Original Article

DOI: 10.7860/JCDR/2023/60535.17536

# Correlation of Serum Testosterone Levels in Men with Severity of Liver Dysfunction in Chronic Liver Disease- An Observational Study at a Tertiary Care Centre in Uttarakhand, India

Internal Medicine Section

NAVEEN KUMAR RAJPUT[1], RESHMA KAUSHIK[2], SHEKHAR KHUSHWAH[3]



## ABSTRACT

**Introduction:** Chronic Liver Disease (CLD) and/or cirrhosis of liver represent different liver disorders of varying severity in which liver injury, inflammation, and fibrosis continue for more than six months. Various aetiologies including drugs toxins, alcohol abuse, infections, autoimmune disorders, genetic and metabolic diseases are implicated for CLD. Regardless, the aetiology of the CLD, the serum testosterone falls as the disease advances.

**Aim:** To study the serum testosterone level in male patients with CLD and its correlation with the severity of the disease.

**Materials and Methods:** A prospective observational study was conducted on patients reporting to Himalayan Hospital in OPD and IPD between June 2021 to May 2022. A total of 58 male patients of CLD were recruited. All patients were examined with clinical history, physical examination, laboratory blood and biochemical and radiological investigations, including total serum testosterone estimation. Testosterone value of <3 ng/mL was considered as low level. Child-Turcotte-Pugh (CTP) scores and Model for End-Stage Liver Disease-sodium (MELD-Na) scores were calculated to assess the severity of CLD.

**Results:** The mean age of the patients was 47.87±10.3 years. The majority of patients, 52/58 (89.65%), had low serum testosterone levels. As the severity of CLD increases, the testosterone falls progressively, and the finding was statistically significant (p-value=0.001). The mean testosterone levels (0.9±0.38) in patients with MELD-Na score of ≥20 was significantly (p-value=0.02) lower than the patients with MELD-Na score of <20. There was a strong negative correlation between low testosterone and CLD severity.

**Conclusion:** Overall, 89.65% of the patients had a low testosterone level. Serum testosterone level can be an independent marker for the severity of CLD in male patients.

**Keywords:** Child-turcotte-pugh scores, Liver injury, Model for end-stage liver disease-sodium

## INTRODUCTION

The CLD is defined as liver inflammation, injury, and/or fibrosis occurring and persistent in the liver for more than six months [1]. CLD is a continuous process of inflammation/injury, destruction, and regeneration of liver parenchyma, which leads to fibrosis and cirrhosis. Various aetiologies are implicated in CLD, which includes drugs, toxins, chronic alcohol abuse, infections, autoimmune diseases, and genetic and metabolic disorders. Generally, aetiology of cirrhosis does not affect the degree of sex hormone imbalance [2]. In males with CLD, the serum testosterone is usually reduced, and regardless of the aetiology it progressively falls with increasing severity of hepatic disease [3].

It has been reported that upto 90% of male patients with cirrhosis have low serum testosterone levels [4]. Androgen levels are decreased with worsening severity of liver failure, as classified by the CTP [3]. It has been recently identified that testosterone deficiency is an independent prognostic marker in cirrhotic patients [4]. Various clinical features of advanced hepatic disease in males are thought to be due to low testosterone level including, anaemia, fatigue, hair loss, gynaecomastia, testicular atrophy, wasting of muscles, and sexual dysfunction. In patients with cirrhosis, testosterone deficiency is an independent predictor of mortality [5,6]. Testosterone has an anabolic effect on haematopoiesis and the musculoskeletal system [2]. Features suggestive of hypogonadism in men, like gynaecomastia, reduced libido, low bone mineral density, infertility and sarcopenia are also present in patients with advanced hepatic disease [2].

The various clinical manifestations of advanced hepatic disease in males, including gynaecomastia, hair loss, testicular atrophy, wasting of muscles, sexual dysfunction, fatigue and anaemia also attributed to low levels of testosterone in these patients [7]. It has been recently demonstrated that increase in mortality is associated with testosterone deficiency in males with advanced hepatic disease which is independent of the MELD score [4]. The mechanism of testosterone deficiency in cirrhosis is most likely multifactorial, and the hypothalamic-pituitary-testicular axis can be affected at all levels [2]. The present study was planned to assess the prevalence of low testosterone levels in male patients with CLD and to find out the correlation with the severity of the disease.

## MATERIALS AND METHODS

A prospective observational study was conducted after obtaining approval from the Institute Ethical Committee (Via letter no HIMS/RC/2021/100) on male patients reporting to Himalayan Hospital in OPD and IPD between June 2021 to May 2022. A convenience sampling technique was used for recruitment; 58 male patients with CLD reporting to OPD during this period were included.

