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**Harini Natvarbhai Patel**
Intern Doctor, GMERS Medical College, Himmatnagar, Gujrat, India

**Sourav Bansal**
Intern, Government Medical College, Amritsar, Punjab, India

**Arghadip Das**
Medical Student, Nilratan Sircar Medical College, Kolkata, West Bengal, India

**Himani J Suthar**
M.B.B.S, GMERS Medical College, Gandhinagar, Gujrat, India

**Minkalbahen Anilkumar Patel**
Junior Resident, Department of Medicine, MP Shah Government Medical College, Jamnagar, Gujrat, India

**Kavan Sunilkumar Nakum**
Intern Doctor, GMERS Medical College Himmatnagar, Gujrat, India

**Dr. Vinodh Boopalraj**
MD, Physician in General Medicine/Pediatric Medicine, Yerevan State Medical University, Armenia

**Kantamneni Dyutika**
MGM, Navi, Mumbai, Maharashtra, India

**Corresponding Author:**
**Harini Natvarbhai Patel**
Intern Doctor, GMERS Medical College, Himmatnagar, Gujrat, India

# To investigate the link between serum prolactin levels and the severity of liver cirrhosis

**Harini Natvarbhai Patel, Sourav Bansal, Arghadip Das, Himani J Suthar, Minkalbahen Anilkumar Patel, Kavan Sunilkumar Nakum, Dr. Vinodh Boopalraj and Kantamneni Dyutika**

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**Abstract**
**Aim:** To investigate the link between serum prolactin levels and the severity of liver cirrhosis.
**Methods:** This cross-sectional research covers 60 chronic liver disease patients (CLD). There are 25 female patients and 35 male patients. Their ages vary from 35 to 58 years, with a mean standard deviation of 52.94±6.99. According to the Modified Child's Pugh score, the cases studied are divided into three groups:
**Group 1:** Consists of 20 individuals with mild liver cirrhosis.
**Group 2:** Consists of 20 individuals with mild liver cirrhosis.
**Group 3:** Consists of 20 individuals with severe liver cirrhosis.
**Results:** This research included 60 patients ranging in age from 35 to 60 years old, with a mean SD of 52.94±6.99 years; there were 35 male patients (58.33 percent) and 25 female patients (41.67 percent). PRL levels range from (5.6-39) ng/ml with a mean S.D of (19.76±10.14 ng/dl). The albumin level ranges from (1.3-4.2) mgdl, with a mean S.D of (3.18±0.95) gdl. Total bilirubin levels range from (1.3-6.8) mg/dl, with a mean standard deviation of (2.71.4 mg/dl). The prothrombin time ranges from (2.8-8.5) sec, with a mean S.D of (8.85.44 sec). Creatinine levels range from (0.7-6) mg/dl, with a mean S.D. of (2.35±1.31 mg/dl). The ultrasonic diameter of the portal vein (PV) varies from (10-19) cm with a mean S.D (13.19±1.84 cm). The child Pugh score ranges from (5 to 14) with a mean S.D of (10.16±4.16). The Roc curve for blood prolactin level as a predictor of severe/moderate liver cirrhosis reveals that at the cutoff point of 19.8 ng/ml, the sensitivity is 68.94%, the specificity is 80.15%, the PPV is 85.5%, and the NPV is 62%.
**Conclusion:** Prolactin levels rise considerably in individuals with severe liver illness, especially those with ascites and hepatic encephalopathy. A high prolactin level might therefore be regarded as a risk factor for liver cirrhosis.

**Keywords:** Serum prolactin, liver cirrhosis

## Introduction

Cirrhosis of the liver (LC) is an irreversible disorder caused by necrosis of hepatocytes, loss of the reticular network, and nodular regrowth of remnant liver tissue [1-4]. There are many ways reported in the literature for determining the severity of cirrhosis. The liver biopsy is the gold standard approach for assessing hepatic fibrosis, but it has significant drawbacks such as being an intrusive, unpleasant treatment with uncommon but potentially life-threatening consequences.

