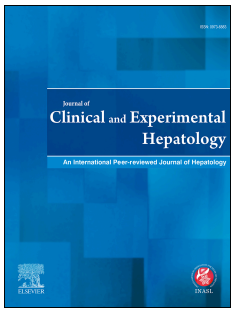

Erectile dysfunction in cirrhosis: Its prevalence and risk factors

Rakesh Kumar Jagdish, Ahmed Kamaal, Saggere Muralikrishna Shasthry, Jaya Benjamin, Rakhi Maiwall, Ankur Jindal, Ashok Choudhary, Vijayaraghavan Rajan, Vinod Arora, Ankit Bhardwaj, Guresh Kumar, Manoj Kumar, Shiv K. Sarin

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Erectile dysfunction in cirrhosis: Its prevalence and risk factors

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Abbreviations

ASMI- Appendicular skeletal muscle mass index; **CTP**- Child Turcotte Pugh; **DEXA-** Dual-energy x-ray absorptiometry; **ED-** Erectile dysfunction; **GAD-** Generalized anxiety disorder; **HRQOL:** Health related quality of life; **IIEF-** International index of erectile function; **q ADAM-** Quantitative androgen deficiency in the aging male questionnaire; **PHQ-** Patient health questionnaire;

ABSTRACT

Background & Aims: Erectile dysfunction (ED) is common in men with cirrhosis. The aim of this study was to assess the prevalence of ED and the factors associated with ED in men with cirrhosis.

Methods: 400 men with cirrhosis [Child Turcotte Pugh (CTP) class A, 44.0 %; CTP class B, 41.0 % and CTP class C, 15.0 %] having high Karnofsky performance score , and living in a stable monogamous relationship with a female partner were included in the study. International Index of Erectile Function (IIEF) questionnaire, and Short Form (36) Health Survey (SF-36) were used to assess erectile function and the health related quality of life (HRQOL) respectively.

Results: ED was found in 289 (72.3%) patients. Patients with ED reported significantly lower SF-36 scores across all the eight domains of SF-36 (i.e. physical functioning score, role physical score, bodily pain score, general health perception score, vitality score, social functioning score, role emotional score, and mental health score); physical component summary score, and mental physical component summary score, as compared to those without ED. On multivariate analysis, factors associated with ED were older age, longer duration of cirrhosis, CTP-C (vs CTP-A), higher HVPG, presence of generalized anxiety disorder (GAD), presence of major depression, and lower appendicular skeletal muscle index measured by Dual-energy X-ray absorptiometry (DEXA ASMI). **Conclusions:** ED is common in men with cirrhosis, and men with ED have poor HRQOL as compared to those without ED. Older age, longer duration of cirrhosis, CTP-C (vs CTP-A) , higher HVPG, presence of GAD, presence of major depression, and lower DEXA ASMI are associated with ED.

Keywords: Cirrhosis, Erectile dysfunction, Health related quality of life

INTRODUCTION

Background:

Erectile dysfunction (ED) is common in men with cirrhosis, with studies reporting prevalence from 25% to 92% [1-11]. ED in men with cirrhosis can be due to multiple factors. Some co-morbidities and risk factors associated with ED may be found in men with cirrhosis as well, including alcohol use, hypertension, diabetes, metabolic syndrome, depression, and hepatitis C virus (HCV) infection [12]. Other factors that may possibly be associated with ED include alterations of the sexual hormones, malnutrition, use of drugs such as diuretics and non-selective beta-blockers (NSBBs) [13].

ED is associated with a poor health related quality of life (HRQOL) [14], and depression [15]. Health Related Quality of Life (HRQOL) measurements are now being recognised as important part of overall management of cirrhosis [16]. Targeting specific symptoms can improve HRQOL [16]. ED in men with cirrhosis is one such symptom which needs attention [17, 18].

There are no large studies that have assessed the prevalence of ED and association of various factors with ED in a single large population of men with cirrhosis.

Aims:

The aims of this study were (i) to evaluate the prevalence and severity of ED, (ii) to assess independent factors (clinical parameters, biochemical and reproductive hormonal factors, anxiety, depression, nutritional factors and hepatic vein pressure gradient) associated with ED and (iii) to assess the impact of ED on the quality of life, in men with cirrhosis.

As poor performance status may itself be associated with ED, we selected men with cirrhosis and high Karnofsky Performance Score (KPS).

METHODS

Study design: This was a single centre observational study. This was a cross sectional study on men with cirrhosis to find out the prevalence of ED in them.

Setting: The study was done at Institute of Liver and Biliary Sciences (ILBS), New Delhi (Department of Hepatology) from June 2018 to December 2019.

The study was approved by the Institutional Review Board (IRB) of the Institute of Liver and Biliary Sciences (D1 Vasant Kunj, New Delhi, India) [Institutional ethical committee number: Number: IEC/2018/60/MA04]

Participants:

The study was conducted on men with cirrhosis attending outpatient department or day care (for endoscopy or hepatic hemodynamic studies) of Department of Hepatology of the Institute of Liver and Biliary Sciences.

