A STUDY ON PREVALENCE OF ADRENAL INSUFFICIENCY IN PATIENTS WITH CHRONIC LIVER DISEASE

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CERTIFICATE

This is to certify that the dissertation titled **"A Study on Prevalence of Adrenal Insufficiency in patients with chronic liver disease"** submitted by **Dr.A.Santhi Selvi** to the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600 032 in partial fulfillment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by her under my direct supervision and guidance.

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DECLARATION

I **Dr. A.Santhi Selvi,** declare that I carried out this work on **"A STUDY ON PREVALENCE OF ADRENAL INSUFFICIENCY IN PATIENTS WITH CHRONIC LIVER DISEASE"** at the Department of Medical Gastroenterology, Govt. Peripheral Hospital and Kilpauk Medical College. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any university, board either in India or abroad.

This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the D.M. Degree examination in Medical Gastroenterology.

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CONTENTS

INTRODUCTION

Liver diseases are prevalent worldwide and also in India. The prevalence of liver disease is on the rise due to various reasons. The liver is one of the most vital organ sub serving several important functions such as synthesis, storage and metabolism, etc. Metabolism of hormones is one of the important functions. Thus, various endocrine disturbances have been reported in several liver diseases. Studies done in animals and humans with cirrhosis demonstrated elevated levels of endotoxin and inflammatory cytokines , thus contributes not only to hemodynamic impairment[1] but also adrenal dysfunction [2]. Since the liver is not only the site for metabolism of adrenal steroid hormones but also the site for cholesterol synthesis, the principal precursor of steroid[2], preexisting hepatic disease can impair hypothalamo-pituitary-adrenal axis activation in the presence of severe sepsis and septic shock. Adrenal dysfunction has been reported in the whole spectrum of disease ranging from acute liver failure, chronic liver disease, compensated and decompensated cirrhosis. Adrenal Insufficiency is also reported in the post liver transplant patients during immediate or late post transplant period.

Presence of adrenal insufficiency in liver disease increases the risk of cardiocirculatory compromise, infections and decompensation in such patients but has to be confirmed yet. But diagnosing adrenal insufficiency

in liver diseases is difficult because symptoms are subtle and overlap with those of cirrhosis[1,3]. In addition, laboratory testing and reference standards were not clearly defined. Evidence shows that critically ill patients with cirrhosis has a worsened outcome when compared with similar patients without adrenal insufficiency. Several studies have reported correlations of adrenal insufficiency with progression of stages of cirrhosis.

All the above findings had lead to the coining of new term called "Hepatoadrenal Syndrome" which indicates presence of adrenal dysfunction in critically ill liver disease patients.

This present study is undertaken to determine the prevalence of adrenal insufficiency in patients with chronic liver disease, its associations with various stages and complications and progression of liver disease.

AIM OF THE STUDY

- To assess the prevalence of adrenal insufficiency in patients with chronic liver disease.
- To evaluate the correlation between adrenal insufficiency and the disease severity scores and the complications of chronic liver disease.

REVIEW OF LITERATURE

Cirrhosis of liver is defined as the histological development of regenerative nodules surrounded by fibrosis bands in response to any chronic liver insult, resulting in the development of portal hypertension and end stage liver disease. Chronic liver disease is a clinical diagnosis whereas cirrhosis is a histological diagnosis.

Epidemiology

Prevalence of cirrhosis is about 0.15% in USA, accounting for more than 25000 deaths. Similar rate of prevalence is seen in European countries whereas the prevalence is much higher in Asian and African countries.

Etiology of chronic liver disease:

- Alcohol
- Hepatitis B
- Hepatitis C
- Non alcoholic steatohepatitis
- Wilsons disease
- Primary biliary cirrhosis
- Autoimmune hepatitis
- Primary sclerosing cholangitis
- Hemochromatosis
- Inherited metabolic liver diseases

Clinical features

Cirrhosis of liver is often silent, asymptomatic until development of complications. Asymptomatic patients are frequently diagnosed incidentally when biochemical or radiological tests indicate liver disease with confirmation by liver biopsy.

