ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 07, Issue, 08, pp.14787-14791, August, 2017

ORIGINAL RESEARCH ARTICLE

Open Access

SERUM PROLACTIN LEVEL AS A BIOLOGICAL MARKER OF SEVERITY IN LIVER CIRRHOSIS

[1]Ramy a. Metwally, [1]Mahmoud Rizk and [2,*]Mohamed Ali Awadein

[1]Internal Medicine Department, Gastroenterology and Hepatology Unit, Faculty of Medicine, Benha University, Egypt
[2]Lecturer in Internal Medicine Department MUST University, Egypt

ARTICLE INFO

Article History:
Received 14th May, 2017
Received in revised form
25th June, 2017
Accepted 23rd July, 2017
Published online 30th August, 2017

Keywords:
AFP, Hepatocellular Carcinoma,
Gene expression,
Cirrhosis,
Golgi protein 73.

ABSTRACT

Background: Cirrhosis of the liver is a chronic disease that involves the whole organ. In liver cirrhosis the gonadal axis is affected. Hyperprolactinemia is often present in these patients as well as hyperestrogenemia, both are responsible for the clinical characteristics of feminization.
Patients and Methods: We investigated 50 patients with cirrhosis. The diagnosis of cirrhosis was based on biochemical evidence and clinical diagnosis including ascites or encephalopathy. Also prognostic indices (Child-Pugh) and prolactin levels are assessed.
Results: Mean age was 51.94±5.99. Mean Child-Pugh score was 9.16±3.16. Mean prolactin levels were 18.76±9.14 ng/ml. Patients with hepatic encephalopathy compared with patients without encephalopathy had significantly higher levels of prolactin. Prolactin levels were also significantly related to ascites degree. In regression analysis prolactin level was significantly dependent on Child-Pugh score.
Conclusions: Prolactin level increases significantly with severity of liver disease particularly in patients with ascites and hepatic encephalopathy. High prolactin level could therefore be considered as a negative prognostic marker of liver cirrhosis.

Corresponding author

Citation: Ramy a. Metwally, Mahmoud Rizk and Mohamed Ali Awadein. 2017. "Serum Prolactin Level as a Biological Marker of Severity in Liver Cirrhosis", *International Journal of Development Research*, 7, (08), 14787-14791.

INTRODUCTION

Liver cirrhosis is the commonest outcome of the liver parenchymal disease due to variety of etiology. liver cirrhosis is reported to further complicate itself into portal hypertension, liver failure and hepatocellular carcinoma (Song *et al*., 2006). Hepatic encephalopathy and ascites are the commonest complications of liver cirrhosis and are associated with a poor quality of life, increased risk of infection, renal failure and endocrinal disturbance (Fullwood, 2014). Prolactin (PRL) is a pituitary hormone that stimulates breast development and milk production in women. Prolactin has no known normal function in men. Physiologically, PRL, is a polypeptide hormone consisting of 199 amino acids. It is regulated by hypothalamic factors. These include prolactin-releasing factors (PRFs) and prolactin-inhibitory factors (PIFs) (Cho, 2013; Maiter, 2014).

Abnormally higher level of serum prolactin hormone in women leads to menstrual dysfunction, amenorrhoea, galactorrhoea, infertility, hirsutism and reduced libido while, the increased level of prolactin hormone in men has a direct reversible effect on the hypothalamus, causing secondary hypogonadism which results in erectile dysfunction and reduced libido (Shindel, 2014). There are many physiological causes of high level of prolactin hormone as pregnancy, puerperium and breast stimulation. Pathological causes include pituitary tumours, head injury, brain surgery, chronic renal failure, hypothyroidism, cushing's syndrome, severe liver disease especially cirrhosis, coeliac disease and polycystic ovarian syndrome (Kars *et al*., 2010; Cheng *et al*., 2015). Many hormonal disturbances occur in liver cirrhosis. It was thought that these disturbances were caused mainly by ineffective elimination of hormones by the diseased liver.

It is now known that the pathogenesis of disturbed hormonal function in liver cirrhosis is rather more complex involving disturbed secretion and feedback mechanisms as well. In fact, in liver disease the metabolic clearance rate of sex-steroids for instance is not significantly altered. The most striking hormonal syndrome associated with the liver cirrhosis is the feminization process which occurs in male patients by percentage from 40 to 50% of male cirrhotic patients (Patel, 2015). Feminization process is characterized by a feminine distribution of hair, gynecomastia, palmar erythema, formation of spider nevi, impotence, infertility and disturbed gonadal function. The role of changes in androgen and estrogen metabolism in causing this process has been elucidated to a large extent and has been the subject of extensive research in recent years (Nieddu, 2010). In the current study, we aimed to assess serum prolactin level as a biological marker of severity in liver cirrhosis.

