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Etiology of Liver Disease and Cardiovascular Abnormalities in Patients on a Liver Transplantation Waiting List

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Background: The classical cardiovascular risk factors and changes in the circulatory system secondary to end-stage liver disease (ESLD) are associated with an increased risk of cardiac abnormalities (CAs) in patients waiting for liver transplantation (LTx).
The aim of this study was to assess the relationship between the etiology of liver disease and the presence of CAs in patients qualified for LTx.

Material/Methods: The study enrolled patients qualified to LTx due to ESLD at the Clinical Hospital of the Medical University of Warsaw between 2013 and 2016. Out of 396 patients: 65, 157, 117, and 57 had ESLD due to the alcoholic liver disease (ALD), viral infections (VIR), autoimmune disorders (AUTO), and different etiologies (OTHER), respectively.

Results: An increased frequency of hypertension and diabetes mellitus were observed in ALD and VIR groups, while for hyperlipidemia, the highest rates were observed in ALD and AUTO groups. Significant differences in CAs rates were observed for resting tachycardia, prolonged QT interval, bradycardia, and left ventricular diastolic dysfunction. After adjustment for age, MELD, and Child-Pugh scores, hyperlipidemia (26% *vs.* 7–15%, p<0.048) was most frequently observed in the AUTO group, while poor aerobic capacity (49% *vs.* 21–34%, p<0.009) dominated in the OTHER group.

Conclusions: The frequency of hyperlipidemia, and poor aerobic capacity were directly related to the etiology of liver disease, while the remaining associations resulted from effects of age, MELD, and Child-Pugh score.

MeSH Keywords: **Cardiomyopathies • Cardiovascular Abnormalities • Liver Cirrhosis • Liver Transplantation**

Abbreviations: **AUTO** – autoimmune disorders; **ALD** – alcoholic liver disease; **CAs** – cardiac abnormalities; **CAD** – coronary artery disease; **CCM** – cirrhotic cardiomyopathy; **CVD** – cardiovascular disease; **CHF** – chronic heart failure; **CI** – confidence interval; **CPET** – cardiopulmonary exercise testing; **CV risk factor** – cardiovascular risk factor; **CVD** – cardiovascular disease; **DM** – diabetes mellitus; **ECG** – electrocardiography; **ESLD** – end-stage liver disease; **HCC** – hepatocellular carcinoma; **LTx** – liver transplantation; **LV** – left ventricular; **MELD** – Model of End-Stage Liver Disease; **NTproBNP** – b-type natriuretic peptide; **OR** – odds ratio; **OTHER** – different etiologies of end-stage liver disease other than AUTO, VIR, and ALD; **SD** – standard deviation; **VIR** – viral infections

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Background

Many liver diseases lead to progressive and irreversible damage, and the only definitive method of treatment is liver transplantation. The multiple etiologies of liver diseases and their different courses affect the heterogeneity in the group of candidates for liver transplantation in terms of age and the occurrence of extrahepatic symptoms and accompanying diseases, among which cardiovascular diseases predominate. An additional clinical burden on these patients is the presence of circulatory irregularities typical of liver failure and portal hypertension. The occurrence of myocardial systolic and/or diastolic dysfunction and electrophysiological abnormalities in the course of cirrhotic cardiomyopathy (cirrhotic cardiomyopathy, CCM) pose a threat of serious complications in situations of high hemodynamic burden, which is a major surgery, such as LTx [1,2]. To safely perform the LTx procedure and improve their distant prognosis, it is necessary to know the risk profile of potential liver recipients. Therefore, the aim of this study was to examine whether the occurrence of cardiovascular abnormalities, as a potential source of complications in the perioperative period, are dependent on the etiology of the liver diseases among patients listed for liver transplantations.

Material and Methods

The study included consecutive patients qualified for LTx as assessed by a specialist cardiologist from May 2013 to July 2016 in a single transplant center. The study group of 396 patients was finally added to the National List of POLTRANSPLANT.

On the basis of etiology of liver disease, the following groups of patients were distinguished: viral (VIR group), alcohol (ALD group), autoimmune (AUTO group), and other (OTHER group).

Assessment included interviews, physical examination, and additional tests. Patients were examined for classical risk factors and diseases of the cardiovascular (CV) system, as well as changes in the circulatory system secondary to liver cirrhosis and portal hypertension.

In the pre-transplantation assessment, the present or past history of CV risk factors such as hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, and heart failure were studied. The additional tests included: resting ECG, Holter ECG, transthoracic echocardiography, and cardiac biomarkers (troponin I and NT-proBNP) in blood serum, and cardiopulmonary exercise testing (CPET).