The inclusion criteria were the following: Male patients, from 21 years to 60 years of age with cirrhosis of any etiology and severity [Child A, B, C], high Karnofsky Performance Score (80-100), and living in a stable monogamous relationship with a female partner.

Exclusion criteria were the following: Low (10-40) or intermediate (50-70) Karnofsky performance scores, overt hepatic encephalopathy; recent upper gastrointestinal (UGI) bleed (within 4 weeks) or hospitalization (within 4 weeks); active alcohol abuse (within the previous 3 months); hepatocellular carcinoma; extra hepatic malignancy; previous urologic surgery; previous liver transplantation; uncontrolled cardiac, respiratory failure; and uncontrolled thyroid diseases.

Variables assessed:

Patients underwent the following investigations at baseline: history and physical examination, complete hemogram, liver biochemistry including international normalized ratio (INR), renal function tests including serum electrolytes, 12-lead electrocardiogram (ECG), etiological workup for cirrhosis as needed, ultrasound abdomen , urinalysis, fasting blood sugar, HbA1c,

serum thyroid stimulating hormone (TSH), alfa feto protein (AFP), serum sex hormone binding globulin (SHBG), serum testosterone (free and total), serum prolactin, serum luteinizing hormone (LH),and serum follicle stimulating hormone (FSH).

Following questionnaires were also administered: Karnofsky Performance Score (KPS) questionnaire, International Index of Erectile Function (IIEF) questionnaire, quantitative Androgen Deficiency in the Aging Male (ADAM) questionnaire, Patient Health Questionnaire (PHQ-9) questionnaire, Generalized Anxiety Disorder 7 (GAD-7) questionnaire, and SF-36 questionnaire. Nutritional assessment [by body mass index (BMI), and whole body Dual-energy X-ray absorptiometry (DEXA)] and hepatic venous pressure gradient (HVPG) (only for patients already posted for HVPG a measurement, no HVPG was done specifically for this protocol) were also done.

Definitions and methods of assessments (measurements):

Cirrhosis and diabetes: Cirrhosis was diagnosed by clinical, radiological criteria or liver biopsy (if required). Twenty g/d of alcohol use was taken as significant [19]. Non-alcoholic steatohepatitis (NASH) cirrhosis was diagnosed as previously described [18].

Diabetes was diagnosed according to standard criteria [18].

Questionnaires administered: Karnofsky Performance Score (KPS) (ranging from 100 to 0) assessment was done as described previously [18, 20].International Index of Erectile Function (IIEF) questionnaire is a 15-item questionnaire assessing five domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) [21]. The IIEF erectile function (IIEF-EF) domain scores range from 1 to 30. IIEF-EF domain scores were used to define ED and its severity: 5 or lower (no attempts at intercourse); 6 to 10 (severe ED); 11 to 16 (moderate ED); 17 to 25 (mild ED); and 26 to 30 (“normal” erectile function i.e. absence of ED) [18, 22]

Quantitative ADAM (qADAM) questionnaire (scores ranging from 10 and 50) [18, 23]; Generalized Anxiety Disorder 7 (GAD-7) questionnaire (with score of ≥10 indicating probable diagnosis of GAD) [18, 24]; and Patient Health Questionnaire (PHQ-9, with score ≥10 indicating major depression) [18, 25] were also administered. Short Form (36) Health Survey was used to assess the health related quality of life (HRQOL). SF-36(v2) measures 4 scales of physical health (physical functioning, role-physical, bodily pain and general health); 4 of mental-health (vitality, social functioning, role- emotional and mental health); and 2comprehensive indexes (physical component summary and mental component summary). The lower scores indicate more disability [18, 26].

All of the above questionnaires used in this study were in both English and a Hindi translated version, and the patients were asked to read in the language they preferred. The questionnaires were administered by interview (by RKJ).

Nutritional assessment and body composition parameters: Dry BMI adjusted for the degree of fluid retention was estimated as previously described [27]. Whole body Dual-energy X-ray absorptiometry (DEXA) was used to assess the appendicular skeletal muscle index (ASMI) [28]. Whole Body DEXA scan was done using fan beam densitometer (Discovery A; Hologic, Bedford, MA) and dedicated software. Appendicular skeletal muscle mass was calculated by adding the lean mass (g) value for left arm, right arm, left leg, right leg. The total lean mass value is converted to kg (gm/1000). Then, the value of appendicular skeletal muscle mass was divided by the square of the height in meters to obtain the ASMI (kg/m^2) [28].

