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Erectile dysfunction in compensated liver cirrhosis

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ABSTRACT

Background: Data on erectile dysfunction (ED) in cirrhotic patients are limited as yet. Aim of this study was to investigate the prevalence of ED and the factors potentially involved in its development in compensated cirrhosis.
Methods: We prospectively enrolled 102 male (mean age 63 ± 10 years) affected by cirrhosis in Child–Pugh Class A. The following questionnaires were used: simplified International Index of Erectile Function (IIEF-5) Questionnaire, Centre of Epidemiologic Studies Depression Scale and ANDROTEST.
Results: ED was found in 57/102(55.9%) patients, and was mild, moderate and severe in 21(36.8%), 6(10.5%) and 30(52.6%) subjects, respectively. ED patients were significantly older than those without (66 ± 10 vs 60 ± 10,p = 0.006); ED prevalence gradually increased with age. There was no statistically significant difference between patients with and without ED concerning the coexistence of diabetes, hypertension, and cardiovascular disease. Age(p = 0.040) and serum haemoglobin(p = 0.027) were identified as predictors of ED on multivariate analysis. Liver-related factors and pharmacological treatment, including β-blockers, were not associated with the presence of ED.
Conclusions: In patients with compensated liver cirrhosis, even in concomitance with other chronic comorbidities, the prevalence of ED is not markedly different from the general population. Compensated cirrhosis per se is not a risk factor for ED occurrence. Older age and low haemoglobin values are significantly associated with ED in cirrhotics.

1. Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain a penile erection long enough to have satisfactory sexual intercourse and may be a disabling clinical entity. Globally, the prevalence of ED increases with age, ranging from 1 to 10% in men younger than 40 years old, up to 50–100% in subjects older than 70 years old [1].

Penile erection is the result of a coordinated neurovascular response mainly driven by neurotransmitters, in particular by nitric oxide (NO), which causes the relaxation of smooth muscle cells in the cavernosal arterioles and sinuses with a subsequent increase of the blood flow into the penis. For this reason, ED is frequently observed in men suffering from arteriogenic chronic diseases such as metabolic syndrome, type-2 diabetes mellitus (T2DM) and chronic cardiovascular disease (CVD) [2,3].

ED has also been significantly associated with some non-arteriogenic diseases such as depressive disorders, hypogonadism, chronic kidney disease (CKD), pulmonary diseases, benign prostatic hyperplasia, the use of different drugs, as well as with lifestyle habits such as smoking, chronic alcohol consumption, limited or absent physical exercise [1,2]. Different questionnaires – alone or in combination with some biochemical tests – have been validated as diagnostic tools for ED, both in the general population and in patients with chronic diseases [3,4].

Patients with liver cirrhosis are often affected by comorbidities and risk factors known to be involved in the development of ED [2]. Furthermore, advanced chronic liver disease itself may predispose to the development of ED [5], being characterized by alterations of the sexual hormones metabolism and the frequent use of drugs

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potentially acting on penile erection, such as non-selective beta-blockers (NSBBs) and diuretics. There is evidence, in fact, that the prevalence of ED may increase in the more advanced stages of the liver disease [6–10], although available data in this context are incomplete so far. The aims of this prospective study were to evaluate the prevalence of ED in patients with compensated liver cirrhosis and to investigate the factors potentially involved in its development.

2. Patients and methods

One hundred and two patients with known liver cirrhosis in class A according to Child–Pugh classification [11], consecutively admitted to the Division of Clinical and Molecular Hepatology of the University Hospital of Messina from January 2015 to December 2016 for diagnostic/therapeutic management of their liver disease, were enrolled in the study. The inpatients setting was chosen because of the need for a quiet and confidential environment and in order to maintain the homogeneity of the blood test results performed for the study purposes.

Diagnosis and staging of cirrhosis were performed according to the established clinical, ultrasound, endoscopic, biochemical, and histological criteria. Alcoholic aetiology of cirrhosis was defined as a daily alcohol intake greater than 30 gr/dL in the absence of other pathogenic factors. Metabolic cirrhosis was diagnosed when viral and alcoholic causes were excluded in the presence of features of the metabolic syndrome [12]. Patients with history of a single episode of ascites decompensation followed by a complete response to diuretic treatment, with no recurrence of ascites and clinically stable for at least 6 months were also included in the analysis.

Coexistence of known risk factors for ED, such as smoking habit, T2DM, arterial hypertension, CVD (i.e. hypertensive cardiopathy, chronic heart failure, valvular or ischemic heart disease, obliterative arteriopathy, clinically significant atherosclerosis) were documented.