On the basis of the performed tests, the following cardiac abnormalities (CA) were distinguished and assessed: Sinus tachycardia (HR >100/min) and extended QT corrected by the Bazett method (>450 ms for men and >460 ms for women) assessed on the ECG; and sinus bradycardia, defined as the HR release below 60/min in the hours of waking or 40/min at night and the complex ventricular arrhythmia assessed in the 24-hour ECG by Holter method. In the echocardiographic examination, the systolic dysfunction was defined as the reduction of left ventricular ejection fraction <50%. Diastolic dysfunction was diagnosed on the basis of the left atrium volume and mitral inflow rate, as well as the mitral ring motion parameters evaluated by tissue Doppler [3]. Elevated cardiac biomarkers were defined as troponin I level exceeded over 0.056 ng/ml and NTproBNP over 126 pg/ml. Based on CPET, poor aerobic capacity was defined as peak oxygen consumption (VO2 peak) below 20 mL/min/kg. Chronotropic response to exercise was defined based on the chronotropic response index (CRI), which was calculated using the formula (HRpeak-HRrest)/(220-age-HRrest). Chronotropic incompetence was defined as CRI was <0.8 or <0.62 on beta-blockers therapy. Patients with portal hypertension without contraindications for treatment with beta-blockers were treated with low-dose carvedilol. CPET was not performed for contraindications such as significant anemia, BP <90/60mmHg, esophageal varices with signs of threatening bleeding, gait disturbances caused by massive edema, orthopedic diseases, or a high degree of hepatic encephalopathy. The study was approved by the University's Research Ethics Committee (KB/126/2013). Written informed consent was obtained from all subjects before the study.

Statistical methods

Statistical analysis consisted of examining the association between the etiology of liver disease and the incidence of CV risk factors and cardiovascular abnormalities (CA). The crude rates of these events were calculated in each group of interest and compared using Fisher's exact test. The adjusted-for-age, MELD, and Child-Pugh score rates were estimated by logistic regression analysis. The analysis was performed using the SAS System 9.4 [4] and supported by the method of van Belle et al. [5]. The p value less than 0.05 was considered statistically significant, while p values lower than 0.10 were regarded as on the verge of significance.

Results

Among patients qualified for LTx (Table 1), the most numerous group was patients with viral etiology (39%), followed by autoimmune etiology (30%), and alcohol (16%) and other etiology (14%). In terms of disease severity, patients with ALD had the highest MELD score, while the lowest MELD scores were found in patients with viral and other etiologies (Table 2).

We found some association of etiology with the presence of CV risk factors in routine cardiac work-up in the pretransplant

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Table 1. Patient characteristics (n=396).

Male, n (%)	237 (60%)
Age, year (mean ±SD)	50.2±12.9
Portal Hypertension, n (%)	371 (94%)
Cirrhosis, n (%)	351 (89%)
Child-Pugh class, n (%)	
A	115 (29%)
B	168 (42%)
C	113 (29%)
MELD score, median (IQR)	12 (9–17.5)
HCC	121 (31%)
Etiology of ESLD, n (%)	
Alcoholic	65 (16%)
Viral	157 (39%)
HCV	109
HBV	21
HCV+HBV	27
Autoimmune	117 (30%)
PSC	46
AIH, PBC	71
Other	57 (14%)
Cryptogenic cirrhosis	9
HVT (BCS)	8
SBC	9
HEHE	6
PLD	4 (2*)
Wilson's disease	4
HCC in non-cirrhotic liver	4 (1*)
HAE	5 (3*)
IHP	2
Caroli disease	2
Meta of GEP-NEN	2 (1*)
Cystadenoma	1
AIP	1

AIH – autoimmune hepatitis; AIP – acute intermittent porphyria; BCS – Budd-Chiari syndrome; IHP – idiopathic hepatic fibrosis; HAE – hepatic alveolar echinococcosis; HBV – hepatitis B; HCC – hepatocellular carcinoma; HCV – hepatitis C; HEHE – hepatic epithelioid hemangioendothelioma; HVT – hepatic vein thrombosis; GEP-NEN – neuroendocrine neoplasms of the gastrointestinal tract; IQR – interquartile range; PBC – primary biliary cirrhosis; PSC – primary sclerosing cholangitis; PLD – polycystic liver disease; SBC – secondary biliary cirrhosis; * number of patients in the group with pseudo-Budd-Chiari syndrome.

Table 2. Age and MELD and Child-Pugh by etiology.