Sample size and statistical methods:

Assuming the prevalence of erectile dysfunction to be 60%, with confidence limits of 5%, and design effect of 1, sample size of 369 was required for a confidence level of 95%. Data was processed using the SPSS version 20.0 software. Comparison of categorical variables

was done using Chi-square and Fisher's exact tests; and that of continuous variables using t-test and Mann-Whitney test as applicable. A univariate logistic-regression analysis was performed for the assessment of variables associated with ED. Variables likely to be associated with ED based on a priori theory were used in multivariate logistic regression analysis, and forward selection was applied at a 5% significance level. Correlation between IIEF erectile function domain scores and the components of SF-36 (eight domains and the two summary scores) was assessed using the Pearson correlation test.

RESULTS

Participants: 400 patients fulfilling the inclusion and exclusion criteria were enrolled for this study (Figure 1).

Baseline patient characteristics: The etiology of the cirrhosis was alcohol in 195(48.8%), NASH in 103(25.8%), hepatitis B in 42(10.5%) and hepatitis C in 19(4.8%) of the patients. Overall, 76 patients (44.0%) were classified as CTP class A, 164 (41.0%) as CTP class B and 60 (15.0%) as CTP class C (Table 1).

Prevalence of erectile dysfunction and general characteristics of patients with ED: Overall, 289 (72.3%) patients had erectile dysfunction (IIEF-EF domain score ≤25); and within those 47 (16.3%) were classified as mild (IIEF-EF domain score 17–25), 78 (27.0%) as moderate (IIEF-EF domain score 11–16), and 118(40.8%) as severe (IIEF-EF domain score 6–10). Whereas 46 (15.9%) made no attempt at intercourse (IIEF-EF domain score ≤5) (Table 1).

Erectile dysfunction and etiology of cirrhosis: There were no significant differences in the etiology of cirrhosis between patients with ED, or without ED (Table 1).

Erectile dysfunction and severity of cirrhosis (and portal hypertension): As compared to patients without ED, patients with ED had higher CTP scores and more likely to have CTP class B/C. However, MELD scores were similar between the two groups. Prevalence of ED was 65.9% (116/176) in CTP-A, 72.6% (119/164) in CTP-B and 90% (54/60) in CTP-C patients respectively (P=0.002). HVPG values were available in a subgroup of 176 patients. Mean HVPG was significantly higher in patients with ED as compared to patients without ED (17.2±3.6 vs 14.9±3.7, P<0.001) (Table 1).

Erectile dysfunction and history of complications of portal hypertension: There were no significant differences in the proportion of patients with history of previous portal hypertension related complications (i.e. SBP, overt HE, AKI, variceal bleed) between patients with ED, or without ED (Table 1).

Erectile dysfunction and medical co morbidities: Prevalence of ED increased with age ; 40 %(4/10) in 18-29 years, 62.6 %(57/91) in 30-39 years, 65.7 %(111/169) in 40-49 years and 90 %(117/130) in 50-60 years age groups respectively (P<0.001). The mean age was significantly higher in patients with ED (46.5±8.0 vs 41.9±7.1 years respectively, P<0.001).

As compared to patients without ED, patients with ED had longer duration of cirrhosis (45.2±19.5 vs 38.2±18.6 months respectively, P=0.001).

However, there were no significant differences in the proportion of patients with history of hypertension, diabetes, coronary artery disease and hypertension between patients with ED, or without ED (Table 1). All the patients were "never smokers" (smoked less than 100 cigarettes in entire life).

Erectile dysfunction and concomitant medicines use:

There were no significant differences in the proportion of patients with history of use of beta-blockers, diuretics, rifaximin, lactulose and branched chain amino-acids between patients with ED, or without ED (Table 1).

Erectile dysfunction and reproductive hormones: Free testosterone levels were lower in CTP-C patients as compared to CTP-A patients (P=0.015). Levels of all other reproductive hormones were not significantly different across the three CTP classes (Supplementary Table 1).

Total testosterone, free testosterone, LH and prolactin were significantly lower in patients with ED. FSH and SHBG did not differ significantly between patients with ED, or without ED (Table 2).

Erectile dysfunction and body composition parameters: BMI not differ significantly between patients with ED, or without ED. DEXA ASMI was significantly lower in patients with ED as compared to patients without ED (Table 2).

Erectile dysfunction, KPS and quantitative ADAM scores: Patients with ED had significantly lower Karnofsky Performance score and quantitative ADAM score as compared to patients without ED (Table 2).

Erectile dysfunction and anxiety (GAD-7) /depression (PHQ-9) scores: GAD-7 score and PHQ-9 score were significantly higher in patients with ED as compared to patients without ED. Also, as compared to patients without ED, patients with ED were more likely to have generalized anxiety disorder (GAD-7 score ≥10, 43.6% vs 19.8%, P<0.001) and major depression (PHQ-9 score ≥10, 51.9% vs 9%, P<0.001) (Table 2).

Erectile dysfunction and health related quality of life (SF-36 v2) scores: Patients with ED reported significantly lower SF-36 scores across all the eight domains of SF-36 (i.e. physical functioning score, role physical score, bodily pain score, general health perception score, vitality score, social functioning score, role emotional score, and mental health score);

physical component summary score, and mental physical component summary score, as compared to those without ED (Table 2). Also there was significant correlation between IIEF erectile function domain scores and all the eight domains of SF-36; physical component summary score, and mental physical component summary score (Supplementary Table 2).

