), higher RAP (13 ±6 vs. 5 ±3 mmHg), and mean PAP (38 ±11 vs. 27 ±11 mmHg) (all $P < 0.05$) (**TABLE 4**). Patients with hypoalbuminemia had lower mean arterial pressure compared with the remaining population (71 ±11 vs. 88 ±16 mmHg; $P < 0.05$). We found strong correlations between bilirubin and mean PAP ($r = 0.49$) and RAP ($r = 0.59$) (both $P < 0.05$).

A multivariable regression analysis revealed that RAP was independently associated with elevated bilirubin ($P < 0.005$) (**FIGURE 3**). There were no correlations between AST, ALT, albumin, and hemodynamic parameters.

DISCUSSION Several laboratory tests to asses liver function are available, each providing different clinical information. Among them, AST and ALT, bilirubin, and albumin are often used.

Elevated ALT, n = 63	Normal bilirubin, n = 103	Elevated bilirubin, n = 86	Normal albumin, n = 105	Decreased albumin, n = 84
41 (65)	63 (61)	66 (77)[a]	70 (67)	59 (70)
68 ±12	70 ±10	67 ±12	69 ±11	68 ±11
125 ±26	134 ±33	120 ±26[c]	130 ±32	124 ±30
33 ±15	39 ±13	30 ±13[c]	36 ±13	34 ±15
63 ±10	59 ±11	65 ±8[c]	61 ±10	62 ±10
20 (32)	35 (34)	12 (14)[c]	22 (21)	25 (30)
33 (52)	59 (57)	48 (56)	68 (65)	39 (46)
9 (14)	26 (25)	9 (10)[b]	18 (17)	17 (20)
23 (37)	18 (17)	29 (34)[a]	17 (19)	25 (34)
15 (24)[a]	36 (35)	28 (33)	41 (42)	23 (28)
33 (52)	69 (67)	41 (48)[a]	67 (68)	42 (52)
32 (51)	47 (46)	43 (50)	49 (50)	41 (51)
20 (32)	44 (43)	33 (38)	46 (47)	31 (38)
38 (60)	63 (61)	63 (73)	78 (74)	48 (57)
41 (65)	62 (60)	68 (79)[c]	75 (72)	55 (65)
24 (38)	27 (26)	51 (59)[c]	46 (44)	32 (38)
38 (60)[b]	65 (63)	75 (87)[c]	79 (75)	61 (73)
12 (19)	13 (13)	29 (34)[c]	20 (19)	22 (26)
36 (57)	60 (58)	60 (70)	70 (67)	50 (59)
58 (39–108)[c]	26 (20–37)	31 (21–57)[a]	26 (20–40)	29 (21–52)
76 (47–108)[c]	25 (17–43)	26 (16–66)	25 (17–38)	26 (17–68)
1.4 (0.9–2.1)[b]	0.8 (0.6–1)	2.0 (1.6–3)[c]	1.1 (0.8–1.9)	1.3 (0.8–2.3)
3.7 (3.5–4)[a]	3.8 (3.5–4)	3.8 (3.5–4)	4 (3.9–4.2)	3.5 (3.2–3.6)[c]
13.5 ±1.8[b]	12.8 ±1.9	13.5 ±1.8[b]	13.1 ±1.7	13.1 ±2
139 ±5	140 ±4	138 ±5[c]	140 ±4	138 ±5[b]
1.3 ±0.4	1.4 ±0.6	1.3 ±0.4	1.27 ±0.6	1.4 ±0.5
24 (18–32)	24 (17–31)	27[a] (21–35)	24 (19–31)	26 (16–35)
7858 (4160–15,632)[c]	4782 (2707–11,431)	6488 (4159–12,504)[a]	4507 (2818–9363)	7978 (4159–15,043)[b]
0.06 (0.02–0.14)	0.05 (0.03–0.2)	0.5 (0.02–0.2)	0.06 (0.03–0.17)	0.05 (0.02–0.14)
4.5 ±0.9	4.5 ±1.2	3.8 ±0.8	3.9 ±0.7	4.3 ±1.1
2.3 ±0.4	2.4 ±0.6	2.0 ±0.3[a]	2.1 ±0.4	2.2 ±0.6
82 ±21	79 ±22	82 ±14	88 ±16	71 ±11[a]
31 ±15	27 ±11	38 ±11[a]	37 ±10	30 ±15
8 ±6	5 ±3	13 ±6[a]	10 ±6	13 ±5
18 ±6	15 ±6	19 ±5	19 ±4	16 ±8