Demographics, clinical information and anthropometric parameters such as body mass index (BMI) and waist circumference were recorded. Haematology [Haemoglobin (Hb), count of red blood cells (RBC), white blood cells (WBC), and platelets (PLT)], liver biochemistry [aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, gamma-glutamyltranspeptidase (GGT)] metabolic profile [serum total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, fasting blood glucose and, in the presence of T2DM, glycosylated haemoglobin (HbA1c)], hormonal profile [serum level of thyroid stimulating hormone (TSH), total testosterone (TT), free testosterone (FTT), sex hormone binding globulin (SHBG), prolactin (PRL)] and prostatic specific antigen (PSA) were evaluated in each patient. Blood sampling was performed after overnight fasting. Levels of TT $\geq$ 112 nmol/L and FTT > 225 pmol/L were considered normal [13]. Ongoing pharmacological treatment – in particular the use of diuretics, NSBBs, anti-hypertensive drugs, hypoglycaemic agents, statins, proton pump inhibitors (PPIs) and drugs acting on the central nervous system such as benzodiazepines and anticonvulsants – was recorded.

In order to identify the presence of ED or factors such as depression and hypogonadism, which have been reported as potential causes of sexual disorders, the following questionnaires were administered: the simplified International Index of Erectile Function (IIEF-5) questionnaire, the Centre of Epidemiologic Studies Depression (CES-D) Scale and the ANDROTEST. To avoid unreliable answers, interviews were performed by male investigators (G.O. and S.M.). No patients had abnormal psycho-cognitive abilities, including absence of whichever grade of hepatic encephalopathy [14], and all were able to express independent judgment and answer investigators' questions.

2.1. Questionnaires

IIEF-5 scale is a validated questionnaire utilized to classify ED in symptomatic individuals. It is a shortened version of the 15-item International Index of Erectile Function (IIEF) [4] and includes 5 questions (each answer scores from 1 to 5) evaluating the presence and severity of ED. Lower scores represent poorer sexual function. Patients with a score ranging from 22 to 25 were considered to have no ED and subjects with a score less than 22 were considered affected by ED [mild (score 17–21), moderate (8–16 points) and severe (5–7 points)] [15].

The CES-D scale is a self-report twenty-item scale including scores from 1 to 4 for each question; a cumulative score of 16 or higher identifies the presence of depressive syndrome. This questionnaire was applied, in our study, to evaluate possible psychological factors that may cause ED [16].

The ANDROTEST was designed to investigate the presence of hypogonadism in patients with sexual dysfunction. The interview consists of 12 items and patients' answers are codified on a 0–3 scale by the interviewer. Patients with an ANDROTEST score higher than 8 are diagnosed with hypogonadism.

2.2. Ethics

The study was performed in accordance with the ethical standards established in the Declaration of Helsinki and its later amendments. Ethical approval for the study was obtained from the Ethics Committee of the University Hospital of Messina. All participants provided written informed consent for taking part in the study.

2.3. Power and sample size

The mean age of the first 50 patients enrolled in the study was 65 years. For sample size calculation, we thus considered the estimated incidence of the primary outcome (ED diagnosed by IIEF-5) in the general population of the same age. In men aged between 60 and 69 years, the incidence of ED has been reported to be between 20% and 40% [1]. Assuming an incidence of ED of 40% in the general population [17,18], an expected incidence in the study of about 55%, a statistical power of 80% and a 2-sided significance level of 0.05, the minimum number of subjects for an adequate study power corresponded to 85 subjects. The sample size was increased by 17 patients (for a whole sample size of 102) in order to account for potential drop-out of up to 20%.

2.4. Statistical analysis

Normally distributed continuous variables are expressed as mean and standard deviation (SD) and categorical variables as frequencies and percentages (%). The non-parametric approach was used when the numerical variables were not normally distributed, as verified by Kolmogorov Smirnov test. The Mann Whitney test or the Student T test were used, as appropriate, to compare all numerical parameters in patents with and without ED. For categorical variables, comparison between groups was performed by the Chi Square test and linear trends of associations were verified by Mantel–Haenszel linear-by-linear association chi-square test. Univariate logistic regression was estimated in order to identify predictive factors of ED. Variables with p value <0.05 in the univariate analysis were then included in the multivariate stepwise logistic regression model. Receiver operating characteristic (ROC)

curves were plotted in order to evaluate the performance of significant predictors of ED. Statistical analysis was performed using SPSS version 20.0 for Windows package. Two-sided $p < 0.05$ was considered to be statistically significant.