	Age# p<.0001	MELD# p<.0004	Child-Pugh# p<.0001
Etiology of ESLD: ALD	56 (52–60)	15 (11–19)	9 (8–11)
VIR	58 (52–61)	11 (8–16)	8 (6–10)
AUTO	43 (31–57)	13 (10–18)	7 (6–9)
Other	43 (34–56)	11 (8–16)	7 (5–8)

p – concerns differences between groups; # median (interquartile range). ALD – alcoholic etiology; AUTO – autoimmune etiology; ESLD – End-Stage Liver Disease; OTHER – another etiology; VIR – viral etiology.

qualification procedure. When compared to AUTO and OTHER groups, the ALD and VIR groups had significantly higher frequencies of hypertension (38% and 45% in ALD and VIR, respectively *vs.* 22% and 31% in AUTO and OTHER, respectively) and diabetes (38% and 31% in ALD and VIR groups *vs.* 14 and 11% in AUTO and OTHER, respectively). Among other CV risk factors, hyperlipidemia was most frequently observed in the AUTO group (23% *vs.* 17%, 13%, and 9%) in ALD, OTHER, and VIR groups, respectively.

We noticed some differences in rates of CAs on additional exams in these 4 etiological groups. QTc prolongation (44% and 37% in ALD and VIR, respectively *vs.* 28% and 23% in AUTO and OTHER groups, respectively) and LV diastolic dysfunction (23% and 16% in ALD and VIR, respectively *vs.* 11% and 8% in AUTO and OTHER groups, respectively) were more common in the ALD and VIR groups. Resting tachycardia on ECG was more frequent in the heterogeneous group of patients (OTHER) than in the remaining etiologic groups (17% *vs.* 3%, 5%, and 6% for OTHER, ALD, VIR, and AUTO groups, respectively), while bradycardia on 24-h Holter ECG was more often observed in patients with autoimmune etiology of ESLD (19% *vs.* 4%, 11%, and 12%) for AUTO, ALD, VIR, and OTHER groups, respectively).

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Table 3. Rates# of CV risk factors and abnormalities depending on etiology of liver disease.

	ALD	VIR	AUTO	OTHER	p
Cardiovascular risk factors					
Hypertension	38%	45%	22%	31%	.001
Diabetes mellitus	38%	31%	14%	11%	.001
Hyperlipidemia	17%	9%	23%	13%	.015
CAD	6%	6%	4%	6%	.91
Cardiovascular abnormalities					
Rest tachycardia	3%	5%	6%	17%	.025
Long QTc	44%	37%	28%	23%	.037
Bradycardia	4%	11%	19%	12%	.021
Diastolic LV dysfunction	23%	16%	11%	8%	.056
Troponin I elevation	5%	8%	6%	4%	.79
NTproBNP elevation	52%	46%	36%	36%	.15
Poor aerobic capacity	32%	32%	28%	35%	.81
Chronotropic incompetence	66%	55%	54%	57%	.55

Crude rates. ALD – alcoholic etiology; AUTO – autoimmune etiology; CAD – coronary artery disease; CV – cardiovascular; LV – left ventricular, NTproBNP – b-type natriuretic peptide, OTHER – another etiology; QTc - corrected QT interval, VIR – viral etiology.

Table 4. Rates of significant CV risk factors and cardiac abnormalities adjusted for age, MELD, and Child-Pugh.

	ALD	VIR	AUTO	OTHER	p
Hyperlipidemia	15%	7%	26%	14%	.048
Resting tachycardia	3%	7%	4%	13%	.067
Bradycardia	10%	21%	31%	18%	.077
Poor capacity	21%	25%	34%	49%	.009

Due to the heterogeneity of etiological groups in terms of MELD, Child-Pugh score, and age, multiple logistic regression analysis was performed to estimate adjusted age, MELD, and Child-Pugh points rates of CAs (Table 3). We found that regardless of age, MELD and Child-Pugh scores, only hyperlipidemia among AUTO patients, and poor aerobic capacity among OTHER patients were significantly higher compared to the remaining ones ($p<.048$, $p<.009$, Table 4). Higher rates of resting tachycardia in OTHER (13%) and bradycardia in AUTO (31%) where observed to be on the verge of significance.

Discussion

A trend of increasing incidence of cardiovascular disease is observed in the general population, resulting in the same trend in patients waiting for LTx. The current experience of transplant centers and improvement of LTx results enable patients with serious complications of end-stage liver disease and cardiovascular diseases to be included on waiting lists. It is known that classic CV factors and cardiovascular diseases, as well as cardiorespiratory changes secondary to liver dysfunction, may result in increased risk of LTx complications. To minimize the risk of cardiac events, improvement of cardiovascular diagnosis is necessary. These disturbances are determined by multiple factors and thus there is no agreement in the content of guidelines how to evaluate them [6]. Therefore, we decided to assess whether the etiology of liver diseases leading to end-stage failure is related to the risk of cardiac abnormalities in patients qualified for LTx. Using standardized qualifications to LTx system based on present medical knowledge (independent of the etiology of liver disease), we observed that the prevalence of CV risk factors and cardiac abnormalities among candidates were related to the etiology of liver disease.