**Inclusion criteria:** Male patients with age between 18 and 69 years. Established case of CLD based on clinical, biochemical, and radiological findings, irrespective of the aetiology.

**Exclusion criteria:** Patients having active cancer with hormonal treatment, end-stage renal disease (estimated glomerular filtration rate <30 mL/min/1.73 $m^2$), malignancy, severe congestive heart failure

{Ejection Fraction <40%, and or New York Heart Association (NYHA) class 3 or 4}, and chronic obstructive pulmonary disease require oxygen therapy. Additional exclusions included patients with organic gonadal pathology, patient receiving testosterone therapy or androgen deprivation therapy.

### Study Procedure

Identification of male patients with CLD was done by reviewing the medical records manually. They were subjected to baseline liver function test, hormonal estimation along with routine biochemistry tests. All patients diagnosed with CLD were undergone detailed clinical history taking, clinical examination and investigations that include full blood counts, blood sugar, serum creatinine, liver function test, INR, urine analysis and serum electrolytes, serum testosterone level, and ultrasonography of abdomen.

Baseline variables such as age and aetiology of CLD were recorded. Baseline biochemistry including serum total testosterone level was measured and recorded. Recognised severity and prognostic markers were calculated and recorded including the MELD score, CTP scores and serum sodium [8,9]. Severity of liver disease, as classified by the CTP, with a scoring system of 5-15: scores of 5 and 6 represent Child-Pugh class A, scores of 7-9 represent class B and scores of 10-15 represent class C. MELD-Na was calculated from serum bilirubin level, Prothrombin Time (PT) with International Normalised Ratio (INR), serum sodium, and serum creatinine.

**Diagnosis of CLD:** The diagnosis of CLD was made on the basis of a combination of biochemical, clinical, and radiological findings. Supportive findings included clinical features of palmar erythema, ascites, spider naevi, dilated veins or caput medusa, parotid swelling, testicular atrophy, gynaecomastia, biochemical findings such as thrombocytopenias, low albumin and increased INR, or radiological features of architectural changes in liver and evidence of portal hypertension, or upper gastrointestinal endoscopic findings of a oesophageal varices, gastric varices and portal gastropathy. At the end of study period, based on above criterias a total of 58 patients were included in the study.

**Baseline variables:** Age, aetiology of liver disease, serum testosterone and prognostic markers including the measured MELD-Na and CTP were recorded.

**Clinical and laboratory assessment:** The following information were collected: morning serum testosterone level, age, liver function tests, serum creatinine, serum electrolytes, measured CTP and MELD-Na scores. The serum testosterone levels were reported in nmol/L (normal males: 3.0-10.0 ng/mL) with values below the normal limit considered as significant low level. Testosterone in all samples was measured with Electrochemiluminescence Immunoassay (ECLIA) in central laboratory of Himalayan hospital.

## STATISTICAL ANALYSIS

Continuous data were described using means and standard deviations; absolute and relative frequencies were used for categorical data. For bivariate analysis, we used the Chi-square and the unpaired t-test for continuous and categorical variables, respectively. The Pearson's correlation coefficient was used to evaluate the correlation between testosterones levels and CTP and MELD scores. Biochemical parameters, age, sex, aetiology of CLD were entered as independent variables. Symptoms, variable organ dysfunctions, and other variables were analysed. Statistical value (p-value) <0.05 was considered as statistically significant. Student t-test, Chi-square, and Fisher's-exact test were used to express the rates, ratios, and proportions. The correlation between testosterone level and severity of CLD were assessed by appropriate test. Data analysis was performed by using SPSS 22 (SPSS, Inc., Chicago, IL) software.

## RESULTS

The mean age of the patients was 47.87±10.3 years. The majority of patients, 52/58 (89.65%), had low serum testosterone levels [Table/Fig-1]. The majority of the patients, 52/58 (89.65%), had low testosterone levels (<3 ng/mL), 6/58 (10.34%) patients had normal testosterone level (3-10 ng/mL), and none had supranormal testosterone level (>10 ng/mL). Overall, 36/58 (62.06%) patients had MELD-Na score more than 20 and 22 (37.93%) patients had score less than 20 [Table/Fig-2a]. As the severity of CLD increases, the testosterone falls progressively, and the finding was statistically significant (p-value= 0.001). The mean testosterone level (0.9±0.38) in patients with MELD-Na score of ≥20 was significantly (p-value =0.02) lower than the patients with MELD-Na score of <20 [Table/Fig-2b]. The serum testosterone level of the patients with CLD negatively correlated with MELD-Na and CTP score [Table/Fig-3-6].