Patients and Method

This cross-sectional study includes 50 patients with chronic liver disease (CLD) who were admitted to Internal Medicine Department and Hepatolog, Gastroenterology, and Infectious Diseases Departments, Benha University Hospita, Egypt. Ninteen patients are females and thirty-one patients are males. Their ages range from 38 to 60 years with a mean ±SD of 51.94±5.99. Studied cases are classified into three groups according to Modified Child's Pugh score:

- **Group1**; includes 19 patients with mild liver cirrhosis.
- **Group2**; includes 15 patients with moderate liver cirrhosis.
- **Group3**; includes 16 patients with severe liver cirrhosis.

Inclusion criteria: All patients above 18 years of age, both sex, with proven liver cirrhosis. Presence of stigmata of chronic liver disease were considered for the support of the diagnosis.

Exclusion Criteria: Non cirrhotic hepatitis C virus (HCV) or hepatitis B virus (HBV) patients. Patients less than 18 years old. Patients receiving interferon therapy. Patients diagnosed with endocrinal disorders. Pregnant and lactating women. Patients on concomitant psychotropic agents. Patients receiving any drugs that influence prolactin level.

Ethical considerations: Informed medical consent was obtained from each patient or his/her relative to participate into the study. The study was approved by Scientific Research Committe of Benha University.

All patients were subjected to the following: History taking including age, sex, past history of risk factors for chronic liver disease as blood transfusion and operations. Also general and local examination was performed to every patient with stress on signs of chronic liver disease e.g jaundice, ascites, palmar erythema, spider naevi, liver size, spleen size, encephalopathy and lower limb edema. Abdominal ultrasonography is done for all subjects. The following laboratory investigations are done for each patient: Seven milliliters of venous blood were withdrawn under aseptic precautions after fasting for 10-12 hours and distributed as follows: two milliliters whole blood was put in EDETA vacutainer (violet cap) and mixed up & down gently and is used to measure CBC. Three milliliters were put in plain tube (red cap) and left to clot then centrifuged (at 2000 rpm for 10 mins). The separated serum was divided into two aliquots:

- One is designated for the immediate assay of liver function tests and kidney function test.
- The second aliquot is stored at -20ºC for subsequent assay of prolactin level.

1.8 milliliters was put in citrated tube(blue topped) for assay of prothrombin time and INR

Laboratory Investigations

CBC: was done for all samples using **Sysmex KX-21N** for red blood cell (RBC) count, hemoglobin level, hematocrite value, WBC count (total and differential) and platelet count.

- **Liver Function Tests:** Alanine transaminase, aspartate transaminase, total bilirubin, albumin, prothrombin time & concentration and INR. Applying kinetic method and using BioSystem.
- **Kidney Function Tests**: Creatinine evaluated with the BioSystems reagent kit provided by BioSystems S.A. (Barcelona, Spain) by modified Jaffee reaction.
- **Serological tests for viral markers:** HBsAg & HCV Abs By using enzyme – linked immunosorbent assay technique (ELISA).
- **Prolactin hormone serum level:**
- Prolactin was measured quantitatively using human Electro-Chemiluminescence Immunoassay (ECLIA) kits provided by Roche Diagnostics GmbH D, Sandhofer, Manheim (reference No. 03203093) with assay range (4.04-15.2 ng/ml), lower detection limit 0.047 ng/ml by device named Cobas Auto-Analyzer.

Test principle: Biotinylated specific monoclonal antibody against prolactin form complex with samples. The well had been precoated with human prolactin monoclonal antibody. The contents of the well were then incubated. Thereafter, prolactin antibodies labeled with ruthenium complex and combined with streptavidin-coated microparticles were added to form an immune complex. And become coated to solid phase by biotin-streptavidin complex. Incubation was repeated, microparticles are magneticaly captured on surface of electrode. Application of voltage to electrode induces chemulumisce emission measured by 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.

Statistical analysis

The collected data were summarized in terms of mean ± Standard Deviation (SD) and range for quantitative data and frequency and percentage for qualitative data. Comparisons between the different study groups were carried out using the Chi-square test (χ^2) and Fisher's Exact Test (FET) to compare proportions as appropriate.

