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Serum cortisol and prolactin levels as prognostic markers for complications of liver cirrhosis

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Abstract
Background: Several endocrine system abnormalities are linked to liver cirrhosis. The objective of this study was to evaluate the prognostic significance of serum cortisol level and serum prolactin level and complications of liver cirrhosis and its severity and follow up mortality on 90 days.
Methods: This prospective cohort research was done on10 control and 50 patients and, aged more than 18 years old, with liver cirrhosis and/or its complications. Patients were categorized into 3 groups: Group I (25 patients): Compensated cirrhosis. Group II (25 patients): Decompensated cirrhosis. Group III (10 standards): Normal healthy participants.
Results: The sensitivity and specificity for mortality were 82% and 74% for cortisol AM at cut off 101, were 88% and 84% for cortisol PM at cut off 97 ng/dl. Specificity and sensitivity for mortality depended on prolactin level cut off 20 were 68%, 72% respectively. In univariate all items except spontaneous bacterial peritonitis were significant and multivariate all items except urea, creatinine, encephalopathy and hepatorenal syndrome were significant.
Conclusions: Higher prolactin and lower cortisol levels could therefore be considered as diagnostic factor of liver cirrhosis Child and its complications. Therefore, cortisol and prolactin can be regarded as a novel prognostic factors of liver cirrhosis and prediction of mortality and morbidity.

Keywords: Cortisol, prolactin, prognostic markers, complications, liver cirrhosis

Introduction
Liver cirrhosis is often linked to a range of disruptions in the endocrine system, which are mostly attributed to the impaired clearance of hormones by the diseased liver. The pathophysiology of disrupted hormonal activity in liver cirrhosis is characterized by complicated changes in secretion and feedback systems [1].
The topic of prolactin levels in individuals with hepatic impairment has been extensively discussed and analysed. The primary cause of elevated prolactin levels is mostly attributed to a decrease in dopamine levels inside the tuberoinfundibular tract [2]. The release of prolactin is primarily controlled by tonic hypothalamic inhibition mediated by dopamine, as well as the stimulatory effects of hypothalamic releasing factors and circulating oestrogens. Elevated levels of circulating oestrogen in liver cirrhosis may be attributed to an augmented peripheral aromatization of testosterone via androstenedione, as well as a reduced hepatic clearance [3].
These estrogenic elicit the release of prolactin by disrupting the production of dopamine from the brain, and by exerting a direct impact on the anterior pituitary gland [4]. Cortisol serves as the primary glucocorticoid in the human body, with its circulating levels being regulated by the hypothalamus-pituitary-adrenal (HPA) axis. The synthesis and secretion of glucocorticoids (GCs) are subject to intricate circadian and ultradian control by the periventricular nucleus located in the hypothalamus [5].
Numerous prognostic scores have been created with the aim of assessing the survival rates of individuals diagnosed with liver cirrhosis. However, the existing prognostic scores suffer from several limitations, prompting a growing interest in the discovery of novel biomarkers that might provide more knowledge. The determination of prognostic indicators in patients with cirrhosis may also be achieved by the measurement of cortisol levels [6].
The prevalence of liver cirrhosis is increasing, particularly among the Egyptian population. However, the prognostic criteria, such as the Child Pugh scoring system, have proven inadequate in providing a comprehensive understanding of the possibility of problems in

patients with liver cirrhosis.
The objective of this study was to evaluate the predictive value of blood prolactin and cortisol levels in relation to the severity of liver cirrhosis and its associated comorbidities, as well as their impact on mortality during a 90-day follow-up period.

Patients and Methods

This research used a prospective cohort design to investigate a group of 50 patients and 10 control subjects who were over the age of 18 and had been diagnosed with liver cirrhosis and/or its associated comorbidities. The research was conducted between February 2021 and July 2021 subsequent to obtaining clearance from the Ethical Committee of Tanta University Hospitals, Egypt. All patients provided informed written permission.