| Features | All patients (n=58) | |
|---|---|---|
| | Mean±SD | Frequency (n=58) |
| Age (years) | 47.87±10.3 | |
| Serum total testosterone (ng/mL) | 1.1±0.3 | |
| Normal testosterone level (3-10 ng/mL) | | 6 (10.34%) |
| Low testosterone level (<3 ng/mL) | | 52 (89.65%) |
| MELD-Na points | 24.01±8.06 | |
| Child-Pugh (Class A,B,C) | | 8 (13.79%): 16 (27.58): 34 (58.62%) |
| **Aetiology of cirrhosis** | | |
| Alcohol | | 40 (68.96%) |
| HBV | | 3 (5.17%) |
| HCV | | 2 (3.44%) |
| NASH- Cryptogenic | | 11 (18.96%) |
| Autoimmune | | 2 (3.44%) |

**[Table/Fig-1]:** Baseline characteristics of patients of CLD.
HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH; Non alcoholic steato hepatitis

| Serum total testosterone (ng/mL) | No. of patients (n=58) |
|---|---|
| Low testosterone (<3 ng/mL) | 52 (89.65%) |
| Normal testosterone (3-10 ng/mL) | 6 (10.34%) |
| **CTP score** | |
| Grade A (score 5-6) | 8 (13.79%) |
| Grade B (score 7-9) | 16 (27.58%) |
| Grade C (score 10-15) | 34 (58.62%) |

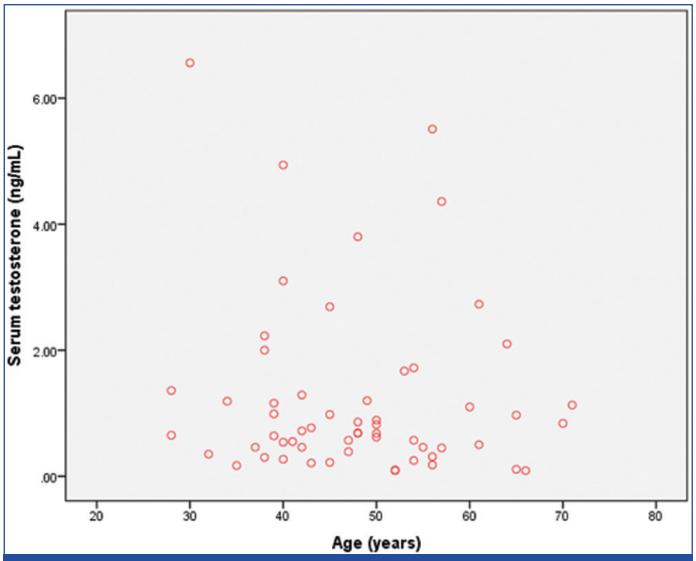
**[Table/Fig-2a]:** Distribution of cases according to serum total testosterone level and CTP score.

| Scores | Severity | N=58 | Mean value of testosterone (ng/mL) | p-value |
|---|---|---|---|---|
| CTP score classification | Grade A | 8 | 3.07±1.96 | 0.01 (A vs B) |
| | Grade B | 16 | 1.22±1.41 | 0.17 (B vs C) |
| | Grade C | 34 | 0.79±0.76 | 0.001 (C Vs A) |
| MELD-Na score | <20 | 22 | 1.78±0.38 | 0.02 |
| | ≥20 | 36 | 0.9±0.97 | |

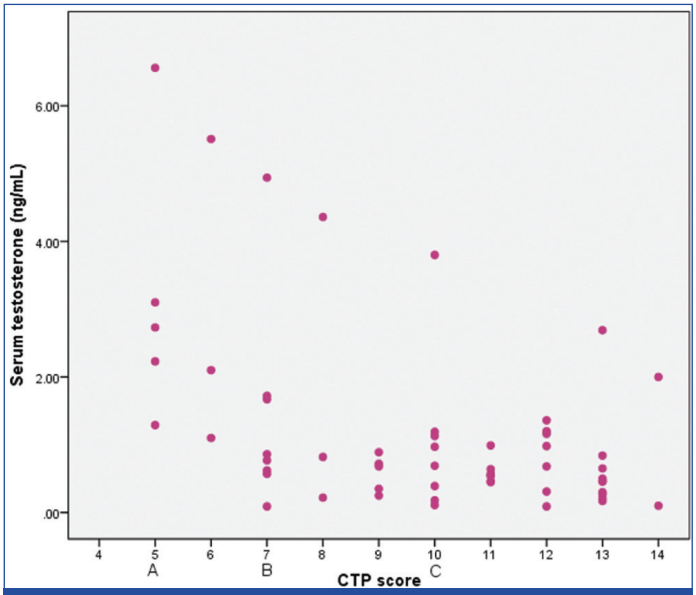
**[Table/Fig-2b]:** Comparison of serum total testosterone levels of patients with Child Pugh Score (CTP).