The Mann-Whitney test (z) was used to compare two groups regarding non-parametric data and the Kruskal Wallis test (χ^2) was used to compare more than two groups. The Spearman correlation coefficient (rho; ρ) was used to assess the correlation between serum prolactin levels and estimated parameters. Receiver Operating Characteristics (ROC) analysis was carried out to evaluate the diagnostic performance of serum prolactin levels as a predictor for liver cirrhosis severity and hepatic encephalopathy. The best cutoff point and the corresponding sensitivity and specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) were estimated. All statistical analyses were carried out in STATA/SE version 11.2 for Windows (STATA Corporation, College Station, Texas).

RESULTS

This study includes 50 patients with age ranging from 38-60 years with Mean ±SD 51.94±5.99 years; they are 31 male patients (62%) and 19 female patients (38%). PRL level is (5.5 -39) ng/ml with mean ±S.D (18.76±9.14 ng/dl).

The albumin level is from (1.2 -4.2) mg\dl with mean±S.D (3.08±0.85 g\dl). Total bilirubin level is from (1.2 -6.8) mg\dl with mean±S.D (2.6±1.3 mg\dl). Prothrombin time is from (2.9 -18.5) sec with mean ±S.D (8.9±5.54 sec). Creatinine level is from (0.7-6) mg\dl with mean ±S.D (2.25±1.21 mg\dl). Portal vein (PV) diameter by ultrasound ranges from (10 -19) cm with mean ±S.D (12.19±1.74 cm). Child Pugh score level is from (5 -14) with mean ±S.D (9.16±3.16). The current study reveals that there is a *statistically significant difference* between severity of cirrhosis and encephalopathy grading. There is *a highly statistically significant difference* between severity of cirrhosis and (degree of ascites, PRL level, albumin level, bilirubin level, prothrombin time and Child Pugh score).
There is *no statistically significant difference* between severity of cirrhosis and PV diameter, creatinine level, Sex or age.

- There was *highly statistical significant increase* regarding PRL level in moderate & severe liver cirrhosis than mild liver cirrhosis.
- There is *highly statistical significant decrease* regarding albumin level in severe liver cirrhosis than mild & moderate liver cirrhosis.

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

Variable (no.=50)		Severity of cirrhosis						Test	P
		Mild (no.=19)		Moderate (no.=15)		Severe (no.=16)			
		No.	%	No.	%	No.	%		
Age (years)	Mean ±SD; (range)	52.31±5.75; (43-60)		51.6±5.07; (42-60)		51.81±7.29; (38-60)		χ^2= 0.26	0.88
Sex	Females	4	21.05	9	60.0	6	37.5	χ^2= 5.40	0.07
	Males	15	78.95	6	40.0	10	62.5		
Encephalopathy	No	15	78.95	4	26.67	11	68.75	FET	0.003 (S)
	Grade 1	1	5.26	3	20.0	1	6.25		
	Grade 2	0	0.0	1	6.67	3	18.75		
	Grade 3	3	15.79	3	20.0	0	0.0		
	Grade 4	0	0.0	4	26.67	1	6.25		
Degree of ascites	No	13	68.42	7	46.67	0	0.0	FET	<0.001 (HS)
	Mild	3	15.79	3	20.0	2	12.5		
	Moderate	3	15.79	4	26.67	3	18.75		
	Severe	0	0.0	1	6.67	11	68.75		

PV: portal vein; S: Significant difference (P<0.05)
HS: Highly Significant differences (P<0.001)
†: significant differences compared to mild liver cirrhosis
‡: significant differences compared to moderate liver cirrhosis