3. Results

Characteristics of the patients are shown in Table 1. Mean age was 63.1 ± 10.4, years. Aetiology of liver disease was virus-related [hepatitis B virus (HBV)-related, hepatitis C virus (HCV)-related, HBV + hepatitis Delta virus (HDV)-related], metabolic-related, and alcohol-related in 46 (45.1%), 38 (37.3%) and 18 (17.6%) cases, respectively. The reason for hospital admission was hepatic venous pressure gradient (HVPG) measurement in 16 cases, second-level investigation for defining and managing ultrasound-detected liver lesions in 48, and endoscopic treatment of gastro-oesophageal varices in 38 cases. A diagnosis of hepatocellular carcinoma (HCC) was set in 27 (26.5%) patients at enrolment in the study.

ED was found in 57/102 (55.9%) patients, and it was defined – according to IIEF-5 score – as mild, moderate, and severe in 21 (36.8%), 6 (10.5%), and 30 (52.6%) subjects, respectively. Patients with ED were significantly older than those without ED (66 ± 10 vs. 60 ± 10 years, $p = 0.006$).

Forty-five (44.1%) patients had T2DM, 45 (44.1%) had history of CVD [37 (36.3%) patients had cardiac and 18 (17.6%) vascular diseases] and 55 (53.9%) were affected by arterial hypertension. There was no statistically significant difference between patients with and without ED concerning the coexistence of T2DM [27/57 (47.4%) vs. 18/45 (40%); $p = 0.457$], CVD [28/57 (49.1%) vs. 17/45 (37.8%); $p = 0.252$] and arterial hypertension [30/57 (52.6%) vs. 25/45 (55.6%); $p = 0.769$] (Table 2). Furthermore, no statistically significant difference was found between patients with compensated diabetes and patients with non-compensated diabetes (HbA1c <7% versus HbA1c ≥7%, $p = 0.324$).

Only 6 patients (4 in the ED group and 2 in the non-ED group, $p = 0.583$) had a creatinine level indicative of clinically significant renal impairment (>1.2 mg/dL).

Hypogonadism – as diagnosed by the ANDROTEST – was found in 39/57 (68.4%) patients with ED and in 24/45 (53.3%) without ED ($p = 0.119$).

No statistically significant difference was found between patients with and without ED concerning smoking habit, chronic alcohol consumption, aetiology of the liver disease, presence of HCC, history of ascites, presence of oesophageal varices and BMI (Table 2).

Symptoms of depression according to CES-D scale were found in 50 (49%) patients, being moderate in 23/50 (46%) and severe in 2/50 (4%). There was no statistically significant difference in the distribution of depression symptoms in patients with and without ED, nor was there an increased incidence of depression symptoms in patients with a concomitant diagnosis of HCC (data not shown).

Total and free testosterone levels, as well as SHBG and PRL values, were not statistically different in patients with or without ED (Table 2). Only 3 patients in the ED group and 1 patient in the non-ED group had a TT lower than normal. Fourteen patients with ED and 6 without ED had a FTT level below the normal range, while 18 patients in the ED group and 15 in the non-ED group had hyperprolactinemia. All these differences were not statistically significant ($p > 0.05$ by Chi square test, for all the comparisons).

Patients with ED compared to those without ED had significantly lower levels of Hb ($p = 0.006$), WBC ($p = 0.021$), AST ($p = 0.039$) and TSH ($p = 0.031$), and higher levels of serum creatinine ($p = 0.021$) (Table 2).

There was no statistically significant difference in the use of diuretics, NSBBs, PPIs, anti-hypertensive, statins, hypoglycaemic

Table 1
Demographic, clinical and biochemical characteristics of 102 patients with cirrhosis in Child Pugh class A.

