THERAPEUTIC CHALLENGES AND PROGNOSIS INFLUENCE OF CARDIOVASCULAR COMORBIDITIES IN CIRRHOTIC PATIENTS

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THERAPEUTIC CHALLENGES AND PROGNOSIS INFLUENCE OF CARDIOVASCULAR COMORBIDITIES IN CIRRHOTIC PATIENTS (Abstract). The effects of advanced liver diseases on heart function, like cirrhotic cardiomyopathy, hepato-pulmonary syndrome or porto-pulmonary arterial hypertension, are well known today. Cardiovascular Diseases (CVD) may affect the liver or increase a pre-existed liver disease in acute or chronic heart failure. The aim of this study was to evaluate the frequency of CV comorbidities in cirrhotic patients and to establish the influence on patients' outcome. **Material and methods**: The current prospective study was conducted over a 16-month period and included 105 patients diagnosed with liver cirrhosis (LC). Patients were extensively analyzed for the presence of CVD, both clinical and echo cardio graphic. **Results**: The main etiology of LC was viral C infection, followed by alcoholic exposure. Dilatative cardiomyopathy, high blood pressure, heart failure with reduced ejection fraction, arrhythmias and deep vein thrombosis were more prevalent in patients with viral liver disease. The valvular diseases were more frequent diagnosed in patients with a worse prognosis (31.4% *vs.* 25.7%, p =0.001), though there were no difference between patients with viral or alcoholic etiology. **Conclusions**: Our study confirmed that there is a high prevalence of different CVD in patients with LC, mostly in patients with viral etiology, and there is a great need for standardized protocols and guidelines for the initial approach, treatment and follow-up of the CV dysfunction in LC patients. **Keywords:** LIVER CIRRHOSIS, CARDIOVASCULAR DISEASES, VIRAL LIVER DISEASE.

Liver cirrhosis (LC) defines the histological reshaping of the liver secondary to a chronic liver injury with the development of regenerative nodules surrounded by fibrous tissue that leads to portal hypertension and end-stage liver disease. Due to its numerous and severe complications, LC represents one of the major causes of morbidity and mortality with a heavy burden on the health care system. The Global Burden of Disease reported an increase in mortality due to cirrhosis complications in the last years with a total of 1 million deaths in 2010 and 1 million due to viral hepatitis

and hepatocellular carcinoma (1). Concerning the cardiovascular diseases (CVD), it is still the first cause of mortality with 17.9 million deaths annually, 31% of all global deaths (2). Taking into consideration the close connections and interactions between liver and heart functions, it is important to routinely assess the CV system on cirrhotic patients, aiming to improve the overall treatment results. It is well known the effect of advanced liver disease on heart function, like cirrhotic cardiomyopathy, hepatic-pulmonary syndrome and porto-pulmonary arterial hypertension. Also, CVD may affect the liver or worsen a pre-existed liver disease in acute or chronic heart failure, either by arterial hypo perfusion in the left-sided heart failure or by passive congestion secondary to increased systemic venous pressure in the right-sided heart failure (3).

CV comorbidities in liver disease represent any simultaneous pathological findings that are neither causes nor consequences of LC but can increase the mortality and have a negative influence on therapeutic outcome. Moreover, the clinical relevance of studying these comorbidities comes from the risks of diagnosis errors that may appear when the two pathologies interfere. Furthermore, the coexisting heart diseases pose important treatment challenges, either by drug interference (i.g.in patients with viral hepatitis C following interferon-free treatment) or drug-induced hepatotoxicity (side effects of CV medication). Given the epidemiological significance, there were conceived comorbidity score systems (CirCom score) that evaluate the total burden of comorbidities on LC patients with a greater mortality prediction(4).

The aims of the current study are to evaluate the frequency of CV comorbidities in LC patients and to establish the influence on patients' outcome.