Fibroscan (Transient elastography) has recently emerged as a potential non-invasive approach to diagnose liver fibrosis, thanks to advancements in diagnostic techniques [5].

Fibroscan is a dependent device with variable outcomes assessed by various assessors.

The modified Child-Pugh scoring system was created to predict mortality in cirrhotic patients, although it may result in inconsistencies in scoring and requires the computation of several component values [5-7].

As a result, a simple, widely available test is required to determine the degree of liver disease and predict its repercussions in real time. Cirrhosis of the liver is known to impact the pituitary gonadal axis [8-10]. Human prolactin (PRL) is a pituitary hormone whose synthesis is regulated by dopamine (a negative regulator) through the hypothalamo-pituitary axis. A decrease in dopamine levels in the hypothalamo-pituitary axis has been seen in liver cirrhosis, leading in increased blood prolactin levels [8-10]. Keeping this in mind, prolactin may be a potential strategy in the hunt for a biomarker for liver cirrhosis.

## Methods and Materials

This cross-sectional research covers 60 chronic liver disease patients (CLD). There are 25 female patients and 35 male patients. Their ages vary from 35 to 58 years, with a mean standard deviation of 52.94±6.99. According to the Modified Child's Pugh score, the cases studied are divided into three groups:

**Group 1:** Consists of 20 individuals with mild liver cirrhosis.

**Group 2:** Consists of 20 individuals with mild liver cirrhosis.

**Group 3:** Consists of 20 individuals with severe liver cirrhosis.

All patients over the age of 20, both sexes, with documented liver cirrhosis were eligible. The presence of chronic liver disease stigmata was regarded to corroborate the diagnosis. Patients with noncirrhotic hepatitis C virus (HCV) or hepatitis B virus (HBV) are excluded. Patients under the age of 20. Interferon treatment is administered to patients. Patients who have endocrinal diseases. Women who are pregnant or nursing. Patients taking psychotropic medications at the same time. Patients taking any medication that affects prolactin levels.

## Methodology

The following procedures were performed on all patients: Taking a history that includes age, gender, and a history of risk factors for chronic liver disease such as blood transfusions and procedures. Every patient had a general and local examination, with a focus on indicators of chronic liver illness such as jaundice, ascites, palmar erythema, spider naevi, liver size, spleen size, encephalopathy, and lower limb edoema. All participants undergo abdominal ultrasonography. Each patient undergoes the following laboratory tests: After fasting for 10-12 hours, seven millilitres of venous blood were extracted and divided as follows: Two millilitres of whole blood were placed in an EDETA vacutainer (violet cap) and gently shaken up and down to determine the CBC. Three millilitres were placed in a simple tube (red cap) and allowed to clot before being centrifuged (at 2000 rpm for 10 mins). The serum was split into two aliquots:

1. One is allocated for the quick analysis of liver and kidney function tests.
2. The second aliquot is kept at -20 $^{o}$C for further prolactin level determination.

A total of 1.8 millilitres was placed in a citrated tube (blue capped) for the determination of prothrombin time and INR.

## Investigations in the Laboratory

All samples were tested for red blood cell (RBC) count, haemoglobin level, hematocrit value, WBC count (total and differential), and platelet count using a Sysmex KX-21N.

- Alanine transaminase, aspartate transaminase, total bilirubin, albumin, prothrombin time and concentration, and INR are all liver function tests. Using the kinetic approach and the Bio System.
- Kidney Function Tests: Creatinine was measured using a modified Jaffee reaction and the Bio Systems reagent kit given by Bio Systems S.A. (Barcelona, Spain).
- Serological assays for viral indicators such as HBsAg and HCV Using the enzyme-linked Immunosorbent assay approach (ELISA).
- Serum prolactin hormone level.
- Prolactin was quantified using human Electro-Chemiluminescence Immunoassay (ECLIA) kits from Roche Diagnostics GmbH D, Sandhofer, Manheim with an assay range of 4.04-15.2 ng/ml and a lower detection limit of 0.047 ng/ml utilising an equipment called the Cobas Auto-Analyzer.