Clinical signs

Compensatory cirrhosis usually presents with jaundice, spider angioma, splenomegaly, white nails, palmar erythemia, duputyrens contracture, and gynaecomastia. Decompensated cirrhosis presents with fetor hepaticus, ascites, gastrointestinal bleed and asterixis.

Complications

Portal hypertension, variceal bleed, ascites, renal failure, coagulopathy, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, portopulmonary syndrome, hepatopulmonary syndrome and primary malignancy of the liver are the most common complications of cirrhosis.

Adrenal Insufficiency (AI) or adrenal dysfunction in cirrhosis is a recently recognized entity. Hepato adrenal syndrome is the newly coined term for adrenal insufficiency in cirrhosis. Adrenal dysfunction is estimated to be reported in 30% of decompensated and 10% of compensated

cirrhotics. This may lead to increased risk of cardiovascular dysfunction, circulatory compromise, infections and decompensation in such patients.

The symptoms in such patients are usually subtle and overlap with those due to cirrhosis, thus causing difficulties in the diagnosis of adrenal insufficiency in liver disease.

Furthermore, laboratory testing and reference standards were not defined clearly. Evidence suggests that critically ill cirrhotics with associated adrenal insufficiency show a poor outcome when compared with similar patients who do not have adrenal insufficiency. However, there is no clear guidelines or consensus on diagnosis or treatment especially regarding the role of steroid replacement therapy.

Historical perspective

In 1855, Thomas Addison quoted: "I believe that adrenal insufficiency is no means of very rare occurrence and we better acquainted with its symptoms and progress and we should probably succeed to detect many cases" .

The role of glucocorticoids in the pathophysiology of critical illness has been established during early part of 20th century after having demonstrated that cortisol is necessary to survive critical illness [5].

In 1980s, studies on steroids in patients with critical illness showed no mortality benefit.

In 1990s smaller doses of corticosteroid therapy for longer duration in septic shock was found to decrease duration of shock and less vasopressor requirement to maintain blood pressure [6].

Further, several authors had showed that in patients with severe sepsis , burns, head trauma and HIV infection, associated abnormalities in liver function coexists. And corticosteroid replacement in such patients improve hemodynamics, faster reversal of shock and survival benefits in a sub group of septic shock patients with adrenal failure.

Definitions

Relative adrenal insufficiency (RAI)

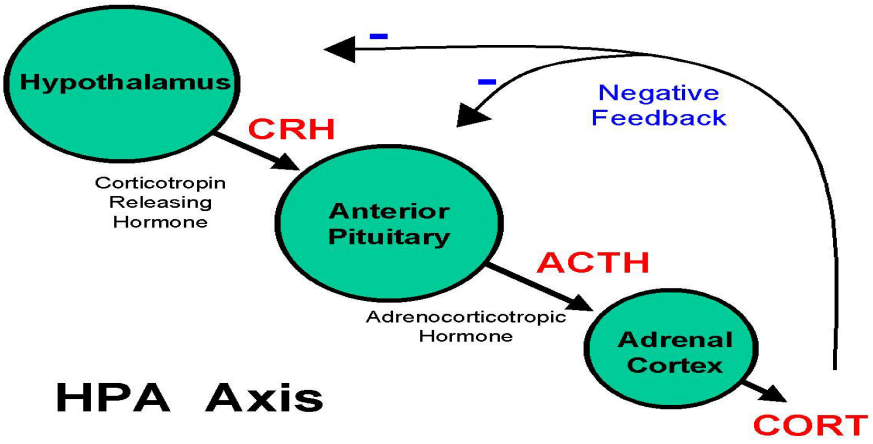
Relative adrenal insufficiency (RAI) is described as a subnormal response to corticotrophin in severe illness, in which cortisol levels even though high in terms of absolute value are inadequate to control the inflammatory process [3].