Patients, n	102
Age	63.1 ± 10.4
Age (decades)	
<50 years	13 (12.7)
50–59 years	26 (25.5)
60–69 years	37 (36.3)
>70 years	26 (25.5)
Aetiology, n (%)	
Viral	46 (45.1)
Metabolic	38 (37.3)
Alcohol-related	18 (17.6)
Responsive ascites, n (%)	26 (25.5)
Esophageal varices (absence vs. presence), n (%)	45/57 (44.1/55.9)
HCC, n (%)	27 (26.5)
Type 2 diabetes, n (%)	45 (44.1)
BMI	26 ± 2.3
Arterial hypertension, n (%)	55 (53.9)
Cardiovasular disease, n (%)	45 (44.1)
ED, n (%)	57 (55.9)
ED mild/moderate/severe[a], n (%)	21(20.6)/6(5.9)/30(29.4)
Smoke, n (%)	62 (60.8)
Alcohol, n (%)	27 (26.5)
Depression (CES-D) absent/mild/moderate/severe, n (%)	52(51)/25(24.5 /23(22.5)/2(2)
Hypogonadism[b], n (%)	63 (61.8)
Concomitant therapy, n (%)	
Diuretics	48 (47.1)
Non-selective beta-blockers	36 (35.3)
Statins	6 (5.9)
Anti-diabetic oral/insulin	18 (17.6)/19 (18.6)
Anti-hypertensives	62 (60.8)
Proton pump inhibitors	62 (60.8)
Anticoagulants	19 (18.6)
Neurotropic drugs	9 (8.8)
Laboratory data	
Hb (g/dL)	12.9 ± 2.2
WBC (n/mmc)	4863 ± 1714
PLT (n/mmc)	110,000 (67,000)
AST (U/L)	38 (33)
ALT (U/L)	36 (43)
GGT (U/L)	104 (124)
Bilirubin (mg/dL)	1 (0.90)
Albumin (mg/dL)	3.9 ± 0.5
Creatinine (mg/dL)	0.8 (0.2)
INR	1.1 ± 0.3
Total cholesterol (g/dL)	150.2 ± 34.6
HDL cholesterol (g/dL)	50.5 ± 13.9
Triglycerides (mg/dL)	59.2 ± 16.9
HbA1c (%)	7.1 ± 1.7
Uric-acid (mg/dL)	4.8 ± 1.6
Total testosterone (ng/mL)	638.1 ± 273.6
Free testosterone (ng/mL)	8.3 ± 3.6
SHBG (nmol/L)	71.1 (62.6)
TSH (μUI/mL)	1.3 (1.1)
Prolactin (μUI/mL)	227.2 (104.6)
PSA (ng/mL)	0.5 (1)

Frequencies are expressed as number (%). Continuous numerical data are expressed as number ± SD or as number (IQR), according to distribution.
Abbreviations: HCC, hepatocellular carcinoma; MELD, model of end-stage liver disease; BMI, body mass index; ED, erectile dysfunction; CES-D, Center of Epidemiologic Studies Depression Scale; Hb, hemoglobin; WBC, white blood cells; PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltranspeptidase; INR, international normalized ratio; HDL, high density lipoprotein; HbA1c, glycosylated hemoglobin; SHBG, sex hormone binding globulin; TSH, thyroid stimulating hormone; PSA, prostate specific antigen; IIEF, International Index of Erectile Function.
[a] According to IIEF-5 scale.
[b] According to ANDROTEST.

Table 2
Comparative analysis between patients with and without ED.

	No-ED N = 45	ED N = 57	p
Age	59.9 ± 10.1	65.6 ± 9.8	**0.006**
Aetiology, n (%)			0.200
Viral	24 (53.3)	22 (38.6)	
Metabolic	16 (35.6)	22 (38.6)	
Alcohol-related	5 (11.1)	13 (22.8)	
Cardiovascular disease, n (%)	17 (37.8)	28 (49.1)	0.252
Type 2 diabetes, n (%)	18 (40)	27 (47.4)	0.457
Arterial hypertension, n (%)	25 (55.6)	30 (52.6)	0.769
Oesophageal varices, n (%)	24 (53.3)	33 (57.9)	0.645
Responsive ascites, n (%)	10 (22.2)	16 (28.1)	0.501
HCC, n (%)	13 (28.8)	14 (24.6)	0.620
Smoke, n (%)	31 (70.5)	31 (55.4)	0.123
Alcohol, n (%)	9 (20)	18 (31.6)	0.188
BMI	26 (3)	26 (3)	0.234
Depression (CES-D), n (%)	24 (53.3%)	26 (45.6%)	0.818
Hypogonadism, n (%)	24 (53.3)	39 (68.4)	0.119
Albumin (g/L)	3.9 ± 0.5	3.8 ± 0.5	0.494
Bilirubin (mg/dL)	1.1 (0.8)	0.7 (0.9)	0.286
Creatinine (mg/dL)	0.7 (0.1)	0.8 (0.3)	**0.021**
INR	1.1 (0.2)	1.1 (0.2)	0.938
Hb (g/dL)	13.6 ± 2.1	12.4 ± 2.1	**0.006**
WBC/mmc	5309 ± 1861	4520 ± 1521	**0.021**
PLT/mmc	110,000 (77,250)	110,000 (63,500)	0.821
AST (U/L)	43.0 (56.8)	36 (29.5)	**0.039**
ALT (U/L)	43.5 (63.8)	29.0 (39.5)	0.056
GGT (U/L)	116 (127.8)	85 (126)	0.295
Total cholesterol (g/dL)	165.2 ± 33.2	152.9 ± 39.3	0.387
HDL cholesterol (g/dL)	47.8 ± 15.5	50.5 ± 14.4	0.410
Triglycerides (mg/dL)	104.9 ± 54.3	94.4 ±46.9	0.318
HbA1c (%)	6.8 ± 1.8	7.3 ± 1.7	0.299
Total testosterone (ng/mL)	669.6 ± 302.4	532.8 ± 250.8	0.368
Free testosterone (ng/mL)	8.8 ± 3.9	7.5 ± 4.3	0.260
SHBG (nmol/L)	62.1 (21.3)	61.3 (48.4)	0.927
TSH (μUI/mL)	1.43 (1.08)	1.14 (1.14)	**0.031**
Prolactin (μUI/mL)	222.9 (120.8)	223.5 (173.8)	0.885
PSA (ng/mL)	0.5 (1)	0.5 (1)	0.797