Sub analysis of patients with erectile dysfunction (ED) according to Child- Turcotte-Pugh (CTP) class: Supplementary Table 3 shows the sub analysis of patients with ED according to the CTP class. As expected, there were significant differences in the three groups with regards to bilirubin, AST, ALT, INR, CTP score, MELD and proportion of patients with ascites at presentation (C>B>A). As compared to CTP-A patients, patients with CTP-B and CTP-C were more likely to have past history of overt HE, AKI, variceal bleed and UTI; and using rifaximin and lactulose. CTP-C patients were more likely to be using beta-blockers and have lower albumin and SHBG levels as compared to CTP-A and CTP-B patients. General health perception scores were significantly less in CTP-B and CTP-C as compared to CTP-A patients. Social functioning scores were significantly less in CTP-C patients as compared to CTP-A and CTP-B patients.

Analysis of variables associated with ED: The following variables were assessed on univariate analysis for association with ED: age, alcohol as etiology of cirrhosis, duration of cirrhosis, haemoglobin, serum albumin, CTP class, past history of SBP, past history of overt HE, past history of AKI, past history of variceal bleed, baseline HVPG, total testosterone, free testosterone, LH, FSH, SHBG, prolactin, history of hypertension, history of diabetes, history of dyslipidemia, history of hypothyroidism, concomitant beta blockers use, concomitant diuretics use, concomitant rifaximin use, concomitant lactulose use, concomitant BCCAs use, presence of GAD (GAD-7 score ≥10), presence of major depression (PHQ-9 score of ≥10), BMI, and DEXA ASMI. History of coronary artery disease was not included in the analysis as only 1 patient had such history. Quality of life was not included as a

variable in analysis, as poor quality of life is a consequence of, rather than contributing to, the ED. Albumin was not used in multivariate analysis, as CTP score contains albumin as a component (hence they are co variables); also, DEXA ASMI is closely linked to serum albumin level. Only free testosterone was used in multivariate analysis (rather than using both total and free testosterone) as both are collinear variables.

On multivariate analysis, factors associated with ED were older age, longer duration of cirrhosis, CTP-C (vs CTP-A), higher HVPG, presence of GAD, presence of major depression, and lower DEXA ASMI (Table 3).

DISCUSSION

In this study, 72.3% of men with cirrhosis had ED. Previous studies have found high (25% to 92%) prevalence of ED in men with cirrhosis [2-11]. Such wide variations in the reported prevalence of ED are likely due to differences in the assessment tools used and differences in the severity of cirrhosis.

There were no significant differences in the prevalence of ED in men with cirrhosis due to different etiologies. Previous studies have found high prevalence of ED in men with cirrhosis due to alcohol (50%-70 %) [5, 7, 8], and viral hepatitis B/C (40%-92%) [6, 8, 9]. However, the prevalence of ED is high even in pre-cirrhotic men [6, 9, 11, 12, 29, 30, 31, 32, 33, 34, 35]. ED prevalence is high irrespective of the etiology, once cirrhosis develops.

It remains to be clarified what is the major driver of ED in men with cirrhosis (cirrhosis per se with its accompanying hormonal, portal hypertensive or nutritional disturbances; or various associated co-morbidities like age, hypertension, diabetes, hyperlipidemia, and coronary artery disease).

On multivariate analysis, older age and longer duration of cirrhosis were among the factors associated with ED in this study. Previous studies have found old age to be an independent

factor associated with ED in the general population, in patients with diabetes and chronic kidney disease [36, 37], in patients with chronic liver disease (including cirrhosis) due to viral hepatitis B/ C, alcohol and NAFLD [3,6,30,31,34]. Advanced age is associated with oxidative stress, decreased nitric oxide (NO) bioavailability, impaired endothelial function, and increased synthesis of vasoconstrictors; and all these factors contribute to development of vasculogenic ED [38].

The contribution of associated co-morbidities to ED in men with cirrhosis remains to be clarified. In the current study, there were no significant differences in the proportion of patients with history of hypertension, diabetes, and coronary artery disease between men with or without ED. Whereas, some studies did not find co-morbidities (diabetes, hypertension, and cardiovascular disease) to be associated with ED among men with cirrhosis [3, 7, 9], other studies have found these to be associated with ED in men with cirrhosis [4, 10, 11].

In this study, on multivariate analysis, CTP-C (vs CTP-A), and higher HVPG (indicative of severity of portal hypertension) were the factors associated with ED. More severe cirrhosis and portal hypertension leads to altered hemodynamics the splanchnic circulation, which could directly impair physiological penile erection, due to insufficient release of vasodilators [39].