It is also known as critical illness related corticosteroid insufficiency (CIRCI).

Regulation of Cortisol secretion

Normally, adrenal glands secrete cortisol, regulated by the feedback mechanism of adreno-corticotrophic hormone (ACTH). Pituitary gland releases ACTH which is stimulated by corticotrophin releasing hormone (CRH). CRH is secreted from the hypothalamus. Under conditions of

stress, levels of ACTH and CRH increase leading to stimulation of cortisol synthesis and release in to the circulation[7].



Cortisol has an inhibitory effects on inflammatory mediators namely neutrophil recruitment and release of cytokines[8]. Moreover, they accelerate vascular tone and also cardiac output.

All the above actions are helpful in critical illness particularly in situations like septic shock were stimulation of inflammatory cascade is dangerous. Moreover, survival after such illness depends on adequate levels of cortisol.

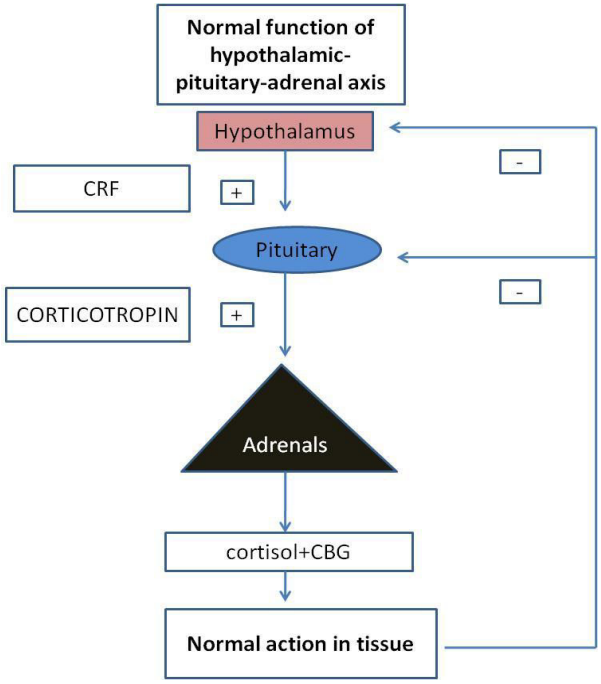
Several factors influence cortisol synthesis and production such as diurnal rhythm of ACTH secretion, negative feedback mechanism etc., Stress is another important factor influencing the production of cortisol.

During severe illness and stress, cytokines and other factors stimulates the hypothalamic pituitary adrenal (HPA) axis, causing increased

CRH secretion. This in turn, stimulates ACTH production, ultimately leading to increased cortisol into the circulatory system[7].

About 90% of cortisol which is in circulation is bound to CBG and also albumin. Less than 10% occurs as the biologically active free form[9]. Among the bound form, more than 80% of circulating cortisol binds to CBG. Albumin binds only smaller amounts of circulating cortisol.

Liver converts cortisol into its inactive metabolite cortisone by the enzyme 11β-hydroxysteroid dehydrogenase. It binds to glucocorticoid receptor after diffusion across the cell membrane. Later it translocates into the nucleus of the cell and exerts its functions[10].



Functions of cortisol

Adequate Cortisol is necessary for:

1. Function of normal immune system
2. Vascular tone maintenance
3. Normal function of Cells

Prevalence of Adrenal Insufficiency

Several studies have reported the increasing prevalence of adrenal insufficiency in liver disease. But significant discrepancies exist about the prevalence in various studies. This is mainly because of the different tests used for diagnosing adrenal dysfunctions. Thus, the existence of adrenal dysfunction differs in decompensated cirrhotics and in stable cirrhotic patients. The prevalence is also different in patients who had received liver transplant.