Biotinylated specific monoclonal antibodies against prolactin create complexes with samples. Human prolactin monoclonal antibody had been used to cover the well. The well's contents were then incubated. Following that, prolactin antibodies tagged with ruthenium complex and streptavidin-coated microparticles were mixed to produce an immunological complex. And biotin-streptavidin combination coats the solid phase. Incubation was repeated, and microparticles were magnetically trapped on the electrode's surface. The application of voltage to an electrode causes chemiluminescence emission, which is measured using a photomultiplier.

**Severity of liver cirrhosis was determined by Modified Child's Pugh score (Table 1) as follow**

**Table 1:** Modified Child's Pugh score

| Points | 1 | 2 | 3 |
|---|---|---|---|
| Encephalopathy | None | Minimal | Advanced (coma) |
| Ascites | Absent | Controlled | Refractory |
| Bilirubin (mg/dl) | < 2 | 2-3 | > 3 |
| Albumin (g/l) | > 3.5 | 3.5 –2.8 | < 2.8 |
| Prothrombin (sec) | < 4 | 4-6 | > 6 |

Child A (5-6) points. Child B (7-9) points. Child C (10-15) points.

## Results

**Table 2:** Comparisons between patients with severe, moderate and mild liver cirrhosis regarding clinical baseline variables

| Parameter | | Severity of cirrhosis | | | | | | Test | P |
|---|---|---|---|---|---|---|---|---|---|
| | | Mild (no.=20) | | Moderate (no.=20) | | Severe (no.=20) | | | |
| | | No. | % | No. | % | No. | % | | |
| Age (years) | Mean ±SD | 52.71±6.75 | | 52.6±4.07 | | 50.81±6.29 | | $\chi^2$= 0.21 | 0.71 |
| Sex | Females | 6 | 30 | 15 | 75 | 14 | 70 | $\chi^2$= 5.50 | 0.06 |
| | Males | 14 | 70 | 5 | 25 | 6 | 30 | | |
| Encephalopathy | No | 14 | 70 | 5 | 25 | 13 | 65 | FET | 0.002 (S) |
| | Grade 1 | 2 | 10 | 4 | 20 | 2 | 10 | | |
| | Grade 2 | 0 | 0.0 | 2 | 10 | 3 | 15 | | |
| | Grade 3 | 4 | 20 | 4 | 20 | 0 | 0 | | |
| | Grade 4 | 0 | 0.0 | 5 | 25 | 2 | 10 | | |
| Degree of ascites | No | 12 | 60 | 10 | 50 | 0 | 0 | FET | <0.00 1 (HS) |
| | Mild | 4 | 20 | 4 | 20 | 3 | 15 | | |
| | Moderate | 4 | 20 | 5 | 25 | 4 | 20 | | |
| | Severe | 0 | 0.0 | 1 | 5 | 13 | 65 | | |

**Table 3:** Comparisons between patients with severe, moderate and mild liver cirrhosis regarding laboratory baseline variables, PV diameter and child Pugh score