| Predictor variables | Dependent variable: Testosterone | | |
|---|---|---|---|
| | r-value | p-value | 95% CI |
| Age (years) | -0.095 | 0.47 | -0.292 to 0.129 |
| MELD-Na score | -0.313 | 0.01 | -0.441 to 0.063 |
| CTP score | -0.475 | 0.01 | -0.452 to 0.009 |

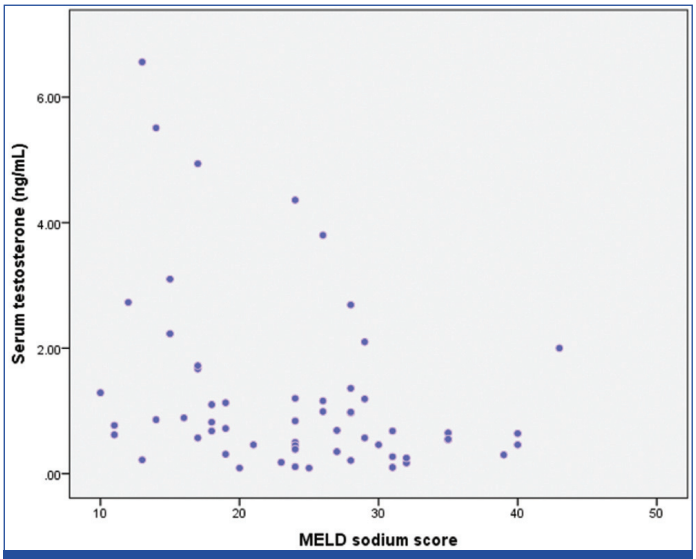
**[Table/Fig-3]:** Correlation of age, MELD-Na score and CTP score with serum testosterone level of the patients with CLD.




**[Table/Fig-4]:** Scatter plot of age against testosterone levels in male patients.




**[Table/Fig-5]:** Scatter plot of CTP score against testosterone levels in male patients.




**[Table/Fig-6]:** Scatter plot of MELD-Na score against testosterone levels in male patients.

## DISCUSSION

The CLD/cirrhosis of the liver is an important cause of morbidity and mortality worldwide. According to the World Health Organisation (WHO), about 800,000 people die annually from cirrhosis [10]. CLD/cirrhosis is one of the leading causes of death, and it is responsible for the majority of clinical burden of liver disease. Various mechanisms cause chronic liver injury, including activation of immunity (innate and adaptive both) and sterile inflammation [11]. CLD is defined by chronic inflammation or injury of the liver and/or fibrosis occurring in the liver for more than six months [1].

Although the liver can adapt to injury through tissue repair, chronic injury results in inflammation, matrix deposition, necrosis and angiogenesis, all of which lead to fibrosis. The key pathogenic feature of underlying liver fibrosis and cirrhosis is the activation of hepatic stellate cells. The characteristic features of liver cirrhosis are the diffuse process with nodule formation (regenerating nodules) and fibrosis as defined anatomically [12].

Clinically, patients may be asymptomatic (compensated) for long periods. The onset of symptoms may be insidious or, less often, abrupt. Symptomatic patients present with non specific symptoms and signs such as fatigue, disturbed sleep, anorexia, malaise, weight loss, muscle wasting, and fever or decompensation (jaundice, ascites, hepatic encephalopathy, or bleeding varices). Decompensation leads to unfavourable prognosis and poor quality of life in cirrhotic patients. Other complications include spontaneous bacterial peritonitis, hydrothorax, hepatorenal syndrome, hepatopulmonary syndrome, cirrhotic cardiomyopathy, portopulmonary hypertension, hepatocellular carcinoma, and portal vein thrombosis, and intercurrent infections may occur in these patients and can accelerate the clinical deterioration. Cirrhotic patients have a low life expectancy, and it is further reduced in the presence of decompensation [13]. The median survival of the compensated patient is about 12 years as compared to 2 years for decompensated patients [14]. Prognostic scoring systems for CLD include the CTP and MELD-Na score. Child-Pugh classification (which depends on serum bilirubin, ascites, hepatic encephalopathy, serum albumin and PT-INR) is a reliable prognostic marker to predict the survival in many liver diseases and also predicts major complications of cirrhosis, such as spontaneous bacterial peritonitis and variceal bleeding [15]. The MELD score is used to predict prognosis and determine the optimum timing for liver transplantation [16].