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

Variable	Severity of cirrhosis						Test	P
		Mild (no.=19)		Moderate (no.=15)		Servere (no.=16)			
		No.	%	No.	%	No.	%		
PRL level (ng/ml)	Mean ±SD; (range)	12.95±7.96;(6.8-29.9)		†23.33±9.68; 9.5-35.2)		†24.51±19.05; (5.5-39)		χ^2= 14.21	<0.001 (HS)
Albumin (g/dl)	Mean ±SD; (range)	3.66±0.44; (2.3-4.2)		3.08±0.89; (1.2-4.2)		††2.39±0.68; (1.2-3.6)		F= 21.92	<0.001 (HS)
Bilirubin (mg/dl)	Mean ±SD; (range)	1.87±0.86; (1.2-4.8)		2.44±1.17; (1.2-5.8)		†‡3.61±1.25; (1.8-6.8)		F= 19.16	<0.001 (HS)
Prothrombin time (sec)	Mean ±SD; (range)	5.55±4.1; (2.9-16.9)		7.97±4.99; (3-16.9)		††13.74±4.11; (6-18.5)		F= 20.73	<0.001 (HS)
Creatinine (mg/dl)	Mean ±SD; (range)	2.43±1.41; (0.8-6)		1.98±0.91; (1.2-4.9)		2.3±1.24; (0.7-5.3)		χ^2= 1.31	0.52
PV diameter (cm)	Mean ±SD; (range)	11.62±1.12; (10-15)		11.95±1.49; (10-14.5)		13.09±2.22; (11-19)		F= 4.85	0.09
Child Pugh score	A	11	57.89	2	13.33	0	0.0	FET	<0.001 (HS)
	B	6	31.58	8	53.33	1	6.25		
	C	2	10.53	5	33.33	15	93.75		
	Mean ±SD; (range)	6.63±2.06; (5-13)		†9.27±2.89; (6-14)		†12.06±1.65; (8-14)		F= 25.01	<0.001 (HS)

PV: portal vein; S: Significant difference (P<0.05)
HS: Highly Significant differences (P<0.001)
†: significant differences compared to mild liver cirrhosis
‡: significant differences compared to moderate liver cirrhosis

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

Variable (no.=50)	Spearman correlation coefficient (rho; ρ)	P
Age (years)	0.011	0.46
Albumin (mg/dl)	-0.29	0.04 (S)
Bilirubin (mg/dl)	0.34	0.01 (S)
Prothrombin time (sec)	0.29	0.04 (S)
Creatinine (mg/dl)	0.07	0.64
PV diameter (cm)	0.14	0.31
Encephalopathy grades	0.71	<0.002(HS)
Ascites grades	0.20	0.17
Cirrhosis severity	0.42	0.003 (S)

Table 5. Variations in the serum prolactin levels by patients' characteristics

Variable		PRL level (ng/.ml)					Test	P
		No.	Mean	±SD	Min.	Max.		
Sex	Females	19	25.2	7.31	9.5	35.2	z= 4.00	<0.001 (HS)
	Males	31	14.4	7.66	5.5	39		
Encephalopathy	No	30	13.22	6.32	5.5	29.3	χ^2= 31.15	<0.001 (HS)
	Grade 1	5	17.54	4.3	12.3	20.8		
	Grade 2	4	23.87	1.96	21.4	25.6		
	Grade 3	6	‡30.37	1.8	29.2	34		
	Grade 4	5	‡32.66	2.76	29.3	39		
Degree of ascites	No	20	18.13	11.38	6.8	35.2	χ^2= 4.70	0.19
	1st degree	8	13.67	6.48	5.5	21.4		
	2nd degree	10	20.05	9.06	10.2	34		
	3rd degree	12	21.06	5.32	15.1	39		
CHILD grades	A	13	13.84	8.99	7.4	29.9	χ^2= 6.35	0.04 (S)
	B	15	19.35	10.6	6.8	35.2		
	C	22	†20.69	7.41	5.5	39		

HS: Highly Significant (P<0.001)
‡Significant differences compared to no encephalopathy
†Significant differences compared to Child grade A

- There is *highly statistical significant increase* regarding bilirubin level in severe liver cirrhosis than mild & moderate liver cirrhosis.
- There was *highly statistical significant increase* regarding prothrombin time in severe liver cirrhosis than mild & moderate liver cirrhosis.
- There was *highly statistical significant increase* regarding Child Pugh score in moderate & severe liver cirrhosis than mild liver cirrhosis. (Table:2) and (Table:3)

Table 6: Diagnostic accuracy with serum prolactin in predicting severe/moderate liver cirrhosis

Best cutoff point		18.8 ng/ml
Sensitivity		67.74%
	Specificity	78.95
PPV		84%
NPV		60%
AUC		0.8158