| Parameter | Severity of cirrhosis | | | | | | | Test | P |
|---|---|---|---|---|---|---|---|---|---|
| | | Mild (no.=20) | | Moderate (no.=20) | | Server (no.=20) | | | |
| | | No. | % | No. | % | No. | % | | |
| PRL level (ng/ml) | Mean ±SD | 13.95±8.96 | | †24.33±10.68 | | †25.51±18.05 | | $\chi^2$= 13.21 | <0.001 (HS) |
| Albumin (g/dl) | Mean ±SD; | 3.76±0.54; | | 3.18±0.99; | | 2.49±0.78; | | F= 20.92 | <0.001 (HS) |
| Bilirubin (mg/dl) | Mean ±SD | 1.97±0.96 | | 2.54±1.17 | | 3.61±1.25 | | F= 18.16 | <0.001 (HS) |
| Prothrombin time (sec) | Mean ±SD | 5.65±5.1 | | 7.87±4.89 | | 14.74±5.11 | | F= 21.73 | <0.001 (HS) |
| Creatinine (mg/dl) | Mean ±SD | 2.53±1.51 | | 1.88±0.81 | | 2.4±1.34 | | $\chi^2$= 1.41 | 0.57 |
| PV diameter (cm) | Mean ±SD | 12.62±1.22 | | 11.95±1.49 | | 13.09±2.22 | | F= 4.95 | 0.08 |
| Child Pugh score | A | 12 | 57.89 | 2 | 10 | 0 | 0.0 | FET | <0.001 (HS) |
| | B | 7 | 31.58 | 11 | 55 | 1 | 5 | | |
| | C | 3 | 10.53 | 7 | 35 | 19 | 95 | | |
| | Mean ±SD | 6.73±2.16 | | 9.37±2.89 | | 12.16±1.65 | | F= 24.01 | <0.001 (HS) |

**Table 4:** Correlation between serum prolactin level (ng/ml) and estimated parameters

| Parameter | Spearman correlation coefficient (rho; ρ) | P |
|---|---|---|
| Age (years) | 0.012 | 0.47 |
| Albumin (mg/dl) | -0.30 | 0.03 |
| Bilirubin (mg/dl) | 0.35 | 0.01 |
| Prothrombin time (sec) | 0.30 | 0.03 |
| Creatinine (mg/dl) | 0.08 | 0.63 |
| PV diameter (cm) | 0.15 | 0.32 |
| Encephalopathy grades | 0.72 | <0.002 |
| Ascites grades | 0.21 | 0.16 |
| Cirrhosis severity | 0.43 | 0.04 |

This research included 60 patients ranging in age from 35 to 60 years old, with a mean SD of 52.94±6.99 years; there were 35 male patients (58.33 percent) and 25 female patients (41.67 percent). PRL levels range from (5.6-39) ng/ml with a mean S.D of (19.76±10.14 ng/dl). The albumin level ranges from (1.3-4.2) mgdl, with a mean S.D of (3.18±0.95) gdl. Total bilirubin levels range from (1.3-6.8) mg/dl, with a mean standard deviation of (2.71.4 mg/dl). The prothrombin time ranges from (2.8-18.5) sec, with a mean S.D of (8.85.44 sec). Creatinine levels range from (0.7-6) mg/dl, with a mean S.D. of (2.35±1.31 mg/dl). The ultrasonic diameter of the portal vein (PV) varies from (10-19) cm with a mean S.D (13.19±1.84 cm). The child Pugh score ranges from (5 to 14) with a mean S.D of (10.16±4.16). The present investigation found a statistically significant difference between cirrhosis severity and encephalopathy grading. There is a very statistically significant difference between cirrhosis severity and (degree of ascites, PRL level, albumin level, bilirubin level, prothrombin time and Child Pugh score). There is no statistically significant relationship between cirrhosis severity and PV diameter, creatinine level, gender, or age.

- There was a statistically significant rise in PRL levels in moderate and severe liver cirrhosis compared to mild liver cirrhosis.
- Severe liver cirrhosis has a statistically significant lower albumin level than mild and moderate liver cirrhosis.

There is a statistically significant rise in bilirubin levels in severe liver cirrhosis compared to mild and moderate liver cirrhosis. Prothrombin time increased much more in severe liver cirrhosis than in mild and moderate liver cirrhosis. In moderate and severe liver cirrhosis, the Child Pugh score increased much more than in mild liver cirrhosis. (Table 2) as well as (Table 3) A statistically significant negative link existed between blood prolactin levels and albumin levels, while a statistically significant positive correlation existed between serum prolactin levels and bilirubin levels, prothrombin time, and cirrhosis severity. A statistically significant positive connection was also discovered between blood prolactin levels and encephalopathy grades. (Table 4).