The exclusion criteria for this study included the following conditions

A previous history of cranial surgery or irradiation, chest wall trauma, diseases affecting the pituitary or hypothalamus, chronic renal failure, herpes zoster, and use of prolactin-elevating medications (e.g., neuroleptics, metoclopramide, methyl dopa, reserpine, cyproterone acetate, aldosterone antagonists, morphine, cimetidine, metiamide, or any drugs that affect cortisol or prolactin levels.

Patients were categorized into to 3 groups

1. **Group I (N=25):** In compensated cirrhosis, there were no vascular or parenchymatous indications of liver failure, thereby preserving liver function.
2. **Group II (N=25):** Decompensated cirrhosis: there is impairment of liver functions, with vascular or parenchymatous signs of liver failure.
3. **Group III (N=10):** Normal healthy individuals were confirmed as free from liver cirrhosis by physical examination, laboratory investigations and pelvi - abdomianl ultrasonography.

A comprehensive medical history was obtained from both patients and controls, and a range of laboratory and radiological tests were performed on the subjects, including abdominal ultrasonography, complete blood count (CBC), random blood sugar, hepatic function, and renal function assessments (blood urea, serum creatinine, urine analysis, prothrombin time, international normalized ratio (INR), and serum Na+). In addition, estimates were made for the Child-Pugh and model for end-stage liver disease (MELD) scores.
Measurement of serum cortisol and prolactin by ELISA was done for all patients and controls.

Specimen collection

A venous blood sample was collected from both the patients and the control group using conventional venipuncture techniques, ensuring perfect aseptic conditions. A portion of the collected serum was used for regular laboratory studies, while another portion was held at a temperature of -20 °C until the time of conducting the Cortisol and Prolactin assays.

Determination of the serum cortisol

By using ELISA kits (Manufactured by Monocent, Inc. 9025 Eton Ave. Ste C, CA91304, USA). The Monocent, Inc.'s Cortisol kit is a solid phase competitive ELISA. The samples are introduced into the wells that have been coated with streptavidin, together with the functioning Cortisol-HRP Conjugate and anti-cortisol biotin solution. The presence of cortisol in the patient's blood results in a competitive interaction with the cortisol enzyme (HRP) conjugate, as both molecules vie for binding sites. The unbound cortisol and cortisol enzyme conjugate are removed by rinsing with a washing buffer. The intensity of colour in the samples exhibits an inverse relationship with the concentration of cortisol upon the introduction of substrate. A positive correlation was seen between the colour intensity and the levels of cortisol in the sample.
Determination of the serum prolactin by using ELISA kits (Manufactured by Chemux Bioscience, 385 Oyster Point Blvd Suite 5-6., South San Francisco, CA 94080). Test principle: The solid phase enzyme coupled immunoabsorbent assay is the basis of the prolactin Quantitative Test Kit. The test technique uses a mouse monoclonal anti-prolactin antibody in the conjugate solution of horseradish peroxidase and one anti-prolactin antibody for solid phase immobilization (microtiter wells). Enzyme-linked antibodies and the solid phase sandwiched the prolactin molecules as a consequence of the test samples and antibodies reacting concurrently. A TMB solution is added, and after 20 minutes of incubation, a blue colour develops. When 2NHCL is added, the colour development is halted, turning the colour yellow and allowing for spectrophotometric measurement at 450 nm. The test sample's colour intensity and prolactin content are directly correlated.

Statistical analysis

The statistical analysis was conducted using SPSS v26, a software developed by IBM Inc. in Chicago, IL, USA. The quantitative variables were reported as the mean and standard deviation (SD) and were compared across the three groups using analysis of variance (ANOVA) with a post hoc test (Tukey). The qualitative variables were represented in terms of frequency and percentage (%) and were subjected to analysis using the Chi-square test. A two-tailed P-value less than 0.05 was deemed to be statistically significant.

Results

There was significant difference were observed between controls and patients as regard aetiology and no difference as regard gender and age. Table 1.