Frequencies are expressed as number (%).
Continuous numerical data are expressed as number ± SD or as number (IQR), according to distribution.
Abbreviations: ED, erectile dysfunction; MELD, model of end-stage liver disease; T2DM, type 2 diabetes mellitus; HCC, hepatocellular carcinoma; BMI, body mass index; CES-D, Center of Epidemiologic Studies Depression Scale; INR, international normalized ratio; Hb, hemoglobin; WBC, white blood cells; PLT, Platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltranspeptidase; HDL, high density lipoprotein; HbA1c, glycosylated hemoglobin; SHBG, sex hormone binding globulin; TSH, thyroid stimulating hormone; PSA, prostate specific antigen; IIEF, International Index of Erectile Function.

(both insulin and oral hypoglycaemic drugs) and neurotropic drugs between patients with or without ED (data not shown).

At univariate logistic regression analysis, presence of ED was significantly associated with age (OR 1.058, 95%CI: 1.015–1.103, p = 0.008) and levels of Hb (OR 0.761, 95%CI: 0.622–0.932, p = 0.008).

At the multivariate analysis, both age (OR 1.047, 95%CI 1.002–1.093, p = 0.040) and Hb values (OR 0.027, 95%CI 0.792–0.644, p = 0.027) were identified as independent predictors of ED (Table 3).

ROC curves were obtained in order to define optimal cut-offs of age and haemoglobin to predict ED. The ROC curve for age and Hb showed an area under the curve (AUC) of 0.64 (95%CI 0.539–0.753, p = 0.003) and 0.67 (95%CI 0.565–0.779, p = 0.012), respectively, with a best cut-off in predicting ED of 62 years (66% sensitivity, 60% specificity) and 13.1 g/dL (61% sensitivity, 63% specificity), respectively. A moderate improvement of the diagnostic performance was obtained combining the above parameters with each other: AUC 70% (95%CI 0.593–0.806, p = 0.001).

In order to better study the influence of age on ED, we stratified patients in four categories: <50 years, 50–59 years, 60–69 years and ≥70 years. Prevalence of ED progressively increased with age, being 3/13 (23.1%), 14/26 (53.8%), 22/37 (59.5%) and 18/26 (69.2%) in the four categories, respectively (p = 0.011 by linear association) (Fig. 1).

Similarly, to investigate the association between ED and Hb values in more detail, we categorized patients in three groups, according to Hb tertiles (serum Hb values <12.1 mg/dL, between 12.1 and 14.2 mg/dL and ≥ 14.3 mg/dL, respectively). Prevalence of ED was 70.6% in the first tertile, 61.8% in the second tertile and 35.3% in the third tertile (p = 0.004 by linear by linear association) (Fig. 2).

Finally, we performed a sub-analysis considering only ED patients, categorizing ED in two groups: mild (21/57 patients, 36.8%) vs. moderate-severe (36/57 patients, 63.2%). Although the small sample size did not allow for a reliable logistic regression analysis to be performed, the coexistence of T2DM, vasculopathy, and smoking habit appeared to be associated with a moderate-severe grade of ED (p = 0.007; p = 0.013; and p = 0.010, respectively), while no association emerged between liver disease related factors (i.e. abnormal liver biochemistry, portal hypertension) and the severity of the sexual dysfunction.