Elevated transaminases are sensitive markers of liver injury, elevated bilirubin usually indicates cholestasis or extensive heme breakdown, and low albumin reflects impaired liver synthetic capabilities. It is worth noting that the magnitude of transaminases' elevation in different pathologic conditions vary dramatically and the cut-offs for clinical significance are usually arbitrary. We assumed that AST and ALT exceeding 3 times the upper normal limit will define marked alteration of transaminases. Surprisingly, the data on the prevalence, pathophysiology, and clinical significance of abnormalities of each LFT in AHF remain limited.[10,12]

Our study shows that abnormal LFTs are common in AHF, with 71% of the patients having at least 1 abnormal test on admission. To the best of our knowledge, this is the first report on the prevalence of abnormal LFTs in contemporary broad spectrum of patients with AHF. Previous papers described this problem in selected subgroups of patients, e.g., the paper by Shinagawa et al.[13] in decompensated patients with the ejection fraction below 40%.[13] The most

TABLE 3 Associations of abnormal liver function tests

Abnormal liver test	Parameter	Univariate model odds ratio (95% CI)	Multivariate model odds ratio (95% CI)
AST	hemoglobin, g/dl	1.3 (1.08–1.56)[b]	1.3 (1.06–1.6)[b]
	bilirubin, mg/dl	1.3 (1.03–1.69)[a]	NS[d]
	NT-proBNP, pg/ml	1.54 (1.1–2.15)[a]	1.59 (1.1–2.28)[a]
ALT	hemoglobin, g/dl	1.29 (1.07–1.55)[b]	1.25 (1.02–1.52)[a]
	bilirubin, mg/dl	4.0 (1.77–9.3)[c]	2.5 (1.02–6.09)[a]
	NT-proBNP, pg/ml	1.46 (1.004–2.04)[a]	1.46 (1.01–2.12)[a]
bilirubin	SBP, mmHg	0.98 (0.97–0.99)[c]	NS[d]
	hemoglobin, g/dl	1.25 (1.05–1.48)[b]	1.29 (1.03–1.59)[a]
	Na^+, mmol/l	0.87 (0.8–0.94)[c]	0.88 (0.8–0.96)[b]
	NT-proBNP, pg/ml	1.48 (1.08–2.04)[b]	NS[d]
	LVEF, %	0.95 (0.92–0.97)[c]	NS[d]
	LVEDD, mm	1.07 (1.03–1.1)[c]	NS[d]
	RVEDD, mm	1.1 (1.05–1.17)[c]	1.07 (1.01–1.13)[a]
	serum osmolarity, mOsm	0.92 (0.89–0.96)[c]	NS[d]
albumin	NT-proBNP, pg/ml	1.58 (1.14–2.17)[b]	1.47 (1.06–2.06)[a]
	Na^+, mmol/l	0.9 (0.84–0.97)[b]	NS[d]

a $P<0.05$, **b** $P<0.01$, **c** $P<0.001$, **d** $P>0.05$

Abbreviations: CI – confidence interval, NA – sodium, NS – nonsignificant, RVEDD – right ventricular end-diastolic diameter, others – see **TABLE 1**

recent analysis of the EVEREST trial showed that the percentage of patients with abnormal LFTs varies from 17% for albumin to 62% for γ-glutamyltranspeptidase.[10] In CHF, the prevalence of abnormal LFTs differs between the authors, ranging from 10% to 40%.[3,5,9,10] Based on our data, we can conclude that the prevalence of LFT abnormalities in contemporary population with AHF is higher than that reported in clinical trials and that described in CHF patients. The latter phenomenon may indicate that liver dysfunction is a part of AHF pathophysiology. Our data also shows that patients with acutely decompensated CHF have higher prevalence of abnormal bilirubin, but not transaminases and albumin, when compared with *de novo* AHF. We can speculate that the difference may reflect the different intensity of pathophysiological processes that lead to liver dysfunction in heart failure (acutely decompensated chronic compared with *de novo*).

As the pathophysiology of the liver dysfunction in heart failure is not completely understood, one may speculate that some of the processes that lead to the development of cardiorenal syndrome may also influence bilateral cardiohepatic interactions.[2] However, our data do not support this hypothesis. Abnormal LFTs were not associated with kidney function tests; moreover, patients with abnormal LFTs were not characterized by worse kidney function when compared with patients with normal LFTs (only patients with elevated bilirubin had higher BUN but not creatinine). This can be explained by the fact that the liver, unlike the kidneys, has dual (portal vein and hepatic artery) blood supply, which should make this organ more resistant to decreased cardiac output and low perfusion state.