Table 1: The table is shown relationship between baseline features of patients and controls

		Compensated	Decompensated	Control	p. value
Age		49.88±8.93	51.44±6.36	49.70±8.81	0.740
Gender	13 (52%)	13 (52%)	11 (44%)	5 (50%)	0.846
	12 (48%)	12 (48%)	14 (55%)	5 (50%)	
Etiology	22 (88%)	22 (88%)	19 (76%)	-	0.027*
	0 (0%)	0 (0%)	2 (8%)	-	
	3 (12%)	3 (12%)	0 (0%)	-	
	0 (0%)	0 (0%)	4 (16%)	-	

Data are demonstrated as Mean ± SD or frequency (%)

Regarding urea, creatinine, bilirubin, albumin, INR, serum Na, MELD score, serum prolactin, serum cortisol AM there were statistically difference between compensated and decompensated patients, decompensated and control with creatinine and no important variance was observed among control and compensated and the relation between compensated, decompensated and control not significant. Regarding portal vein diameter (PV. Dia), there was statistically difference between compensated and decompensated patients, decompensated and control. And between compensated and control and the relation between compensated, decompensated and control was significant. Regarding serum cortisol PM there was difference between compensated and decompensated patients, no important variance between decompensated and control and no significant difference was observed between compensated and control and the relation between compensated, decompensated and control with serum cortisol PM was significant. Table 2.

Table 2: Comparison among studied groups regarding MELD score and laboratory investigations

			p. value	
Urea (mg/dl)	Compensated	18.68±7.94	0.001*	P1=0.005*
	Decompensated	18.68±7.94		P2=0.086
	Control	18.68±7.94		P3=0.001*
Creatinine (mg/dl)	Compensated	1.16±0.40	0.009	P1=0.019*
	Decompensated	1.50±0.63		P2=0.293
	Control	0.97±0.13		P3=0.006*
Bilirubin (mg/dl)	Compensated	1.24±0.18	0.010*	P1=0.001*
	Decompensated	2.69±0.97		P2=0.603
	Control	1.11±0.17		P3=0.001*
Albumin (mg/dl)	Compensated	3.79±0.30	0.001*	P1=0.001*
	Decompensated	2.71±0.45		P2=-0.091
	Control	4.03±0.28		P3=0.001*
INR	Compensated	1.17±0.19	0.010*	P1=0.001*
	Decompensated	1.71±0.33		P2=0.179
	Control	1.04±0.11		P3=0.001*
PV. Dia (mm)	Compensated	11.96±1.59	0.001*	P1=0.001*
	Decompensated	16.16±1.93		P2=0.001*
	Control	9.40±1.65		P3=0.001*
Serum Na (mEq/L)	Compensated	139.28±3.80	0.010*	P1=0.001*
	Decompensated	131.24±8.35		P2=0.698
	Control	138.40±2.32		P3=0.002*
MELD Score	Compensated	7.15±2.59	0.001*	P1=0.001*
	Decompensated	19.24±16.19		P2=0.871
	Control	6.50±1.27		P3=0.002*
Serum prolactin (ng/ml)	Compensated	15.52±5.26	0.010*	P1=0.001*
	Decompensated	34.16±11.55		P2=0.238
	Control	11.80±3.16		P3=0.001*
Serum cortisol AM (ng/ml)	Compensated	132.72±56.67	0.001*	P1=0.001*
	Decompensated	65.32±43.85		P2=0.239
	Control	154.60±40.44		P3=0.001*
Serum cortisol PM (ng/ml)	Compensated	81.74±55.39	0.047*	P1=0.028*
	Decompensated	52.04±44.00		P2=0.355
	Control	65.50±19.04		P3=0.443

Data are presented as Mean ± SD. P1: significant. P value between compensated and decompensated patients. P2: significant. P value between compensated and control. P3: significant. P value between decompensated and control. INR: international normalized ratio. PV. Dia: portal vein diameter. MELD: Model for end-stage liver disease.

The relation between compensated, decompensated and control with varices, ascites, encephalopathy, gastrointestinal tract (GIT) haemorrhage, hepatorenal syndrome and spontaneous bacterial peritonitis (SBP) were significant (p value <0.05).