4. Discussion

To the best of our knowledge, this is the first study evaluating the prevalence of ED and the factors associated with its development and severity in a cohort of cirrhotic patients in Child Pugh class A. Our data highlight the fact that liver cirrhosis per se, when well compensated, is not associated with ED, and that the occurrence and severity of this disorder in Child Pugh class A patients are mainly related to the risk factors classically associated with ED in the general population.

The reported prevalence of ED in the general population varies from 5 to 64%, with wide ranges also reported for different clusters of age [1,7]. This broad variability highlights the heterogeneity of published data and the difficulty in obtaining this information without selection bias. In the type-2 diabetes population, for example, the prevalence of ED has been reported to range from 50% to 75% [19,20]. In patients with end-stage CKD, the prevalence of ED also reaches values as high as 70% [21]. In the cohort of patients with compensated liver cirrhosis, we found a prevalence of ED of 55.9%, which is similar to what has been reported in a limited series of Child Pugh A individuals included in a recently published European study [22], but much lower than the one found in Japanese patients with chronic viral liver disease [6].

Consistent with most of the previous reports on this topic, older age was identified as an independent predictor of the sexual dysfunction. In fact, in our cohort, mean age of patients with ED was significantly higher than mean age of patients without ED, and the prevalence of ED gradually increased with ageing. This is in agreement with what has been reported for the general population, as well as for patients affected by T2DM [21,24] and patients with CKD [23]. Furthermore, patients with more severe ED were significantly older, suggesting that also the severity of ED tends to increase with age.

It is well documented that advanced age is associated with an impaired endothelial function, mainly related to a decreased NO bioavailability [24], an augmented synthesis of potent vasocontrictors such as endotheline-1 and with increased oxidative stress [25]. Endothelial dysfunction plays a pivotal role in the development of vasculogenic ED, as well as in the occurrence of chronic cardiovascular disease [26], and people with a more advanced age are more likely to be affected by the above-described chronic comorbidities that can potentially influence sexual function [27].

Table 3
Parameters significantly associated with ED at univariate and multivariate logistic regression analysis.

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age	1.058	1.015–1.103	0.008	1.047	1.002–1.093	0.040
Aetiology			ns			
Cardiovascular disease			ns			
Type 2 diabetes			ns			
Arterial hypertension			ns			
Oesophageal varices			ns			
Ascites			ns			
HCC			ns			
Smoke			ns			
Alcohol			ns			
BMI			ns			
Depression (CES-D)			ns			
Hypogonadism			ns			
Albumin (g/L)			ns			
Bilirubin (mg/dL)			ns			
Creatinine (mg/dL)			ns			
INR			ns			
Hb (g/dL)	0.761	0.622–0.932	0.008	0.027	0.792–0.644	0.027
WBC (n/mmc)			ns			
PLT (n/mmc)			ns			
AST (U/L)			ns			
ALT (U/L)			ns			
GGT (U/L)			ns			
Total cholesterol (g/dL)			ns			
HDL cholesterol (g/dL)			ns			
Triglycerides (mg/dL)			ns			
HbA1c (%)			ns			
Total testosterone (ng/mL)			ns			
Low total testosterone			ns			
Free testosterone (ng/mL)			ns			
Low free testosterone			ns			
SHBG (nmol/L)			ns			
TSH (μUI/mL)			ns			
Prolactin (μUI/mL)			ns			
Concomitant therapy[a]			ns			

Abbreviations: HCC, hepatocellular carcinoma; BMI, body mass index; CES-D, Center of Epidemiologic Studies Depression Scale; MELD, model of end-stage liver disease; INR, international normalized ratio; Hb, hemoglobin; WBC, white blood cells; PLTs, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltranspeptidase; HDL, high density lipoprotein; HbA1c, glycosylated hemoglobin; SHBG, sex hormone binding globulin; TSH, thyroid stimulating hormone; PSA, prostate specific antigen; IIEF, International Index of Erectile Function.

[a] Concomitant therapy: diuretics, non-selective beta-blockers, calcium-antagonists, neurotropic drugs, hypoglycaemic agents, statins.

An insufficient release of vasodilators, and primarily of NO, from hepatic endothelial cells is a well-recognised element in the pathogenesis of portal hypertension, in particular with regards to its sinusoidal component. This is attributed to a dysfunction of the endothelial nitric oxide synthase (eNOS) system, which is largely associated to an increased intrahepatic oxidative stress [28]. Hence, an evaluation of endothelial dysfunction and degree of portal hypertension (ideally measured by HVPG), as well as of inflammatory markers and cytokines serum levels in patients with decompensated cirrhosis in relation to ED would be of secure interest.