MATERIAL AND METHODS

The current study was conducted over a 16-month period and included 105 patients (74 men and 31 women), admitted in the Gastroenterology Clinic of "Sf. Spiridon" County Clinical Emergency Hospital (60 patients) and in Infectious Diseases Hospital (45 patients) for LC of various etiologies. All patients were supplementary evaluated in the Cardiology Clinic, where a detailed medical history, physical examination, blood pressure measuring, electrocardiogram recording, and echocardiography evaluation were performed. The data were collected from patients'personal files where they have signed an informed consent regarding the current study. The diagnosis of LC was established based on clinical manifestations and biological, endoscopic and ultrasound changes suggestive for advanced liver disease and portal hypertension and confirmed by a non-invasive method Fibromax or Fibro Scan. Liver function was quantified by Child-Pugh and Model of End-Stage Liver Disease (MELD) scores.

The exclusion criteria were the refusal of patients, patients with pathological conditions that prevented a correct echocardiography examination (thoracic surgery, extreme obesity, severe osteo-articular chest pain), patients with neuropsychiatric pathologies or special socio-cultural beliefs who refused a physical exam or who did not sign the written consent.

The study was conducted in accordance with the Helsinki Declaration and all patients were consecutively enrolled in the study after providing written informed consent.

We assessed the patients using a GE Vivid V7 echocardiograph (2D-echo, M-Mode, pulsed-wave Doppler (PW), continuous-wave Doppler (CW), tissue Doppler (TDI), color Doppler, the parameters being described as follows: (a) Systolic function using ejection fraction (EF) of the left ventricle (LV); (b) diastolic dysfunction (impaired relaxation: E/A<1, E/e' ratio<9, pseudo-normal: E/A > 1 with E/A ratio<1 after Valsalva maneuver and a TDI determined e'/a'<1, E/e'=9-15; restrictive pattern-E/A>2, E/e' ratio >15); (c) Valvopathies visual assessment, color flows, velocities and pressure gradients; (d) dilated cardiomyopathy: LV diameter > 57 mm (or >112% of maximum physiological diameter corrected with age and body surface area) with global heart dilatation and systolic dysfunction (EF<45% and/or fractional shortening (FS)<25%).

All data was statistically analyzed using the *SPSS 20.0*, *Microsoft Excel* 2010 and *EpiInfo* 7®. A p value <0.05 was considered statistically significant.

RESULTS

The patients mean age was 54.6 years and 70.47% were males. We divided our patients into two groups based on age for comparative analysis: aged ≥ 60 years (31.42%) and patients < 60 years (68.58%).

Regarding the etiology of LC, the viral etiology was present in 83 cases (56 men and 27 women, p=0.19) while the alcoholic and mixed (viral and alcoholic) etiology was found only in males (12, respectively 4 cases). Autoimmune origin was more common in females than in males (4 cases compared to 1 case, p= 0.01). We observed an important association between alcoholic etiology of the cirrhosis and male sex (p= 0.01) while the autoimmune etiology was specifically encountered in women (p= 0.01).

As for the relationship between the incidence of specific CV comorbidities and the etiology of LC, dilated cardiomyopathy (DCM) was statistically significant correlated with alcoholic etiology (p= 0.01),high blood pressure (p= 0.01) and heart failure with reduced ejection fraction (p= 0.01). Moreover, there was a statistically significant correlation between viral etiology and the presence of arrhythmias (p= 0.04) and, respectively, deep venous thrombosis/ chronic venous insufficiency (p= 0.04). More detailed information can be found in first table.

TABLE I

Correlations between various cardiac comorbidities and the etiology of cirrhosis

Cardiac pathology	Viral etiology	Toxic etiology	Total	p value
DCM	9 (9.47%)	5 (5.26%)	14 (14.73%)	0.004
HBP	35 (36.84%)	10(10.52%)	45 (47.36%)	0.007
IHD	13 (13.68%)	1 (1.05%)	14 (14.73%)	0.503
HFrEF	10 (10.52%)	5 (5.26%)	15 (15.78%)	0.008
HFpEF	20 (21.04%)	2 (2.1%)	22 (22.14%)	0.564
Valvular diseases	52 (54.73%)	8 (8.42%)	60 (63.15%)	0.787
Arrhythmias	31 (32.63%)	1(1.05%)	32 (33.68%)	0.046
DVT	21 (22.09%)	0	21 (22.09%)	0.048