Table 3: Comparison among studied groups according to varices, ascites, encephalopathy, GIT haemorrhage, hepatorenal syndrome and SBP

		Compensated	Decompensated	Control	P-value
Varices	No	25 (100.0%)	7 (28.0%)	10 (100.0%)	0.001*
	Yes	0 (.0%)	18 (72.0%)	0 (.0%)	
Ascites	No	25 (100.0%)	4 (16.0%)	10 (100.0%)	0.001*
	Mild	0 (.0%)	7 (28.0%)	0 (.0%)	
	Moderate	0 (.0%)	9 (36.0%)	0 (.0%)	
	Severe	0 (.0%)	5 (20.0%)	0 (.0%)	
Encephalopathy	No	23 (92.0%)	7 (28.0%)	10 (100.0%)	0.001*
	1	2 (8.0%)	4 (16.0%)	0 (.0%)	
	2	0 (.0%)	2 (8.0%)	0 (.0%)	

	3	0 (.0%)	9 (36.0%)	0 (.0%)	
	4	0 (.0%)	3 (12.0%)	0 (.0%)	
GIT hemorrhage	No	25 (100.0%)	20 (80.0%)	10 (100.0%)	0.018*
	Yes	0 (0.0%)	5 (20.0%)	0 (.0%)	
Hepatorenal syndrome	No	25 (100.0%)	12 (48.0%)	10 (100.0%)	0.001*
	Yes	0 (0.0%)	13 (52.0%)	0 (.0%)	
SBP	No	25 (100.0%)	17 (68.0%)	10 (100.0%)	0.002*
	Yes	0 (0.0%)	8 (32.0%)	0 (.0%)	

Data are presented as frequency (%). P value<0.001 significant. P value<0.05 significant. P1: significant. P value between compensated and decompensated patients. P2: significant. P value between compensated and control. P3: significant. P value between decompensated and control. SBP: spontaneous bacterial peritonitis. GIT: gastrointestinal tract

Regarding child score the relation between patients and control with child plough grading was significant (p value<0.05). Regarding 3-month mortality there was no significant relation between controls and patients. Table 3

Table 4: Comparison between studied groups as regard Child Score and 3-month mortality

		Patient	Control	
Child Score	A	25 (50.0%)	10 (100.0%)	0.014*
	B	9 (18.0%)	0 (.0%)	
	C	16 (32.0%)	0 (.0%)	
3-month mortality	Survivor	40 (80.0%)	10 (100.0%)	0.121
	Dead	10 (20.0%)	0 (.0%)	

Data are presented as frequency (%)

A statistically significant negative association was observed between serum prolactin levels and albumin levels, as well as serum sodium levels. Conversely, a statistically significant positive correlation was found between serum prolactin levels and bilirubin levels, urea levels, creatinine levels, international normalized ratio (INR), and portal vein (PV) measurements. The topic of discussion pertains to the etiologic and associated consequences of liver cirrhosis. (p value=0.001). Moreover, there was a statistically significant positive correlation was found between serum cortisol AM, and serum Na and significant negative correlation with Age, Urea, Creatinine, Bilirubin, INR, PV. Dia, hepatorenal syndrome and other parameters (p value<0.05) and as regard cortisol PM there was a statistically significant positive correlation was found between serum cortisol PM with albumin and Serum Na and no significant correlation with Age, Urea, creatinine, bilirubin, INR, PV. Dia (p value<0.05). There is significant negative correlation between serum cortisol AM with HR hepatorenal syndrome (p value=0.001) and significant negative correlation with other parameters. As regard serum cortisol PM there is significant negative correlation between serum cortisol PM with varices, ascites, and hepatorenal syndrome and no correlation with encephalopathy and GIT haemorrhage. Table 5.