In this cohort, ED was also significantly related to lower levels of haemoglobin. Low serum haemoglobin can indicate a more advanced liver disease and a more severe degree of portal hypertension. It has also been disclosed that anaemia worsens the hyperdynamic circulation typically associated with cirrhosis [29]. This is characterized by splanchnic vasodilation and peripheral vasoconstriction, which also influence the penile circulation, thus potentially contributing to ED [30]. Furthermore, lower haemoglobin levels reduce the oxygen delivery to the tissues, including the corpora cavernosa, thus potentially compromising erectile function [31].

The aetiology of ED is generally multi-factorial, with the implication of vascular, endocrinological, lifestyle, neurological and psychological, as well as iatrogenic/pharmacological factors, which often coexist [32,33]. In this cohort, the presence of ED did not correlate with any of the risk factors classically reported in the general population, such as T2DM, CVD, chronic kidney or pulmonary disease, and smoking habit, as well as with the coexistence of depressive symptoms or hypogonadism [1]. However, T2DM, vasculopathy and smoking habit were significantly associated with a more severe grade of ED, when this was present.

Hyperglycaemia and insulin-resistance, as well as smoking, are indeed factors notoriously associated with CVD, endothelial dysfunction and oxidative stress, and their role in the development of ED is well recognized [35,36]. Poor glycaemic control has been shown to increase the risk of ED two to five fold compared with good control [34]. In contrast, we did not find any difference in the incidence of ED among patients according to HbA1c values [35]. This could be related to the fact that, in the group of patients affected by ED, the mean value of HbA1c was only moderately higher than 7%, indicating that diabetes was fairly well compensated in the study population.

Alcohol abuse has been reported as an independent cause of sexual dysfunction in the general population [36]. However, data regarding the influence of alcoholic aetiology of cirrhosis on the development of ED are conflicting [8–10]. In our cohort, we did not find any significant difference in the prevalence or severity of ED according to alcoholic aetiology or to alcohol consumption. This may be related, on one hand, to the relatively small number of both alcohol-related cirrhosis patients and heavy drinkers in the study population and, on the other, to the coexistence, in the set of

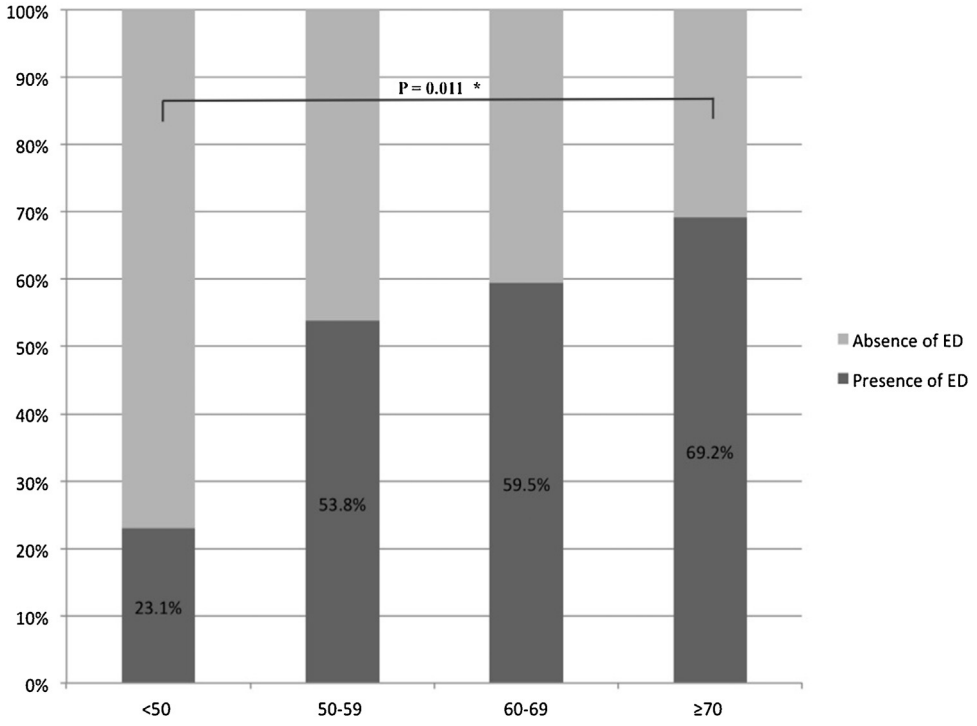

Fig. 1. Prevalence of ED according to patients' age. *By Mantel–Haenszel linear-by-linear association chi-square test. *Abbreviations*: ED, erectile dysfunction.