DCM: dilated cardiomyopathy; HBP: high blood pressure; IHD: ischemic heart disease; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; DVT: deep vein thrombosis

Analyzing the associated risk factors for CVD, there were important differences between patients with viral etiology versus patients with toxic LC. Metabolic risk factors were highly associated with toxic etiology in terms of increased body mass index (18.07% *vs.* 66.66%, p< 0.01) and the presence of diabetes mellitus (7.22% *vs.* 33.33%, p=0.05). However, the diagnosis of dyslipidemia could not be associated with a specific etiology of cirrhosis (p=0.79). Anemia was common in cirrhotic patients and it also represented a common cause for heart failure decompensation, being significantly correlated with a viral origin of cirrhosis (p= 0.04). Another important CV risk factor was the advanced age, the presence of a toxic LC being highly associated with patients aged over 55 years (p= 0.02).

Following the echocardiography assessment of the diastolic function, the negative modification of this parameter was highly associated with toxic etiology (83.33% with toxic LC *vs.* 53.01% with viral etiology, p= 0.04). The global systolic function of the left ventricle was also modified in patients with toxic LC (p = 0.04) while regarding the pathologies of the aortic or mitral valve there was not significantly correlation with a specific etiology (p= 0.24).

There were certain differences between men and women concerning the CV comorbidities thus pointing out the importance of an individualized approach for every patient. Thus, high blood pressure was more common in cirrhotic females (61.29%in women *vs.*35.13%in men, p = 0.01), as well as the valvular pathology (74.19%in women *vs.*50%in men, p =0.02). On the other hand, deep vein thrombosis was significantly associated with male sex (25.67% in men *vs.* 6.45%in women, p= 0.02). Chronic virus C hepatitis remained the etiology of LC in the majority of patients (36 men and 20 women) without significant difference regarding the gender (p= 0.20). Also, we found no statistically relevant differences between men and women for chronic virus B hepatitis etiology (p= 0.31) or for the ones with a mixed virus B and virus D etiology of LC (p= 0.45).

Regarding the evolution of the patients, 41.90% presented a severe prognosis. Over 1-year monitoring, 9 patients died while out of 34 patients on the liver transplant waiting list, 5 patients have been transplanted (tab. II).

TABLE II

Evolution of the cirrhotic patients according to their cardiac pathology

Cardiac pathology	Deceased/transplant list patients (41.90%)	Stable patients (58.10%)	Total (100%)	p value
DCM	6 (5.71%)	8 (7.62%)	14 (13.33%)	0.938
HBP	14 (13.33%)	31 (29.52%)	45 (42.85%)	0.05
IHD	6(5.71%)	8(7.62%)	14 (13.33%)	0.938
HFrEF	6(5.71%)	9 (8.57%)	15 (15.78%)	0.871
HFpEF	9(8.57%)	13 (12.38%)	22 (20.95%)	0.915
Valvular diseases	33 (31.42%)	27 (25.71%)	60 (57.14%)	0.001
Arrhythmias	10 (9.52%)	22 (23.15%)	32 (32.67%)	0.142
DVT	11 (10.47%)	10(9.52%)	21 (20%)	0.276

DCM: dilated cardiomyopathy; HBP: high blood pressure; IHD: ischemic heart disease: atherosclerosis; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; DVT: deep vein thrombosis

Negative long-term prognosis was associated with the presence of valvular diseases ($p<0.01$) while an increased blood pressure at the initial examination was a significant marker for a more stable evolution of LC ($p=0.05$). Other CV comorbidities did not present any significant correlations with the outcome of the patients. By analyzing the CV comorbidities among the deceased patients, we found a statistically significant correlation only with the presence of deep vein thrombosis ($p=0.05$).