Somehow unexpectedly, we found that abnormal LFTs (all but albumin) were associated with high hemoglobin levels. It is surprising since anemia is a well-established, independent factor of unfavorable outcome in heart failure.[14,15] High hemoglobin may be a marker of low fluid status (hemoconcentration), which subsequently may lead to hypoperfusion and liver cell dysfunction/damage. This pathomechanism may at least in part explain our findings. However, abnormal LFTs were also associated with elevated NT-proBNP – a marker of fluid overload, which shows that pathophysiology of the phenomenon is more complex and needs to be further studied.

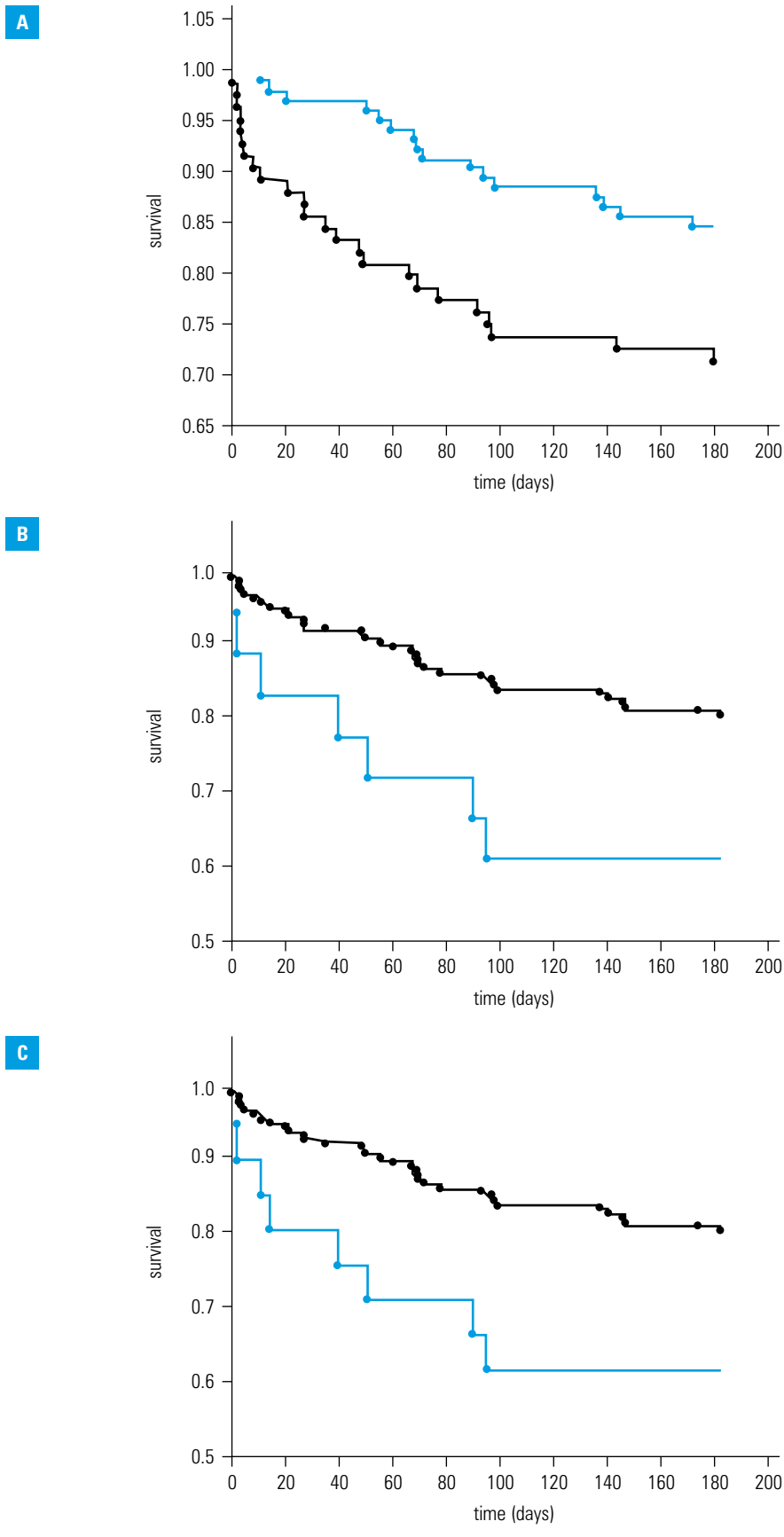
Our data support the hypothesis that liver dysfunction may have adverse effect on prognosis in AHF patients. Interestingly, unlike other authors, we did not observe higher mortality in patients with elevated bilirubin.[10,13,16] It has already been demonstrated that in CHF bilirubin is independently associated with morbidity and mortality.[3] In a nontrial population of more than 16,500 CHF patients, Yu et al.[5] observed that low albumin and elevated bilirubin were risk factors of total mortality. Batin et al.[16] has also demonstrated that AST along with bilirubin have prognostic importance in CHF patients.[16] Shinagawa et al.[12,13] studied clinical implications of liver dysfunction in AHF and found elevated total bilirubin on admission to be a marker of poor prognosis.[12,13] Only recently, Ambrosy et al.[10] identified high bilirubin and low albumin, but not elevated ALT, to have prognostic importance in AHF. The discrepancy with our findings may be explained by the fact that they analyzed the population of selected patients participating in the clinical trial. It may not accurately reflect liver dysfunction across the whole spectrum of AHF patients (the prevalence of abnormal LFTs was lower than in our study). Additionally, they presented mortality analysis with longer follow-up, and such prognosticators may be different than ours.