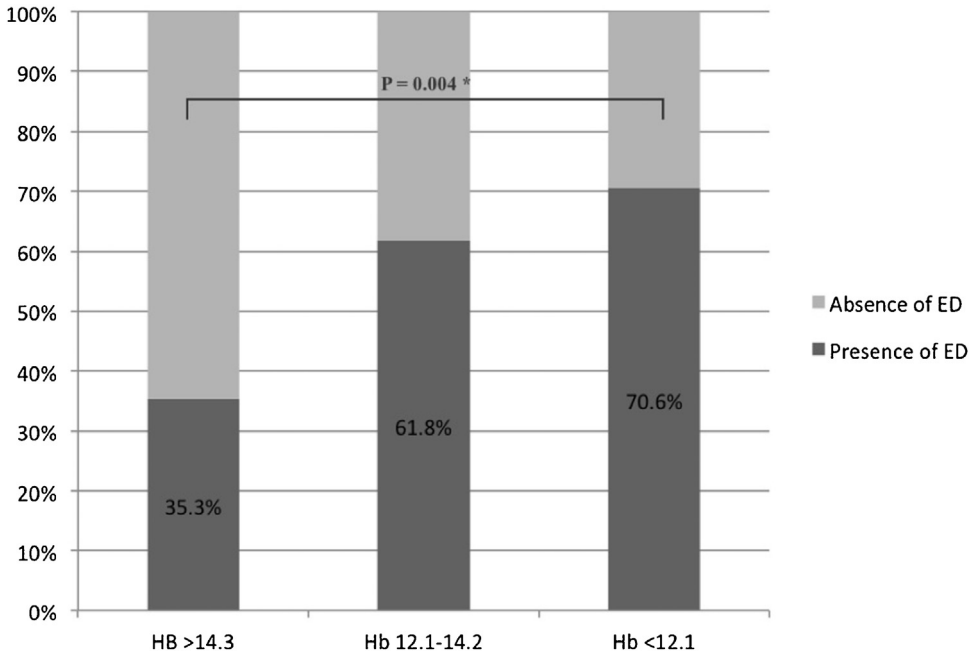

Fig. 2. Prevalence of ED according to haemoglobin levels (tertiles).
*By Mantel–Haenszel linear-by-linear association chi-square test.
Abbreviations: ED, erectile dysfunction; Hb, haemoglobin.

patients affected by metabolic cirrhosis, of factors such as T2DM, arterial hypertension and CVD, which can, per se, favour the occurrence of ED, thus nullifying a potential difference in ED prevalence according to alcohol consumption.

It is well known that advanced stages of liver cirrhosis are characterized by hyperestrogenism and a reduction of serum levels of testosterone [37]. In this cohort, hormonal profile (in particular the levels of TT, FTT and PRL) was not associated with ED. This is likely because hormonal profile is still not markedly altered in Child Pugh A cirrhosis. In fact, circulating androgens have been reported to progressively decrease with the severity of liver disease [37]. As a note, hypogonadism as diagnosed by the ANDROTEST was not a sensitive test to identify patients affected by ED in our cohort.

Interestingly, none of the clinical (presence or absence of oesophageal varices, diuretic-controlled ascites and HCC) or biochemical parameters related to the liver disease itself was significantly associated with the diagnosis of ED. Similarly, the use of drugs conventionally reported as associated with an increased

risk of developing ED, such as antihypertensive agents, NSBBs and diuretics was not associated with an increased prevalence of ED in our population.

As a note, to further confirm our results we are at present planning to perform, in the nearest future, a case-control study which would include patients without liver disease and patients with mild/moderate chronic hepatitis without cirrhosis as control groups.

In conclusion, this study showed that ageing plays a fundamental role in the development and progression of ED in patients with chronic liver disease as in the general population. In this cohort, no specific liver-related risk factor of ED was identified. The prevalence of ED in patients affected by compensated cirrhosis seems not much different from the prevalence registered in the general population, even in concomitance with important chronic comorbidities notoriously associated with sexual dysfunction. However, the coexistence of T2DM, vasculopathy and smoking habit might increase the risk of developing a more severe grade of ED, when this dysfunction is present.

Conflict of interest

None declared.

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