Table 5: Correlation of serum cortisol AM, PM and serum prolactin with different parameters and complications of liver cirrhosis

	Serum cortisol AM		Serum cortisol PM		Serum prolactin	
	r	P value	r	P value	r	P value
Age	-0.300	0.034*	-0.060	0.679	0.164	0.255
Urea	-0.291	0.040*	-0.221	0.123	0.529	0.001*
Creatinine	-0.301	0.033*	-0.188	0.191	0.321	0.023*
Bilirubin	-0.426	0.002*	-0.209	0.145	0.595	0.001*
Albumin	0.520	0.001*	0.347	0.014*	-0.639	0.001*
INR	-0.465	0.001*	-0.392	0.005*	0.699	0.001*
PV. Dia	-0.471	0.001*	-0.330	0.019*	0.654	0.001*
Serum Na	0.524	0.001*	0.365	0.009*	-0.512	0.001*
Complications						
Varices	-0.422	0.002*	-0.350	0.013*	0.484	0.001*
Ascites	-0.558	0.001*	-0.450	0.001*	0.722	0.001*
Encephalopathy	-0.411	0.003*	-0.255	0.074	0.589	0.001*
GIT haemorrhage	-0.141	0.328	-0.078	0.591	0.293	0.039*
Hepatorenal syndrome	-0.438	0.001*	-0.285	0.044*	0.740	0.001*
SBP	-0.316	0.026*	0.003	0.983	0.444	0.001*

INR: international normalized ratio. PV. Dia: portal vein Dia meter. MELD: Model for end-stage liver disease. SBP: spontaneous bacterial peritonitis. GIT: gastrointestinal tract

40 patients survived at age between (38-67). 21 of them was male and19 was female and 10 patients died at age between (40-66) 3 of them was male and 7 was female within 3 month follow up mortality and morbidity. There was significant positive relation between survivors and dead liver cirrhotic patients with different parameters, varices, ascites, encephalopathy, SBP, serum prolactin, serum cortisol AM, PM and child score. There was no relation between survivors and dead liver cirrhotic patients with GIT haemorrhage. Table 6

Table 6: Comparison between survivors and dead as regard demographic data, different parameters, complications of liver cirrhosis, serum prolactin, serum cortisol AM andserum cortisol PM

		Survivor	Dead	p. value
Age		52.18±8.86	56.80±8.47	0.143
Sex	**Male (%)**	21 (52.5%)	3 (30%)	0.203

	Female (%)	19 (47.5%)	7 (70%)	
Urea		19.93±8.18	32.80±13.70	0.001*
Creatinine		1.21±0.38	1.80±0.84	0.002*
Bilirubin		1.68±0.77	3.09±1.08	0.001*
Albumin		3.45±0.56	2.45±0.42	0.001*
INR		1.33±0.33	1.87±0.25	0.001*
PV. Dia		13.23±2.30	17.40±1.65	0.001*
serum Na		137.38±5.30	126.80±9.65	0.001*
MELD Score		8.31±4.85	32.73±16.97	0.001*
serum prolactin		22.85±11.09	32.80±17.05	0.028*
serum cortisol AM		110.20±60.69	54.30±35.54	0.001*
serum cortisol PM		74.87±52.41	35.00±35.43	0.028*
Complications of liver cirrhosis				
Varices	No	31 (77.5%)	1 (10.0%)	0.001*
	Yes	9 (22.5%)	9 (90.0%)	
Ascites	No	28 (70.0%)	1 (10.0%)	0.001*
	Mild	7 (17.5%)	0 (.0%)	
	Moderate	4 (10.0%)	5 (50.0%)	
	Severe	1 (2.5%)	4 (40.0%)	
Encephalopathy	No	27 (67.5%)	3 (30.0%)	0.002*
	1	6 (15.0%)	0 (.0%)	
	2	1 (2.5%)	1 (10.0%)	
	3	6 (15.0%)	3 (30.0%)	
	4	0 (.0%)	3 (30.0%)	
GIT haemorrhage	No	36 (90.0%)	9 (90.0%)	1.0
	Yes	4 (10.0%)	1 (10.0%)	
SBP	No	36 (90.0%)	6 (60.0%)	0.001*
	Yes	4 (10.0%)	4 (40.0%)	
Child Score				
A		25 (62.5%)	0 (.0%)	0.001*
B		9 (22.5%)	0 (.0%)	
C		6 (15.0%)	10 (100.0%)	
Serum prolactin		22.85±11.09	32.80±17.05	0.028*
Serum cortisol AM		110.20±60.69	54.30±35.54	0.001*
Serum cortisol PM		74.87±52.41	35.00±35.43	0.028*

Data are presented as Mean ± SD. or frequency (%). INR: international normalized ratio. PV. Dia: portal vein Dia meter. MELD: Model for end-stage liver disease. SBP: spontaneous bacterial peritonitis. GIT: gastrointestinal tract.