We have demonstrated that patients with markedly elevated transaminases as well as those with low albumin concentration have significantly higher mortality at 180 days. It is worth noting that albumin concentration may not only reflect liver function itself but also may be a marker of hemodilution due to fluid overload and the patient's nutritional status. This is in line with our finding that low albumin was independently predicted by elevated NT-proBNP levels.

With as few as 40 events at 180 days of follow-up, we were restricted to perform multivariable analyses taking into account only 4 variables. After adjustment for age, NT-proBNP (reflecting severity of AHF and being a well-established prognosticator) and creatinine/eGFR (renal function), we found that markedly elevated ALT and low albumin remained significant prognosticators of adverse outcome. Replacing NT-proBNP with LVEF in the model did not affect the results.

Recent hemodynamic studies have demonstrated that both elevated RAP and decreased CI results

FIGURE 2 Kaplan-Meier survival analysis comparing patients with: **A** – decreased albumin (black curve) vs. normal albumin (blue curve); **B** – markedly elevated AST (blue curve) vs. rest of the population (black curve); **C** – markedly elevated ALT (blue curve) vs. the remaining population (black curve) Abbreviations: see **TABLE 1**



in the elevation of both transaminases and total bilirubin,[9,12,17] whereas reduced CI alone leads to an increase in AST, ALT and direct but not total bilirubin.[9] Thus, both hypoperfusion and congestion play an important role in the development of liver dysfunction in heart failure. Since most of these studies were performed in CHF, our data extend these findings to acute conditions. We observed a strong effect of deteriorated hemodynamics on bilirubin and a weak effect on other LFTs. Patients with elevated bilirubin had lower CI and higher pressures in the right side of the heart (RAP, PAP) and tended for higher PCWP. We observed a strong correlation between RAP and bilirubin,

TABLE 4 Univariate and multivariable model of 180-day all-cause mortality

Liver function tests	Univariate model		Multivariable model[a]	
	hazard ratio (95% CI)	*P*	hazard ratio (95% CI)	*P*
markedly elevated AST	2.53 (1.06–6.03)	<0.05	2.38 (0.98–5.75)	0.05
age, y	1.03 (1.00–1.07)	<0.05	1.06 (0.99–1.06)	0.1
NT-proBNP, pg/ml	1.0018 (1.0023–1.034)	<0.05	1.0 (0.99–1.0)	>0.05
creatinine, mg/dl	1.8 (1.24–2.65)	<0.05	1.69 (1.09–2.59)	<0.05
markedly elevated ALT	2.4 (1.06–5.44)	<0.05	2.28 (1.01–5.16)	<0.05
age, y	1.03 (1.00–1.07)	<0.05	1.03 (0.99–1.06)	0.06
NT-proBNP, pg/ml	1.0018 (1.0023–1.034)	<0.05	1.0 (0.99–1.00)	0.5
creatinine, mg/dl	1.8 (1.24–2.65)	<0.05	1.64 (1.06–2.54)	<0.05
low albumin	2.13 (1.13– 4.0)	<0.05	2.19 (1.14–4.2)	0.05
age, y	1.03 (1.00–1.07)	<0.05	1.03 (0.99–1.07)	0.051
NT-proBNP, pg/ml	1.0018 (1.0023–1.034)	<0.05	1.0 (0.99–1.00)	0.8
creatinine, mg/dl	1.8 (1.24–2.65)	<0.05	1.74 (1.1–2.7)	<0.05