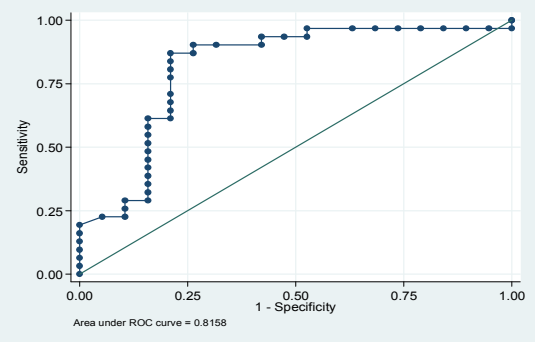

Figure 1. ROC analysis for serum prolactin level as a predictor for severe/moderate liver cirrhosis

There was *a statistically significant negative correlation* between serum prolactin level and albumin level, there was *a statistically significant positive correlation* between serum prolactin level and bilirubin level, prothmbin time and cirrhosis severity. Also *a statistically highly significant positive correlation* was found between serum prolactin level and encephalopathy grades. (Table:4). There were a statistically highly significant differences found in the serum prolactin level and sex, statistically highly significant differences were found in the serum prolactin level and hepatic encephalopathy grades and statistically significant differences in the serum prolactin level and Child grades. There was highly statistical significant increase regarding PRL level in grade 3&4 encephalopathy than no encephalopathy. There was statistical significant increase regarding PRL level in Child Pugh grade C than Child Pugh grade A. (Table:5). By using Roc curve for serum prolactin level as a predictor for severe/moderate liver cirrhosis it is found that at the cutoff point 18.8 ng/ml, the sensitivity is 67.74%, the specificity is 78.95, the PPV is 84%, and the NPV is 60%.

DISCUSSION

Cirrhosis is a gradually developing, chronic disease of the liver which always involves the organ as a whole. It is the irreversible consequence and final stage of various chronic liver diseases of different etiology or the result of long-term exposure to various factors. The extent of the morphological changes depends on the cause and stage of cirrhosis. Accordingly, there is a wide spectrum of morphological findings and clinical symptoms. The variations of this disease range from symptom-free conditions, non-characteristic complaints and different laboratory findings through to life-threatening complications (Parke *et al*., 2015).

The polypeptide human prolactin (HPL) hormone is synthesized and secreted from the lactotrophic cells of the anterior pituitary gland. The human PRL molecule is arranged in a single chain of 199 amino acids (A.A) with three intramolecular disulfide bonds. (Freeman, 2000) The gonadal axis is notably affected in liver cirrhosis. Hyperprolactinemia is often present in these patients as well as hyperestrogenemia, both responsible for the clinical characteristics of feminization. Hyperprolactinemia and hyperestrogenemia can contribute to the genesis of hypogonadism (Arafa *et al*., 2012). The present study aims to assess serum prolactin level as a biological marker of severity in liver cirrhosis. The current study shows highly significant relation between severity of cirrhosis and PRL level (P< 0.001), where serum prolactin hormone level increases with the severity of liver cirrhosis and this increasing of prolactin is attributed mainly to the fall in dopamine levels in the tuberofundibular tract. Hormonal disturbance in cirrhosis have been evaluated by few researchers, and the studies have been established lower T3 and cortisol level with raised prolactin in the serum (Velissaris *et al*., 2008). Decompensated liver function leads to an alteration in the type of amino acids entering the central nervous system. Concentration of circulating aromatic amino acids have been found to increase leading to an increase in the synthesis of false neurotransmitters such as phenylethanolamine and octopamine (Als-Nielsen *et al*., 2003).

These false neurotransmitters may inhibit the dopamine release contributing to hyperprolactinemia. Hyperprolactinemia leading to hypogonadism in patients with cirrhosis (Karaginnis, 2005). This consistent with the study carried out by Ferrini *et al*. (2015) who reported that increased estradiol and prolactin levels and decreased serum testosterone level were observed in patients with liver cirrhosis, compared to normal person. Low testosterone and high prolactin levels were determined to be correlated with the cirrhosis severity. LH and FSH levels were not determined to be high in cirrhotic patients; response was obtained against the external gonadotropins and serum testosterone levels increased and consistent with the study reported by Mukherjee *et al*. (2015) where severity of hepatic cirrhosis had positive correlation with level of serum prolactin. There was significant negative correlation between serum prolactin level and albumin where r=-0.29 p=0.04 and this consistent with the study reported by Arafa *et al*. (2012). Whereas there was a significant negative correlation between serum prolactin concentration and serum albumin (Arafa *et al*., 2012). There was significant positive correlation between serum prolactin level and severity of cirrhosis where r=0.42 p=0.003 and this consistent with the study reported by Arafa *et al*. (2012) where serum level of prolactin significantly increased with progression of liver disease from Child A to Child C (Arafa *et al*., 2012).