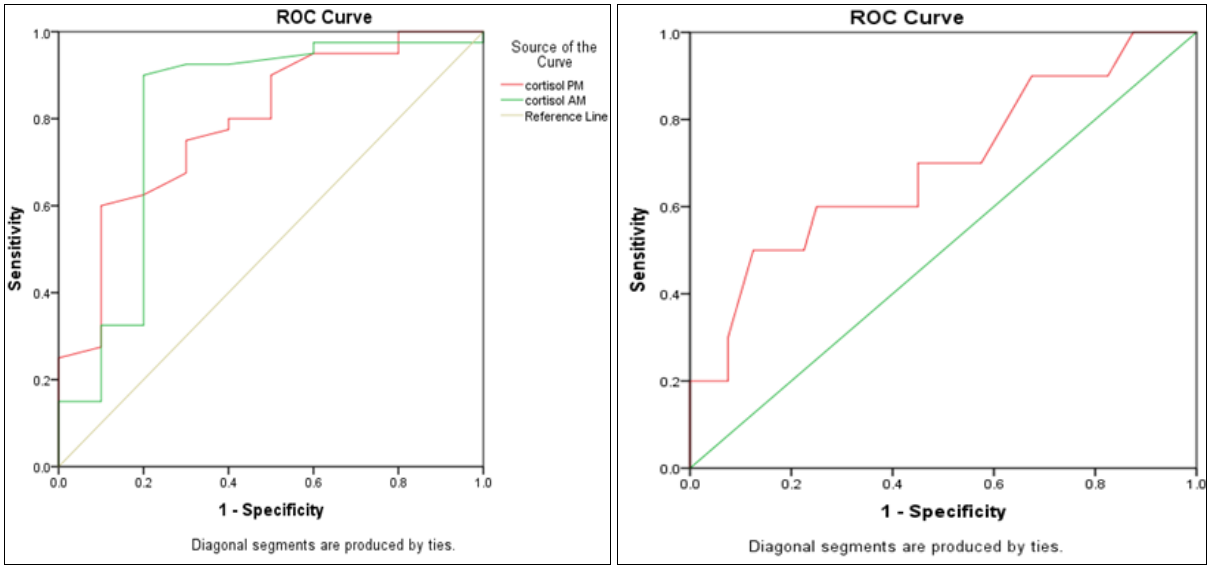
The relation between child score with MELD score. Serum prolactin, serum cortisol AM and serum cortisol PM was significant. Table 7.

Table 7: Comparison between child score with MELD score, serum prolactin, serum cortisol AM and PM

			p. value	
MELD Score	A	7.15±2.59	0.001*	P1=0.482
	B	10.07±7.25		P2= .001*
	C	24.41±17.68		P3=0.002*
Serum prolactin	A	15.52±5.26	0.001*	P1= 0.001*
	B	24.456±10.57		P2=0.001*
	C	39.56±8.21		P3=0.001*
Serum cortisol AM	A	132.72±56.67	0.005*	P1= 0.033*
	B	90.67±55.65		P2= 0.002*
	C	51.06±28.67		P3=0.060
Serum cortisol PM	A	81.74±55.39	0.001*	P1= 0.492
	B	93.89±46.94		P2= .001*
	C	28.50±16.75		P3=0.001*

Data are presented as Mean± SD. P value<0.001 significant. P value<0.05 significant. P1: significant. P value between compensated and decompensated patients. P2: significant. P value between compensated and control. P3: significant. P value between decompensated and control.