DISCUSSION

It is known for years that heart and liver are intimately related existing a broad spectrum of acute and chronic CV pathologies that can influence the treatment and outcome of cirrhotic patients. On the other hand, chronic liver injuries can affect heart function in the absence of other CVD or, at least, they may accelerate the natural progression of pre-existing heart diseases. The epidemiological data regarding the etiology of LC and gender distribution revealed similarities with other international studies, but also some particular aspects. Thus, in our study, the vast majority of patients presented a viral etiology (79.04%), followed by a toxic one (11.42%), very similar to the results obtained by Wang *et al.* on a large-scale study (80.62% and 5.68%, respectively) that included 8080 cirrhotic patients (5)highlighting and confirming that emerging countries like China and Romania are areas with a high prevalence of chronic viral hepatitis, opposed to the trend revealed by a study conducted in Germany by Sivanathan V. where the most frequent etiology was related to alcohol consumption (52%) (6).

In this prospective and observational study, we found a very high rate of CVD among cirrhotic patients (80%), many of them being unaware about these diagnoses. More than half of the patients (56.83%) presented diastolic disfunction, an early marker of cardiac dysfunction in the presence of LC. These findings are similar to the ones found by Wong et al (7), its pathophysiological foundation being the initial hypertrophy (due to hyperdynamic circulation) and subsequent fibrosis and myocardial stiffness that alter the left ventricle filling pressures. However, diastolic dysfunction cannot be attributed only to cirrhosis *per se*, but also to DCM, especially the one caused by alcohol abuse. In fact, alcohol may represent a “bridge” between cardiac and hepatic pathology, being an exponent of how diastolic dysfunction can occur via two different pathways.

In our study DCM was highly associated with alcoholic etiology of the cirrhosis ($p=0.04$), further confirming this bidirectional relationship between diastolic dysfunction and liver injury via retrograde congestion. Similar to previous studies demonstrating that diastolic dysfunction precedes systolic dysfunction (8) we observed that only 20% of patients presented an ejection fraction (EF) <50%, being well known that cirrhotic patients generally have a preserved contractility. More interesting, patients with impaired EF were significantly associated with a toxic etiology of cirrhosis ($p=0.042$), basically diagnosed with DCM, but being unmasked in situations with an increased demand for cardiac output associated to impaired myocardial contractility such as in conditions of hemodynamic stress - infections, physical effort, certain medication or surgery (especially liver transplant) (9).

Summarizing the above information, a significant proportion of cirrhotic patients (37.2% of total cases) presented a degree of

heart failure (HF), either with or without systolic dysfunction. Even if toxic etiology of LC was highly associated with DC Mand with HF with reduced EF (p=0.08), viral etiology of the cirrhosis and especially the one caused by hepatic C virus (HCV) presents high interest from the therapeutic point of view. Several studies have previously confirmed an association between hepatitis C virus infection and cardiomyopathy, but none could really establish a pathogenic relationship (10). These issues have arisen because the interferon (IFN)-based therapy for HCV infection has severe cardiac side-effects, thus limiting its use in patients with advanced HF. Promising preliminary results are presented by Poller *et al.* (11) who observed a positive cardiac effect of the new IFN-free regimens in patients with advanced HF (NYHA III-IV classes). They reported a case of a patient with NYHA IV scheduled for heart transplant who entered in NYHA II class at the end of the treatment with an IFN-free medication and heart transplant being no longer considered. The explanation was that HCV was etiopathogenetically involved in myocardial dysfunction for at least two reasons: the IFN-free therapy does not eliminate any other cardiotropic virus (e.g. Coxsackie B3) nor does it have any antifibrotic or cardiac anti remodeling action.

Patients with high BP may develop normal BP during the progression of liver fibrosis due to vasodilatation with low overall systemic vascular resistance and high arterial compliance. In our study 42.8% of patients presented BP>140/90 mmHg at the initial check, more common in women than in men (61.29% *vs.* 35.13%, p= 0.01) and, interestingly, being associated with a better outcome (p=0.05). On the other hand, high BP was incriminated as an independent risk factor for non-alcoholic steatohepatitis, that can progress to cirrhosis, a direct correlation being already proved in multiple studies (12, 13).