As compared to patients without ED, patients with ED were more likely to have generalized anxiety disorder and major depression, and on multivariate analysis, presence of GAD and presence of major depression were independently associated with ED in this study. There is a proven association between anxiety/ depression and ED in patients without cirrhosis [40, 41]. Few previous studies have also found depression to be associated with ED amongst patients with chronic hepatitis (B and C) [31] and cirrhosis [11].

In this study, patients with ED reported significantly lower SF-36 scores across all the eight domains of SF-36 (i.e. physical functioning score, role physical score, bodily pain score, general health perception score, vitality score, social functioning score, role emotional score, and mental health score), physical component summary score, and mental physical component summary score, as compared to those without ED. Also there was significant correlation between IIEF erectile function domain scores and all the eight domains of SF-36; physical component summary score, and mental physical component summary score. Thus, men with ED had poor quality of life as compared to men without ED. Previous studies in have demonstrated that ED in men with chronic liver disease due to hepatitis B/C is associated with a worse HRQOL as compared to those without ED. [6, 12, 42, 43].

In this study beta- blockers and diuretics use were not associated with ED. Previous studies have also found that NSBBs and diuretics were not associated with the presence of ED [3, 4, 44].

In this study total testosterone, free testosterone, LH and prolactin were significantly lower in patients with ED; but FSH and SHBG did not differ significantly between patients with or without ED. However, on multivariate analysis, none of these hormones levels were associated with ED. Men with cirrhosis have low testosterone levels, which could be an explanation for the high ED prevalence [45].

On multivariate analysis, lower DEXA ASMI was independently associated with ED in this study. This is a novel finding of our study. Reduced production of albumin in men with cirrhosis may affect free to albumin-bound testosterone ratio, thus modifying the cell or tissue responses to testosterone [6]. Muscle mass and muscle strength is decreased due to protein malnutrition (which is common in cirrhosis). Decreased muscle mass has been found to be associated with prevalent and incident severe erectile dysfunction in older men and men with

diabetes [46, 47]. Decreased muscle mass may be due to low androgen levels; as low androgen levels can lead to decreased skeletal muscle anabolism [48].

Smoking has been described as one of the risk factors for ED in men with cirrhosis [10]. However, in our study all the subjects were categorised as "never smokers". This is unusual, as it is generally seen that patients who drink alcohol are more likely to smoke also. The discrepancy could be due to various factors including the criteria used to define smoking, religious practices of the patients, and exclusion of patients with poor performance status in our study. The use of the 100-cigarettes screen (used in our study) appears to underestimate the number of smokers [49] 54]. It is not clear that the 100-cigarette criterion should be discarded. The screen is commonly used to distinguish regular, established smokers from more transient smokers, since the 100-cigarettes screen helps to identify those in a population who are more likely to suffer the greater health harms of smoking than lighter or non-consumers [50].

There are few limitations of our study. As ED is associated with stigma in the society, the possibility of underreporting remains. This study also included patients with high Karnofsky performance scores only. Patients with low or intermediate performance scores are even more likely to have ED. Our study could not prove a causal relationship between ED and the various factors studied, due to its cross-sectional design. The impact of social status and occupation on ED was also not evaluated in the study. Also, we did not assess patients for minimal hepatic encephalopathy (MHE). One recent study from France found that MHE was associated with ED in men with cirrhosis on univariate analysis, but not in multivariate analysis [51].

In conclusion, ED is common in men with cirrhosis, and men with ED have poor HRQOL as compared to those without ED. Older age, longer duration of cirrhosis, CTP-C (vs CTP-A), higher HVPG, presence of GAD, presence of major depression, and lower DEXA ASMI are associated with ED.

LEGEND TO FIGURES:

Figure 1: Participant flow in the study

Figure 2: Prevalence of erectile dysfunction according to etiology of cirrhosis and Child Turcotte Pugh score.

AUTHOR CONTRIBUTIONS: RKJ, MK and SKS developed the protocol. RKJ, MK and AB enrolled participants in the study. SMS, AK, JB, RM, AJ, AC, VR, and VA reviewed and provided inputs to the protocol and manuscript. Guresh Kumar helped with statistical analysis and protocol development.

DATA TRANSPARENCY: All data, materials and software applications support the published claims and comply with field standards.

COMPLIANCE WITH ETHICAL STANDARDS:

Funding: No funding was taken from any pharmaceutical company, and funding was done by the Institute of Liver and Biliary Sciences research fund.