Abbreviations: see TABLES 1 and 3

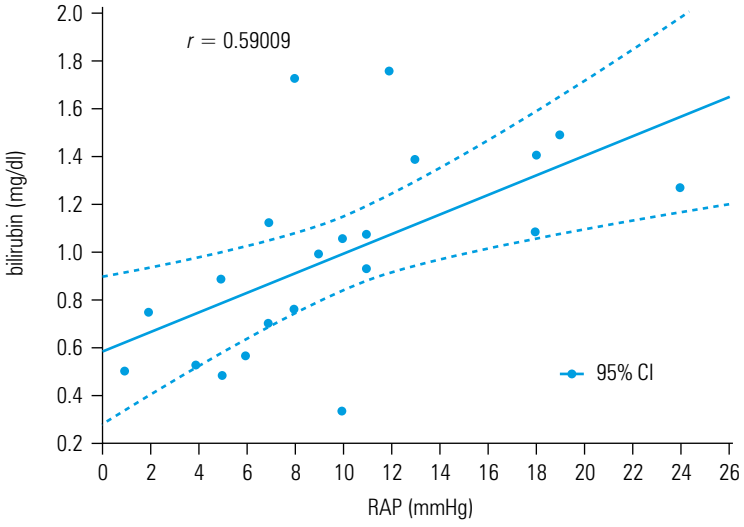


FIGURE 3 Correlation between right atrial pressure and bilirubin in 21 patients subject to hemodynamic monitoring Abbreviations: see TABLES 2 and 3

indicating that bilirubin may be a marker of venous pressure and tissue congestion. It is worth noting that since invasive hemodynamic monitoring is not a part of routine AHF patient assessment, it was performed only in 21 patients in whom it was judged as clinically mandatory. A limitation of our study is the small and selected subpopulation of patients who underwent right heart catheterization.

In conclusion, abnormal LFTs are common in AHF and may identify patients with worse outcome. Elevated bilirubin is strongly correlated with RAP indicating that congestion is an important process leading to hyperbilirubinemia in AHF; however, further investigations are needed.

Acknowledgments This research was financially supported by the National Science Centre (Poland) grant No. 6543/B/T02/2011/40 (granted to E.A.J and P.P.).

REFERENCES

1 Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol. 2009; 53: 557-573.

2 Ronco C, Haapio M, House AH, et al. Cardiorenal syndrome. J Am Coll Cardiol. 2008; 52: 1527-1539.

3 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.

4 Felder L, Mund A, Parker JG. Liver function tests in chronic congestive heart failure. Circulation. 1950; 2: 286-297.

5 Yu SB, Cui HY, Qin M, et al. [The prevalence and prognostic value of liver function abnormalities in patients in patients with chronic systolic heart failure]. Zhonghua Yi Xue Za Zhi. 2011; 18; 91: 2673-2637. Chinese.

6 Szyguła-Jurkiewicz B, Wojnicz R, Lekston, et al. [Effect of elevated bilirubin levels on the long-term outcome in patients with chronic heart failure due to hypertension]. Pol Arch Med Wewn. 2007; 117: 227-233. Polish.

7 Poelzl G, Ess M, Mussner-Seeber Ch, et al. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. Eur J Clin Invest. 2012; 42: 153-163.

8 Poelzl G, Eberl Ch, Achrainer H, et al. Prevalence and prognostic significance of elevated gamma-glutamyltransferase in chronic heart failure. Circ Heart Fail. 2009; 2: 294-302.

9 van Deursen VM, Damman K, Hillege HL, et al. Abnormal liver function in relation to hemodynamic profile in heart failure patients. J Cardiac Fail. 2010; 16: 84-90.

10 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.

11 Dickstein K, Cohen-Solal A, Filippatos G, et al.; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2008; 29: 2388-2442.

12 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.

13 Shinagawa H, Inomata T, Koitabashi T, et al. Increased serum bilirubin levels coincident with heart failure decompensation indicate the need for intravenous inotropic agents. Int Heart J. 2007; 48: 195-204.

14 Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes insights from a cohort of 12 065 patients with new-onset heart failure. Circulation. 2003; 107: 223-225.