Valvular pathology, whether aortic or mitral, is associated with an increased risk in cirrhotic patients, especially in those on transplant awaiting list. If a valve replacement is urgently required (due to acute heart failure or increased risk of sudden death), interventional, minim invasive techniques are preferred, with high advantages in terms of mortality compared to classic surgery (14), mainly because of the high bleeding risk of cirrhotic patients.

Diabetes is probably the most studied comorbidity in cirrhosis, being highly associated with the etiologies related to alcohol abuse and non-alcoholic fatty liver disease. Literature data have shown that diabetes is a predictor of fibrosis, accelerated fibrosis progression, increased liver-related mortality and development of hepatocarcinoma (15). It was also highlighted the synergy between a high alcohol intake and the exacerbated effect of diabetes in cirrhotic patients (16). On12976 Danish cirrhotic patients included in the CirCom study, diabetes without complications was not associated with mortality whereas diabetes with complications did increase mortality (17).Other studies revealed that insulin use was associated with increased risk of hepatocarcinoma and increased mortality, while the use of oral drugs like metformin or thiazolidinediones was linked to a decreased risk (18).Definitely, there are other researches that infirmed the link between diabetes and mortality: a study from the Netherlands including 226 patients diagnosed with cirrhosis in 2001-2011 found that diabetes was not associated with all-cause and liver-related mortality (19). We recorded a similar result in our cohort of 105 patients, diabetes

not being associated to the overall mortality rates.

The limitations of the current study include a small number of analyzed patients, lack of details given specific alcohol intake or exposure to other toxic, the absence of full medical data records to attest liver disease duration, unspecified CV comorbidities or other previous treatments.

CONCLUSIONS

Our study confirmed that there is a high prevalence of different CVD in patients with LC, mostly in patients with viral etiology. New large-scale prospective studies are needed to identify more specific aspects and standardize protocols or guidelines for the initial approach, treatment and follow-up of CV dysfunction in cirrhotic patients.

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NEWS

CONTRAST ENHANCED DIGITAL MAMMOGRAPHY

With the adoption of digital mammography as a replacement for film mammography, work began in the early 2000's to develop a technique that would allow digital mammography to be used with contrast enhancement to depict cancers that would otherwise be occult on standard unenhanced mammography. Those efforts resulted in the development and clinical testing of contrast-enhanced digital mammography (CEDM) using the dual energy subtraction technique. Today CEDM is available commercially for clinical use. It is estimated that over 200,000 CEDM examinations have been performed to date in both research and clinical settings. To perform a CEDM examination, an intravenous is placed in the forearm or antecubital vein and a low osmolar iodinated contrast agent is administered at approximately 3ml/s using a power injector. Contrast agents with iodine concentration between 300 mg/ml and 370 mg/ml are typically used. The volume of contrast is similar to that used for a CT scan, approximately 1.5 ml/kg body weight, typically around 90- 150 ml. After a delay of at least 90 seconds from the end of the injection, the patient is positioned for 2 standard mammography views (craniocaudal and mediolateral oblique) of each breast. Rather than a standard single energy mammogram, however, the CEM device acquires dual-energy image pairs in each projection. Since there is less than 1 second between the low-energy and high energy images, the imaging time is the same as that needed for a standard mammogram. Additional projections may be obtained since optimally enhanced images can typically be obtained up to 7-10 minutes following injection. Following image acquisition, contrast-enhanced subtraction images are produced using a weighted logarithmic subtraction of the low energy image from the high energy image. (John Lewin, Maxine Jochelson, Contrast enhanced digital mammography. https://www.sbi-online. org/ RESOURCES/ WhitePapers/ TabId/595/ ArtMID/1617/ArticleID/601/Contrast-Enhanced-Digital-Mammography.aspx).