Conflict of interest: None for all the authors

Ethics approval: The study was approved by the Institutional Review Board (IRB) of the Institute of Liver and Biliary Sciences, New Delhi, India, where the study was conducted (Institutional ethical committee number: IEC/2018/60/MA04).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Table 1. Baseline clinical characteristics of men with and without erectile dysfunction

Parameters	All patients (n=400)	With erectile dysfunction (n=289)	No erectile dysfunction (n=111)	P value
Age (years)	45.2±8.0	46.5±8.0	41.9±7.1	<0.001
Having children, n(%)	345 (86.3%)	245(84.7%)	100(90.1%)	0.167
Etiology of cirrhosis				
Alcohol/ NASH /HBV/HCV/others	195(48.8%)/103(25.8%)/42(10.5%)/19(4.8%)/41(10.3%)	136(47.1%)/81(28.0%)/32(11.1%)/15(5.2%)/25(8.7%)	59(53.2%)/22(19.8%)/10(9.0%)/4(3.6%)/16(14.4%)	0.195
Duration of cirrhosis diagnosis (months)	43.3±19.5	45.2±19.5	38.2±18.6	0.001
HR (per min)	70.7±10.5	71.5±11.2	68.5±8.1	0.003
MAP (mm Hg)	82.3±7.7	82.3±6.8	82.5±9.7	0.800
Hb ((g/dL)	9.9±2.0	9.8±1.9	10.4±1.9	0.002
TLC ((10^3cells/mm^3)	5.9±2.5	5.9±2.4	6.0±2.5	0.755
Platelet (10^5cells/mm^3)	82.1±37.1	82.3±37.6	81.4±35.9	0.819
Creatinine (mg/dL)	0.9±0.4	0.9±0.5	0.9±0.4	0.419
Serum sodium (meq/L)	133.7±7.6	133.5±8.5	134.1±4.3	0.432
Bilirubin(mg/dL)	2.3±2.3	2.4±2.5	1.9±1.6	0.058
AST(IU/L)	42.8±29.2	43.6±30.3	40.9±26.2	0.414
ALT(IU/L)	29.8±20.9	30.5±21.6	28.2±19.4	0.338
Serum albumin(g/L)	2.8±0.7	2.7±0.6	3.2±0.7	<0.001
INR	1.5±0.4	1.5±0.4	1.5±0.3	0.382
CTP score	7.4±0.2	7.6±2.1	6.8±1.7	0.001
CTP class (A/B/C)	176(44.0%)/164(41.0%)/60(15.0%)	116(40.1%)/119(41.2%)/54(18.7%)	60(54.1%)/45(40.5%)/6(5.4%)	0.002
MELD	14.3±4.9	14.5±5.1	13.7±4.8	0.204
LSM (kPa)	37.4±15.3	37.2±15.5	37.6±14.6	0.831
Ascites at presentation [yes/no], n (%)	64(16.0%)/336(84.0%)	47(16.3%)/142(83.7%)	17(15.3%)/94(84.7%)	0.880
Ascites grade in patients having ascites [1/2/3], n (%)	64(100%)/0/0	47(100%)/0/0	17(100%)/0/0	1.000
Past h/o SBP, n (%)	72(18.0%)/	49(17.0%)	23(20.7%)	0.386
Past h/o overt HE, n (%)	86(21.50%)	59(20.4%)	27(24.3%)	0.416
Past h/o AKI, n (%)	84(21.0%)	58(20.10%)	26(23.4%)	0.494
Past h/o variceal bleed, n (%)	126(31.50%)	88(30.4%)	38(34.2%)	0.473
History of UTI, n (%)	56(14.0%)	44(15.2%)	12(10.8%)	0.334
Baseline HVPG done in, n	176	122	54	
HVPG (mmHg)	16.6±3.8	17.2±3.6	14.9±3.7	<0.001
HVPG > 10 mm Hg, n (%)	168/176(95.5%)	120(98.4%)	48(88.9%)	0.011
HVPG > 12 mm Hg, n (%)	145/176(82.4%)	108(88.5%)	37(68.5%)	0.002
Medical history				
History of Hypertension, n (%)	52(13.0%)	40(13.8%)	12(10.8%)	0.508
History of Diabetes, n (%)	115(28.7%)	83(28.7%)	32(28.8%)	0.825
Current diabetic therapy, n (%)				
Insulin only/ Oral only/ Insulin+ oral/ None	37/115(31.9%)/49/115(42.2%)/30/115(25.9%)/0	20/83(23.8%)39/83(46.4%)/25(29.8%)/0	17/32(53.1%)/10/32(31.3%)/5/32(15.6%)/0	0.010
History of Coronary artery disease, n (%)	1(0.25%)	1(0.3%)	0	1.000
History of Hypothyroidism, n (%)	25(6.3%)	18(6.2%)	7(6.3%)	1.000
Concomitant medications for cirrhosis				

Beta-blockers, n (%)	290(72.5%)	212(73.4%)	78(70.3%)	0.543
Propranolol, n(%)	123/290(42.4%)	89/212(42.0%)	33/78(41.8%)	1.000
Carvedilol, n(%)	167/290(57.6%)	123/212(58.0%)	46/78(58.22%)	1.000
Diuretics, n (%)	157(39.3%)	116(40.1%)	41(36.9%)	0.570
Rifaximin, n (%)	125(31.3%)	93(32.2%)	32(28.8%)	0.549
Lactulose, n (%)	185(46.3%)	136(47.1%)	49(44.1%)	0.655
BCAA, n (%)	170(42.5%)	123(42.6%)	47(42.3%)	1.000

Data are n (%) or mean±SD .