The nearly a 10-year age difference between patients with ALD and those with viral etiology of liver disease, and the difference in severity of liver failure in the groups prompted us to

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perform additional analysis to exclude the effects of observed differences that may be responsible for the relationships of interest. This reasoning became the basis for stating that the different CV risk profiles in individual groups results from the direct effect of the etiological factor on the development of disorders in the cardiovascular system and the increased morbidity in different age ranges, as well as various degrees of hepatic insufficiency as assessed by MELD score. Among those qualified for LTx, the highest number of CV risk factors should be expected in etiologies with a long-term course of disease, in which the need for LTx results from advanced liver failure in the course of cirrhosis, such as ALD and chronic viral hepatitis.

The higher prevalence of hyperlipidemia in the group of patients with autoimmune liver diseases can be explained by the fact that cholestasis (primary biliary cirrhosis, primary sclerosing cholangitis, and overlap syndromes) is a very common disorder in autoimmune liver diseases. Abnormalities in lipids associated with cholestatic liver diseases are due to impaired bile flow and impaired biliary cholesterol excretion, as well as impaired hepatic metabolism and intestinal absorption. However, according to current knowledge, changes in metabolism and the distribution of lipids and lipoproteins are not reflected in routine laboratory measurements [7,8]. Therefore, it is difficult to assess the clinical significance of the increased risk of CV associated with this disorder in patients with cholestasis [9–11].

Referring to the issue of increased frequency of bradycardia in the group of patients with autoimmune diseases intended for LTx, the role of autoantibodies in its pathogenesis should be considered. The literature reports a relationship between the occurrence of bradycardia and autoimmunity in diseases such as systemic lupus erythematosus (SLE), systemic sclerosis, rheumatoid arthritis, and myasthenia gravis [12–15]. Dysfunction of the sinus and ventricular node in these diseases and disturbances of intraventricular conduction result from the ongoing inflammatory process in the myocardium and small vessels and increased fibrosis [12]. It can be assumed that antibodies present in patients with immunological liver diseases by analogy are responsible for destruction of the heart muscle cells the conducting system.

Among patients waiting for liver transplantation, a large group suffers from impaired venous blood flow and the development of primary or secondary Budd-Chiari syndrome, caused, among other factors, by compression by abnormal structures, including echinocyclitis and polycystic kidney syndrome with the presence of cysts in the liver and liver tumors [16,17], which may explain why resting tachycardia, which reflects the clinical presentation of liver disease with developed collateral circulation and hyperkinetic circulation, does not always correlate with the severity of hepatic dysfunction, especially in patients without liver cirrhosis [18,19].

We can assume that because in the group of different etiologies (OTHER) we have so many patients with developed hyperkinetic circulation, they should also be more likely to have poor aerobic capacity (regardless of age and liver function), as demonstrated by our results study. An additional factor presumably affecting the reduction of peak oxygen absorption is the difficulty in performing exercise caused by a significant increase in abdominal circumference caused by strained ascites, high organ enlargement, or coexistence of neoplastic disease and emaciation, which are common among patients with etiologies in this selected group [21,22].

In summary, by applying a uniform method of cardiac evaluation of patients waiting for LTx (the method was independent of the etiology of liver disease), it may be possible to observe differences in the frequency of CV abnormalities between the etiological groups of interest. To predict the serious cardiac consequences of these abnormalities during the LTx waiting period, during surgery, and in follow-up after LTx, it is essential to explore the differences between the groups in terms of incidence of CV disorders (e.g., prolonged QTc interval, diastolic LV dysfunction, hypertension, and diabetes mellitus), even though these differences result from the MELD score and age. Consideration of the direct effect of the etiology of liver disease on the pathomechanism of hyperlipidemia, bradycardia, and resting tachycardia, and its impact on exercise capacity of patients, should lead to a more individual diagnostic and therapeutic approach in the course of liver transplantation just by taking into account the effect of the etiological factor.

Limitations of the study

The MELD and Child-Pugh scores, which are intended to be used as indicators of liver failure severity, do not take into account all the features of liver damage. This study used the classic MELD score values. It is possible that the currently used modified MELD indicators would be better for use in this work (e.g., MELD-Na or HCC-MELD) [23]. The number of patients with heart failure and history of ventricular arrhythmias was too small (especially among ALD patients) to be included in statistical analysis. CPET trials were not performed in 15% of patients; however, the percentage of disqualified patients in the individual groups did not differ significantly. Although the OTHER group consisted of patients with common features (ascites, emaciation), it was as a whole a heterogeneous set of patients.