Low serum testosterone level is commonly associated with chronic disease of the liver, heart, kidney, and lungs. Signs and symptoms of androgen deficiency are also associated with low testosterone levels in these diseases [17,18]. The mechanism and causes of both clinical features and biochemical changes consistent with androgen deficiency are complex and multifactorial in these chronic diseases [19]. About 50-70% of male patients with CLD of any cause have impaired testosterone and sperm production, and it is more common in those having liver failure, cirrhosis, sexual dysfunction, testicular atrophy, and gynaecomastia [3,6,20]. This study demonstrates a correlation between testosterone levels and the severity of the CLD. In males with CLD, testosterone levels fall parallel with the worsening severity of the CLD. Reduced testosterone may be a useful prognostic marker in males with CLD, as it predicts severity independent of the MELD score. A significant association between mortality and reduced testosterone levels is found in an observational study related to 171 male patients who were referred for liver transplantation [4].

Many complications of CLD in males may be attributed to testosterone deficiency, and it may also influence severity and prognosis. Here, this study measured the testosterone level only at a single point in time, so it is not possible to assess the prognostic value of change in serum testosterone level with time in the course of the disease. Changes in hypothalamic-pituitary-testicular axis can occur with alteration in systemic health and may lead to a decrease in total serum testosterone [21]. Spironolactone also has an antiandrogenic effect; this medication could also reduce total serum testosterone levels [21].

Serial measurement of serum testosterone level can be done in men with CLD, but whether it has clinical significance needs further study. The benefits of testosterone therapy have not yet been

adequately investigated in long-duration studies. Long-duration prospective research is required to evaluate testosterone therapy in men with CLD. Testosterone levels of patients with cirrhosis should be checked as replacement therapy promotes bone density and increase muscle mass. A level below 300 ng/dL is generally considered the threshold to start treatment, especially if there are symptoms. This study also provides a scientific rationale to evaluate the benefits of testosterone replacement therapy in males with CLD.

The selection of an appropriate candidate for liver transplantation remains an important step. It requires a multidisciplinary approach to identify comorbid conditions and other potential issues impairing outcomes. Organ allocation is often determined by severity, as reflected by the MELD-Na score. CTP and MELD-Na scoring system includes more than one clinical and investigation value, whereas a single testosterone value can give a fair idea about the severity of the disease. The limiting step for the procedure is often the waiting list for a donor organ, which is continuously growing. These findings provide a scientific rationale for evaluating the utility of low testosterone in patients who are waiting for liver transplantation to determine the allocation priority for donor's livers.

### Limitation(s)

The study was conducted in a single centre and with a limited sample size. A multicentric prospective cohort study needs to confirm these findings.

## CONCLUSION(S)

The prevalence of reduced testosterone levels in male patients with CLD is very high, and it significantly correlates with the severity of the disease. This parameter can be used as an independent marker of the severity of CLD in males. Measuring serum testosterone levels in every male CLD patient will provide insight into the progression of the disease.

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**PARTICULARS OF CONTRIBUTORS:**

1. Assistant Professor, Department of Medicine, Himalayan Institute of Medical Science, SHRU, Dehradun, Uttarakhand, India.
2. Professor and Head, Department of Medicine, Himalayan Institute of Medical Science, SHRU, Dehradun, Uttarakhand, India.
3. Junior Resident, Department of Medicine, Himalayan Institute of Medical Science, SHRU, Dehradun, Uttarakhand, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**

Naveen Kumar Rajput,
Assistant Professor, Department of Medicine, Himalayan Institute of Medical Science, SHRU, Dehradun, Uttarakhand, India.
E-mail: naveenrajputmd@gmail.com



**PLAGIARISM CHECKING METHODS:** [Jain H et al.]

- Plagiarism X-checker: Oct 04, 2022
- Manual Googling: Nov 22, 2022
- iThenticate Software: Dec 08, 2022 (16%)

**ETYMOLOGY:** Author Origin

**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Oct 03, 2022**
Date of Peer Review: **Nov 14, 2022**
Date of Acceptance: **Dec 10, 2022**
Date of Publishing: **Feb 01, 2023**