The sensitivity and specificity values for mortality prediction using a cortisol AM level cut-off of 101 were found to be 82% and 74% respectively. Similarly, the sensitivity and specificity values for mortality prediction using a cortisol PM level cut-off of 97 ng/dl were determined to be 88.84% respectively. The sensitivity and specificity values for death, using a prolactin level cut-off of 20, were found to be 68% and 72% respectively. The sensitivity and specificity values for death, using a prolactin level cut-off of 20, were found to be 68.72% and respectively. Figure 1.



a) b)

Fig 1: ROC curve showing mortality based on (A) cortisol (B) prolactin level

In univariate all items except SBP significant and multivariate all items except urea, creatinine, encephalopathy and hepatorenal syndrome were significant. Table 8.

Table 8: Prognostic Independent Risk Factors and Their Logistic Regression Analysis for Patients' 90-Day Mortality

	Univariate		Multivariate	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Urea	0.597 (0.264 – 0.793)	0.034*	0.854 (0.476 – 1.253)	0.106
Creatinine	0.689 (0.572 – 0.764)	0.039*	0.625 (0.397 – 1.523)	0.126
Bilirubin	0.542 (0.176– 0.732)	0.016*	0.732 (0.469 – 0.761)	0.042*
Albumin	2.531 (1.488 – 4.362)	0.005*	1.875 (1.036 – 3.654)	0.027*
INR	0.762 (0.472 – 0.732)	0.021*	0.732 (0.524 – 0.859)	0.036*
PV. Dia	0.584 (0.413 – 0.802)	0.001*	0.493 (0.176 – 0.659)	0.031*
Serum Na	2.954 (1.578 – 6.524)	0.004*	2.035 (1.742 – 5.945)	0.027*
MELD Score	0.529 (0.329 – 0.753)	0.001*	0.475 (0.231– 0.856)	0.009*
Serum prolactin	0.384 (0.035 – 0.583)	0.001*	0.436 (0.163 – 0.598)	0.012*
Serum cortisol AM	1.745 (1.302 – 3.204)	0.001*	1.352 (1.036 – 2.521)	0.018*
Serum cortisol PM	2.215 (1.524 – 4.532)	0.001*	1.865 (1.147 – 3.318)	0.028*
Varices	0.482 (0.230 – 0.754)	0.002*	0.621 (0.296 – 0.754)	0.042*
Ascites	0.531 (0.418 – 0.785)	0.001*	0.621 (0.287 – 0.743)	0.024*
Encphalopathy	0.531 (0.287 – 0.745)	0.006*	0.854 (0.716 – 2.451)	0.137
Hepatorenal syndrome	0.624 (0.441 – 0.765)	0.018*	0.542 (0.361 – 1.326)	0.184
SBP	0.624 (0.241 – 2.305)	0.205	-	-
Child Score	0.351 (0.234 – 0.453)	0.001*	0.561 (0.307 – 0.856)	0.031*

INR: international normalized ratio. PV. Dia: portal vein Dia meter. MELD: Model for end-stage liver disease. SBP: spontaneous bacterial peritonitis

Discussion

The current investigation highlights the significant involvement of cortisol and prolactin in the progression and severity of liver failure, as well as their potential as prognostic indicators for death in individuals diagnosed with liver cirrhosis.

The current investigation observed elevated levels of prolactin in patients classified as Child Pugh Class B and C, with the highest recorded level being 66 ng/ml in a patient classified as Class C. Moreover, Zeitz *et al.* [7] demonstrated that the levels of prolactin were found to be significantly elevated in those classified as Child Pugh Class C.

The findings of this research indicate a positive correlation between elevated blood prolactin levels and the severity of problems observed in patients with liver cirrhosis, namely those experiencing decompensation. These consequences include hepatic encephalopathy, hepatic renal syndrome, coagulopathy, oesophageal varices with upper gastrointestinal bleeding, and spontaneous bacterial peritonitis. In a study conducted by Koller *et al.* [8], it was shown that patients with more severe ascites and encephalopathy, together with higher INR levels, had elevated prolactin scores. In a study conducted by Arafa *et al.* [9], it was shown that individuals diagnosed with hepatic encephalopathy had elevated levels of prolactin, with a positive correlation between the severity of encephalopathy and the magnitude of prolactin rise.