Conclusions

The increased frequency of hyperlipidemia in the autoimmune group and increased rates of poor aerobic capacity in a group of OTHER etiologies were directly related to the etiology of

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liver disease, as these relationships were obtained after adjustment for age and liver dysfunction.

References:

1. Johnston SD, Morris JK, Cramb R et al: Cardiovascular morbidity and mortality after orthotopic liver transplantation. Transplantation, 2002; 73: 901–6
2. Ripoll C, Yotti R, Bermejo J, Bañares R: The heart in liver transplantation, J Hepatol, 2011; 54: 810–22
3. Lang RM, Badano LP, Mor-Avi V et al: Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging, 2015; 28: 1–39
4. SAS/STAT® 9.4, User's Guide, Volume1, 2, 3. SAS Institute Inc., Cary, NC, USA, 2015
5. van Belle G, Fisher LD et al: Biostatistics. A methodology for the health sciences. John Wiley & Sons, Inc., 2004
6. Donovan RJ, Choi C, Ali A et al: Perioperative cardiovascular evaluation for orthotopic liver transplantation. Dig Dis Sci, 2017; 62: 26–34
7. Nemes K, Åberg F, Gyllinget H, Isoniemi H: Cholesterol metabolism in cholestatic liver disease and liver transplantation: From molecular mechanisms to clinical implications. World J Hepatol, 2016; 8: 924–32
8. Su TC, Hwang JJ, Kao JH: Hypercholesterolemia in primary biliary cirrhosis. N Engl J Med, 2007; 357: 1561–62
9. Propst A, Propst T, Lechleitner M et al: Hypercholesterolemia in primary biliary cirrhosis is no risk factor for atherosclerosis. Dig Dis Sci, 1993; 38: 379–80
10. Cash WJ, McCance DR, Young IS et al: Primary biliary cirrhosis is associated with oxidative stress and endothelial dysfunction but not increased cardiovascular risk. Hepatol Res, 2010; 40: 1098–106
11. Floreani A, Variola A, Niro G et al: Plasma adiponectin levels in primary biliary cirrhosis: A novel perspective for link between hypercholesterolemia and protection against atherosclerosis. Am J Gastroenterol, 2008; 103: 1959–65
12. Mandell BF: Cardiovascular involvement in systemic lupus erythematosus. Semin Arthritis Rheum, 1987; 7: 126–41
13. Volta U, Villecco AS, Bianchi FB et al: Antibodies to cardiac conducting tissue in progressive systemic sclerosis, Clin Exp Rheumatol, 1985; 3: 131–35
14. Shivamurthy P, Parker MW: Cardiac manifestations of myasthenia gravis: A systematic review. IJC Metab Endocr, 2014; 5: 3–6
15. Lee HC, Huang KT, Wang XL, Shen WK: Autoantibodies and cardiac arrhythmias. Heart Rhythm, 2011; 8: 1788–95
16. Grus T, Lambert L, Grusová G et al: Budd-Chiari syndrome. Prague Med Rep, 2017; 118: 69–80
17. Cnossen WR, Drenth JP: Polycystic liver disease: an overview of pathogenesis, clinical manifestations and management. Orphanet J Rare Dis, 2014; 9: 69.
18. Akamatsu N, Sugawara Y, Kokudo N: Budd-Chiari syndrome and liver transplantation. Intractable Rare Dis Res, 2015; 4: 24–32
19. Biggins S W, Colquhoun S, Gish RG, Runyon BA et al: Model for End-Stage Liver Disease (MELD) exception for ascites. Liver Transpl, 2006;12(Suppl. 3): S88–90
20. Nudo CG, Yoshida EM, Bain VG et al: Liver transplantation for hepatic epithelioid hemangioendothelioma: The Canadian multicenter experience. Can J Gastroenterol, 2008; 22: 821–24
21. Epstein SK, Ciubotaru RL, Zilberberg MD et al: Analysis of impaired exercise capacity in patients with cirrhosis. Dig Dis Sci, 1998; 43: 1701–7
22. Jones JC, Coombes JS, Macdonald GA: Exercise capacity and muscle strength in patients with cirrhosis. Liver Transpl, 2012; 18: 146–51
23. Martin EF, O'Brien C: Update on MELD and organ allocation. Clinical Liver Disease, 2015; 5: 105–7

Conflicts of interest

None.

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