Conclusion

Prolactin levels increase significantly with severity of liver disease particularly in patients with ascites and hepatic encephalopathy. High prolactin level could therefore be considered as a negative prognostic marker of liver cirrhosis.

REFERENCES

Als-Nielsen B, Korets RL, Kjaergard LL. *et al*. 2003. Branched chain amino acid for hepatic encephalopathy. Cochrane Database Sys Rev 2: 19-39.

Arafa M, Besheer T, El-Kanneshy G. *et al*. 2012. Features of hormonal disturbances in cirrhotic patients with hepatic encephalopathy. *Euroasian J H Gastroentrol* 2: 84-89.

Arafa M, Besheer T, El-Kanneshy G. *et al*. 2012. Features of hormonal disturbances in cirrhotic patients with hepatic encephalopathy. *Euroasian J H Gastroentrol* 2: 84-89.

Cheng, Jianjun and Alan P. Kozikowski 2015. Developing Serotonin 2C (5-HT 2C) Receptor Agonists for The Treatment of CNS Disorders. *Chem Med Chem.,* 10.12:1963-1967.

Cho KR, Jo KI, Shin HJ 2013. Bromocriptine therapy for the treatment of invasive prolactinoma: the single institute experience. *Brain Tumor Res Treat* 1: 71-77.

Engin, H. and C. Bilir 2015. Low Testosterone Levels and Increased Serum C Reactive Protein Levels in Cancer Patients with Refractory Cachexia. *European Journal of Cancer* 51- 5.

Ferrini M, Wang C, Swerdloff RS, *et al*. 2001. Aging-related increased expression of inducible nitric oxide synthase and cyto- toxicity markers in rat hypothalamic regions associated with male reproductive function. *Neuroendocrinology* 74(1): 1-11.

Freeman ME, Kanyicska B, Lerant A, *et al* 2000. Prolactin: structure, function, and regulation of secretion. *Physiol Rev* 80(4): 1523-1631.

Fullwood, Danielle and Suzanne Sargent 2014. Complications in Acute Liver Failure: Managing Hepatic Encephalopathy and Cerebral Oedema. *Gastrointestinal Nursing* 12.3: 27-34.

Karaginnis A and Harsoulis F 2005. Gonadal dysfunction in systemic. Eur J Endocrinol 152: 501-513.

Kars M, Dekkers OM, Pereira AM, *et al*. 2010. Update in prolactinomas. *Neth J Med* 68: 104-112.

King LY, Canasto-Chibuque C, Johnson KB, *et al*. 2015. A genomic and clinical prognostic index for hepatitis C-related early-stage cirrhosis that predicts clinical deterioration. Gut 64: 1296-1302.

Maiter D and Delgrange E, 2014. Therapy of endocrine disease: the challenges in managing giant prolactinomas. *Eur J Endocrinol* 170: R213-227.

Nieddu, Maria *et al* 2010. Determination of Four Thiophenethylamine Designer Drugs (2C-T-4, 2C-T-8, 2C-T-13, 2C-T-17) In Human Urine by Capillary Electrophoresis/Mass Spectrometry. Rapid Communications in Mass Spectrometry 24.16: 2357-2362.

Parke, Chong Y., Paul Martin, and Suphamai Bunnapradist 2015. Renal Dysfunction in Cirrhosis. *Clinical Liver Disease* 5.6 :150-153.

Patel, Nishita and Santiago J. Muñoz 2015. Bone Disease in Cirrhosis. Clinical Liver Disease 6.4: 96-99.

Shindel, A.W 2014. Hormone Abnormalities Are Not Related To The Erectile Dysfunction And Decreased Libido Found In Many Men With Infertility. Yearbook of Urology 2014: 150-151.

Song Jy, Jung SJ, Park CW. *et al* 2006. Prognostic significance of Infection Acquisition Sites in Spontaneous Bacterial Peritonitis: Nosocomial versus Community Acquired. *J Korean Med Sci* 21: 666-671.

Velissaris D, Karanikolas M, Kalogeropoulos A, *et al*. 2008. Pituitary hormone circadian rhythm alterations in cirrhosis patients with subclinical hepatic encephalopathy. *World J Gastroenterol* 14(26): 4190-4195.

****