In the current research, the assessment of individuals suffering from end-stage liver disease was effectively conducted using the Model for MELD score, which exhibits a positive correlation with mortality. This finding corresponds to the research conducted by Kamath *et al.* [10].

The current investigation revealed a positive correlation between the amount of prolactin and the MELD score. This

observation implies that the measurement of prolactin levels might serve as a potential signal for assessing the extent of liver failure. The no-survival group had substantially elevated prolactin levels compared to the survival group over the 90-day follow-up period. According to Fawzy *et al*. [11], there is a proposed correlation between elevated prolactin levels and increased death rates among patients.

However, Marik *et al*. [12] found that adrenal insufficiency was present in 72% of liver failure patients.

According to Marik *et al*. [13], the current study's findings suggest that decreased cortisol levels are likely to correlate adversely with the degree of liver failure and may portend a bad prognosis.

The current research found that cortisol levels were positively correlated with patient survival rates, and that cortisol was a critical factor in predicting liver failure death. According to Piano *et al*. [14], as liver failure worsened, peripheral blood cortisol levels dropped and the incidence of RAI progressively rose ($p< 0.05$).

According to the current research, cortisol levels dropped as MELD scores rose. This suggested that cortisol levels could be one way to measure the mortality caused by liver disease. Ninety days after follow-up, cortisol levels in the no-survival group were considerably lower than those in the survival group. Previous research has shown a correlation between cortisol levels and the prognosis of decompensated cirrhosis, chronic liver disease, and liver failure. It has also been proposed that a decrease in cortisol levels is connected with an increase in patient mortality [15].

In the current research, prolactin and cortisol levels were an independent risk factor, while PV Diameter, MELD score, Child Score, and Ascities were independent variables impacting the prognosis of patients with liver failure at 90 days. Binary logistic regression analysis, as reported by Zhang *et al*. [16], revealed that cortisol level and MELD score were independent risk factors.

Levels below this cut off were associated with increased mortality and morbidity, and this was similar to a study by Zhang *et al*. [16] in which the cut-off values for the prediction of mortality were identified for cortisol levels (252.3 nmol/L equal to 105 ng\dl). In this study, the sensitivity and specificity for mortality based on cortisol AM level cut off 40ng/dl was 92,80, and the sensitivity and specificity for mortality based on cortisol PM level cut off 25 ng/dl was 88,80, respectively. Conversely, in this investigation, the sensitivity and specificity for death determined by the prolactin level cutoff of 37ng/dl were, respectively, 92 and 80. Levels beyond this threshold were decompensated with various liver cirrhosis consequences.

Sun *et al*.'s study [17] examined the correlation between peripheral blood cortisol levels and the health and prognosis of individuals suffering from chronic acute liver failure linked to HBV.

The level of cortisol in the current research progressively dropped as the degree of liver failure increased. Furthermore, in line with Sun *et al*. [17], cortisol levels rose with time in the survival group and fell over time in the no-survival group. Additionally, according to Fan *et al*. [18], the cortisol level in the group experiencing liver failure in its early stages (17.97±3.16 μg/dL) was substantially greater than the levels in the groups experiencing liver failure in its medium stages (11.01±2.94 μg/dL) and end stages (6.66±2.60 μg/dL). ALB, MELD, and cortisol were suggested to be independent risk factors for the prognosis of patients with HBV-associated acute on chronic liver failure after they observed the dynamic pattern of serum cortisol level in patients with HBV-associated liver failure and discovered that cortisol levels increased in the survival group.

It is theoretical to utilize cortisol when assessing the prognosis of patients with liver failure after 90 days since our research revealed a correlation between the level of cortisol and the degree of liver failure.

This research was carried out with a small sample size; therefore, it still has a few constraints.

Conclusion

Higher prolactin and lower cortisol levels could therefore be considered as diagnostic factor of liver cirrhosis Child Childs and its complications. Therefore, cortisol and prolactin can be regarded as a novel prognostic factors of liver cirrhosis and prediction of mortality and morbidity.

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