Abbreviations: NASH- Nonalcoholic steatohepatitis; HBV-Hepatitis B virus; HCV-Hepatitis C virus; BMI- Basal metabolic rate; HR- Heart rate; MAP- Mean arterial pressure; Hb- Hemoglobin; TLC- Total leukocyte count; AST- Aspartate aminotransferase; ALT- Alanine aminotransferase; INR- International normalized ratio; CTP score- Child turcotte pugh score; MELD- Model for end-stage liver disease; LSM- Liver stiffness measurement;; SBP- Spontaneous bacterial peritonitis; HE- Hepatic encephalopathy; AKI- Acute kidney injury; UTI- Urinary tract infection; HVPG- Hepatic vein pressure gradient;; BCAA- Branched chain amino acids

Table 2. Baseline hormonal data, questionnaires, and body composition parameters of men with and without erectile dysfunction

Parameters	All patients (n=400)	With erectile dysfunction (n=289)	No erectile dysfunction (n=111)	P value
Hormonal Data				
Total testosterone(ng/dl)	265.3±199.1	248.2±194.0	309.9±206.2	0.005
Free testosterone(pg/ml)	14.2±15.7	12.1±14.7	19.6±16.9	<0.001
LH(mIU/ml)	4.1±1.7	4.3±1.8	3.8±1.7	0.027
FSH(mIU/ml)	5.1±1.8	5.1±1.9	5.3±1.8	0.227
SHBG(nmol/L)	79.8±47.7	81.2±49.4	76.1±42.9	0.346
Prolactin(ng/ml)	20.3±17.0	21.7±19.0	16.8±9.5	0.001
TSH (U/mL)	2.5±1.2	2.5±1.2	2.6±1.2	0.649
IIEF Questionnaire				
Total IIEF score [Max 75]	36.6±21.3	25.3±12.1	66.1±7.3	
IIEF erectile function domain score [Max 30]	15.2±9.3	10.3±5.7	28.0±1.6	<0.001
IIEF erectile function severity, n (%)				
No ED (26-30)	111(27.8%)	0	111(100%)	<0.001
Mild (17–25)	47(11.8%)	47(16.3%)	0	
Moderate (11–16)	78(19.5%)	78(27.0%)	0	
Severe (6–10)	118(29.5%)	118(40.8%)	0	
No attempt at intercourse (≤5)	46(11.5%)	46(15.9%)	0	
IIEF orgasmic function domain score [Max 10]	4.5±3.2	2.9±2.1	8.6±1.5	<0.001
IIEF sexual desire domain score [Max 10]	5.9±2.6	4.9±2.3	8.7±1.2	<0.001
IIEF sexual desire domain score ≤4, n(%)	153(38.3%)	153(52.9%)	0(0)	<0.001
IIEF intercourse satisfaction domain score [Max 15]	6.4±4.5	4.2±2.7	12.2±2.8	<0.001
IIEF overall satisfaction domain score [Max 10]	4.5±3.2	2.9±2.1	8.5±1.7	<0.001
SF-36(v2) Questionnaire				
Physical functioning score	68.7±29.1	61.7±29.5	86.9±18.1	<0.001
Role physical score	55.2±34.8	41.6±28.4	90.8±22.8	<0.001
Bodily pain score	63.6±26.4	52.1±20.9	93.3±12.3	<0.001
General health perception score	17.8±12.2	13.6±9.2	28.9±11.8	<0.001
Vitality score	42.7±8.9	40.6±8.1	48.3±8.3	<0.001
Social functioning score	52.4±23.5	42.7±18.7	77.7±14.1	<0.001
Role emotional score	63.8±27.6	53.6±21.6	90.5±23.8	<0.001
Mental health score	38.7±9.7	36.2±9.2	45.30±7.3	<0.001
Physical component summary score	37.6±12.1	36.2±12.2	41.2±10.9	<0.001
Mental component summary score	43.1±12.1	41.7±12.2	46.7±10.9	<0.001
Other Questionnaires				
Karnofsky Performance score	96.2±5.4	95.4±5.6	98.1±4.1	<0.001
q ADAM score	28.5±11.3	23.2±7.0	42.2±8.0	<0.001
GAD-7 score	8. ±5.3	9.4±5.0	5.4±4.9	<0.001
GAD-7 score ≥10, n (%)	**148(37.0%)**	126(43.6%)	22(19.8%)	<0.001
PHQ-9 score	9.2±5.8	10.5±5.7	5.7±4.3	<0.001
PHQ-9 score ≥10, n (%)	160(40.0%)	150(51.9%)	10(9.0%)	<0.001
Nutritional and body composition parameters				
Height (cm)	168.8±5.8	168.7±5.6	168.8±6.3	0.937
Weight (kg)	75.7±12.3	75.3±12.1	76.7±12.9	0.312
BMI (kg/m^2)	26.5±4.2	26.4±4.2	26.9±4.1	0.361
DEXA ASMI(kg/m^2)	8.5±1.3	8.4±1.4	8.8±0.9	<0.001

Data are n (%) or mean±SD .