15 Kaldara-Papatheodorou EE, Terrovitis JV, Nanas JN. Anemia in heart failure. Pol Arch Med Wewn. 2010; 120: 354-360.

16 Batin P, Wickens M, McEntegart D, et al. The importance of abnormalities of LFTs in predicting mortality in chronic heart failure. Eur Heart J. 1995; 16: 1613-1618.

17 Kubo SH, Walter BA, John DH. Liver function abnormalities in chronic heart failure influence of systemic hemodynamics. Arch Intern Med. 1987; 147: 1227-1230.

ARTYKUŁ ORYGINALNY

Testy czynnościowe wątroby u pacjentów z ostrą niewydolnością serca

Jan Biegus[1], Robert Zymliński[1], Mateusz Sokolski[1,2], Sylwia Nawrocka[1], Paweł Siwołowski[1], Joanna Szachniewicz[1], Ewa A. Jankowska[1,2], Waldemar Banasiak[1], Piotr Ponikowski[1,2]

1 Ośrodek Chorób Serca, 4 Wojskowy Szpital Kliniczny, Wrocław
2 Katedra i Klinika Chorób Serca, Wydział Nauk o Zdrowiu, Uniwersytet Medyczny we Wrocławiu, Wrocław

SŁOWA KLUCZOWE

ostra niewydolność serca, rokowanie, wyniki testów czynnościowych wątroby, zaburzenia czynności wątroby

STRESZCZENIE

WPROWADZENIE Ostra niewydolność serca (ONS) jest zespołem chorobowym związanym z niewydolnością wielonarządową, co może niekorzystnie wpływać na rokowanie.

CELE Badaliśmy częstość występowania, determinanty kliniczne i konsekwencje prognostyczne nieprawidłowych wyników testów wątrobowych (TW) w populacji pacjentów z ONS.

PACJENCI I METODY Przeprowadziliśmy retrospektywą analizę danych pacjentów z ONS, u których przy przyjęciu do szpitala wykonano następujące TW: stężenie bilirubiny w surowicy, aktywność aminotransferazy asparaginianowej (AST) i alaninowej (ALT) oraz stężenie albuminy. Nieprawidłowe wyniki TW zdefiniowano jako wartości przewyższające górną granicę normy w przypadku bilirubiny, AST i ALT lub jako wartości poniżej dolnej granicy normy w przypadku albuminy.

WYNIKI Do analizy włączono 189 pacjentów (wiek: 68 ±11 lat, mężczyźni: 69%, *de novo* ONS 25%). Odsetek nieprawidłowych TW wynosił: AST u 46% pacjentów, ALT u 31%, bilirubinę u 33% i albuminę u 44%. Tylko 29% pacjentów miało wyniki wszystkich TW w granicach normy. Następujące zmienne miały niezależny wpływ na nieprawidłowe wyniki TW: w przypadku AST – duże stężenie hemoglobiny i wysoki poziom N-końcowego propeptydu natriuretycznego typu B (NT-proBNP); w przypadku ALT – duże stężenie hemoglobiny i bilirubiny oraz wysoki poziom NT-proBNP; w przypadku bilirubiny – duże stężenie hemoglobiny, małe stężenie sodu i powiększony wymiar prawej komory serca; w przypadku albumin – wysoki poziom NT-proBNP (wszystkie $p < 0,05$). U 21 chorych przeprowadzono monitorowanie hemodynamiczne, które ujawniło, że w obrębie TW jedynie zwiększone stężenie bilirubiny niezależnie koreluje z podwyższonym ciśnieniem w prawym przedsionku ($p < 0,005$). W jednoczynnikowym modelu Coxa, wśród TW, małe stężenie albumin i znacznie zwiększone AST i ALT (>3 razy powyżej górnej granicy normy) były związane ze zwiększonym ryzykiem zgonu w ciągu 180-dniowej obserwacji.

WNIOSKI Nieprawidłowe wyniki TW często występują u pacjentów z ONS i mogą mieć znaczenie prognostyczne. Wśród nich jedynie zwiększone stężenie bilirubiny było skorelowane z zaburzeniami parametrów hemodynamicznych.

Adres do korespondencji:
lek. med. Jan Biegus, Ośrodek Chorób Serca, 4 Wojskowy Szpital Kliniczny, ul. Weigla 5, 50-981 Wrocław, tel./fax: 71-766-02-50, e-mail: janbiegus@o2.pl
Praca wpłynęła: 25.07.2012.
Przyjęta do druku: 03.10.2012.
Publikacja *online*: 04.10.2012.
Nie zgłoszono sprzeczności interesów
Pol Arch Med Wewn. 2012; 122 (10): 471-479