There were statistically significant differences between blood prolactin levels and sex, statistically significant differences between serum prolactin levels and hepatic encephalopathy grades, and statistically significant differences between serum prolactin levels and Child grades. There was a statistically significant rise in PRL level in grade 3&4 encephalopathy compared to no encephalopathy. Child Pugh grade C had a statistically significant higher PRL level than Child Pugh grade A. The Roc curve for blood prolactin level as a predictor of severe/moderate liver cirrhosis reveals that at the cutoff point of 19.8 ng/ml, the sensitivity is 68.94%, the specificity is 80.15%, the PPV is 85.5%, and the NPV is 62%.

## Discussion

Cirrhosis is a chronic liver disease that develops gradually and always affects the whole organ. It is the irreversible end result of numerous chronic liver disorders of diverse etiologies or the outcome of long-term exposure to various causes. The severity of morphological alterations is determined by the aetiology and stage of cirrhosis. As a result, there is a broad range of morphological findings and clinical symptoms. This disease's manifestations vary from asymptomatic illnesses, non-specific symptoms, and various test abnormalities to life-threatening consequences [11]. The lactotrophs cells of the anterior pituitary gland manufacture and emit the polypeptide hormone human prolactin (HPL). The human PRL molecule is made up of 199 amino acids (A.A) linked together by three intramolecular disulfide bridges. 2000 (Freeman) The gonadal axis is significantly impacted by liver cirrhosis. These individuals often have hyperprolactinemia as well as hyperestrogenism, which are both responsible for the clinical signs of feminization. Hypogonadism may be caused by hyperprolactinemia and hyperestrogenism [12]. (Arafa *et al.*, 2012). The purpose of this research is to look at blood prolactin levels as a biological measure of severity in liver cirrhosis. The current study found a highly significant relationship between the severity of cirrhosis and PRL level (P 0.001), where serum prolactin hormone level increases with the severity of liver cirrhosis, and this increase in prolactin is primarily attributed to a decrease in dopamine levels in the tuberoinfundibular tract. Few investigations have been conducted on hormonal disturbances in cirrhosis, and the studies have demonstrated reduced T3 and cortisol levels with elevated prolactin in the blood [13]. Decompensated liver function changes the sort of amino acids that reach the central nervous system. The concentration of circulating aromatic amino acids has been reported to rise, increasing the creation of fake neurotransmitters including phenylethanolamine and octopamine.

These erroneous neurotransmitters may impede dopamine release, resulting in hyperprolactinemia. Cirrhotic individuals with hyperprolactinemia and hypogonadism. This is consistent with the findings of the Ferrini *et al.* investigation (2015) [14]. Who reported that individuals with liver cirrhosis had higher oestrogen and prolactin levels and lower blood testosterone levels than normal people? Low testosterone and high prolactin levels were shown to be associated to the severity of cirrhosis. LH and FSH levels were not found to be high in cirrhotic patients; however, a response to external gonadotropins was obtained, and serum testosterone levels increased, which was consistent with the study reported by Ferrini *et al.* (2015) [14], in which the severity of hepatic cirrhosis had a positive correlation with serum prolactin levels. There was a strong negative association between serum prolactin levels and albumin (r=-0.30 p=0.03), which was similar with the findings of Arafa *et al.* (2012) [12]. In contrast, there was a strong inverse relationship between serum prolactin levels and serum albumin (Arafa *et al.*, 2012). There was a strong positive association between serum prolactin level and severity of cirrhosis (r=0.43 p=0.004), which is similar with the findings of Arafa *et al.* (2012), who found that serum prolactin levels rose with development of liver disease from Child A to Child C [12].

## Conclusion

Prolactin levels rise considerably in individuals with severe liver illness, especially those with ascites and hepatic encephalopathy. A high prolactin level might therefore be regarded as a risk factor for liver cirrhosis.

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