Abbreviations: LH- Luteinizing hormone; FSH- Follicle-stimulating hormone; SHBG-Sex hormone binding globulin ; TSH- Thyroid stimulating hormone; IIEF- International index of erectile function; q ADAM- Quantitative androgen deficiency in the aging male questionnaire; PHQ- Patient health questionnaire; GAD- Generalized anxiety disorder; BMI- Body mass index; DEXA- Dual-energy x-ray absorptiometry; ASMI- Appendicular skeletal muscle mass index

Table 3: Analysis of factors associated with erectile dysfunction

Variable	Univariate analysis OR (95% CI), P value	Multivariate analysis OR(95% CI), P value
Age	1.074(1.04-1.106), P<0.001	1.052 (1.021-1.110), P=0.011
Etiology of cirrhosis Non-alcohol Alcohol	 1 1.276(0.823-1.979), P=0.275	
Duration of cirrhosis	1.019(1.007-1.032), P=0.002	1.029(1.006-1.052), P=0.012
Hemoglobin	0.845(0.758-0.941),P=0.002	0.953(0.767-1.183), P=0.661
Serum albumin#	0.397(0.285-0.555),P<0.001	
Child-Turcotte-Pugh Class A B C	 1 3.403(1.369-8.459), P=0.008 4.655(1.894-11.440), P=0.001	1 1.156(0.480-2.786), P=0.746 5.614(1.414-22.289), P=0.014
Past history of SBP No Yes	 1 1.280(0.737-2.224), P=0.381	
Past history of overt HE No Yes	 1 1.235(0.745-2.106), P=0.395	
Past history of AKI No Yes	 1 1.218(0.721-2.060), P=0.461	
Past history of variceal bleed No Yes	 1 1.189(0.747-1.893), P=0.466	
Baseline HVPG	1.193(1.083-1.314), P<0.001	1.159(1.033-1.299), P=0.012
Baseline total testosterone*	0.998(0.997-0.999), P=0.006	
Baseline free testosterone	0.972(0.959-0.985), P=<0.001	0.984(0.960-1.008), P=0.188
Baseline LH	1.155(1.012-1.319), P=0.033	1.034(0.804-1.243), P=0.675
Baseline FSH	0.932(0.831-1.045), P=0.227	
Baseline SHBG	1.022(0.997-1.007), P=0.347	
Baseline prolactin	1.020(1.005-1.036), P=0.011	1.026(0.995-1.059), P=0.104
History of hypertension No Yes	 1 0.755(0.380-1.498), P=0.421	
History of diabetes No Yes	 1 1.005(0.620-1.630), P=983	
History of dyslipidemia No Yes	 1 1.001(0.765-1.120), P=0.785	
History of hypothyroidism No Yes	 1 1.013(0.411-2.497), P=0.977	
Concomitant beta blockers use No Yes	 1 0.858(0.529-1.392), P=0.536	
Concomitant diuretics use No Yes	 1 0.874(0.556-1.372), P=0.557	
Concomitant rifaximin use No Yes	 1 0.854(0.529-1.378), P=0.518	
Concomitant lactulose use No Yes	 1 0.889(0.573-1.381), P=0.601	
Concomitant BCCAs use No Yes	 1 0.991(0.636-1.543), P=0.968	
Presence of GAD (GAD-7 score ≥10) No	 1	1

Yes	3.127(1.857-5.267), P=<0.001	2.842(1.056-8.514), P=0.040
Presence of major depression (PHQ-9 score ≥10) No Yes	 1 10.899(5.469-21.749), P=<0.011	 1 6.828(1.641-28.409), P=008
Baseline BMI	0.976(0.927-1.028, P=0.361	
Baseline DEXA ASMI#	0.717(0.592-0.869), P=0.001	0.633(0.443-0.904), P=0.012

Abbreviations:; SBP- Spontaneous bacterial peritonitis; HE- Hepatic encephalopathy; AKI- Acute kidney injury; HVPG- Hepatic vein pressure gradient; LH- Luteinizing hormone; FSH- Follicle-stimulating hormone; SHBG-Sex hormone binding globulin ; BCAA- Branched chain amino acids; ; PHQ- Patient health questionnaire; GAD- Generalized anxiety disorder; BMI- Body mass index; DEXA- Dual-energy x-ray absorptiometry; ASMI- Appendicular skeletal muscle mass index

Albumin was not used in multivariate analysis, as CTP score contains albumin as a component (hence they are covariables); also, DEXA ASMI is closely linked to serum albumin level.
* Only free testosterone was used in multivariate analysis (rather than using both total and free testosterone) as both are collinear variables.