Prevalence of adrenal dysfunction in critically ill liver cirrhotics

Most studies that were done to show the prevalence of adrenal dysfunction in critically ill liver cirrhotics used SD-SST. Whereas only a few studies used LD-SST to diagnose adrenal dysfunction.

Reported prevalence of adrenal dysfunction in such patients using SD-SST was between 10%[11] and 87%[12], whereas using the LD-SST, the prevalence of adrenal dysfunction was reported between 33%[13] and 60%[14].

Prevalence of adrenal dysfunction in non-critically ill patients along with liver cirrhosis

Prevalence of adrenal dysfunction in stable cirrhotic patients varies from 9%[15] to 64%[16] in various studies.

Prevalence of Adrenal insufficiency after liver transplantation

Studies have reported the prevalence of adrenal dysfunction in both early as well as late post liver transplant period. The prevalence has been reported to about 92% [13]in patients who underwent liver transplantation.

Pathogenesis

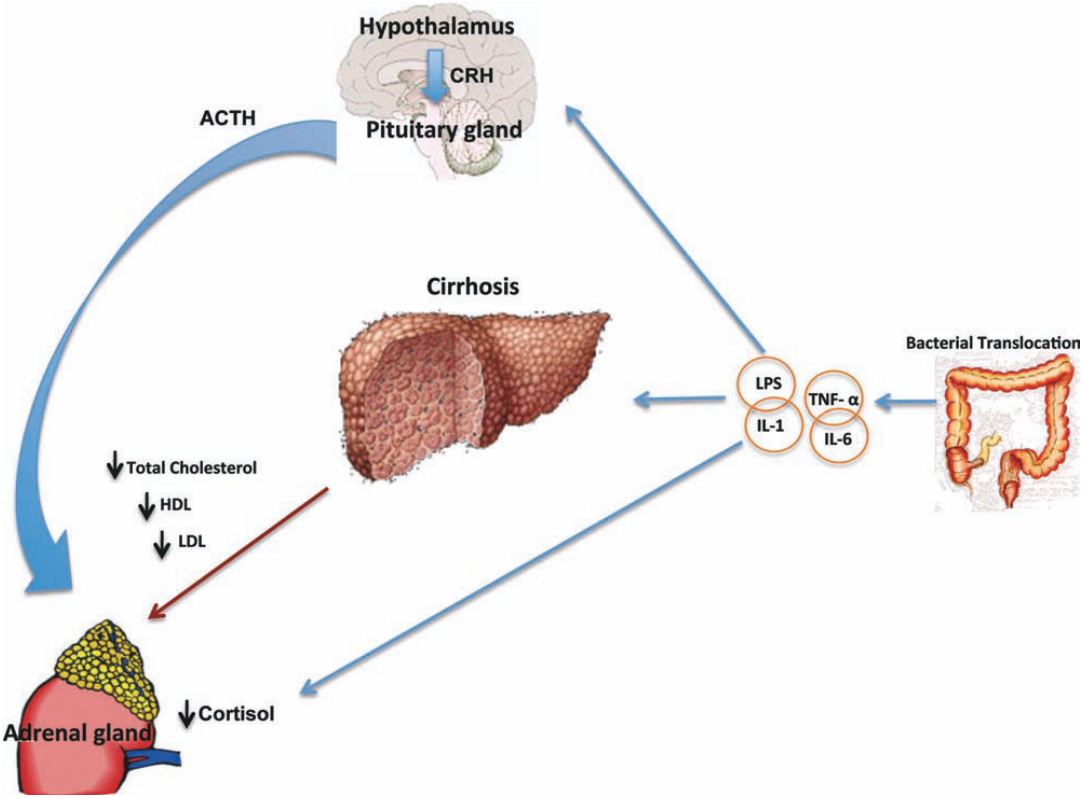
The pathogenetic mechanism of adrenal insufficiency is not completely understood.

Some proposed mechanisms include endotoxemia, decreased levels of apolipoprotein A-1, HDL cholesterol and LDL cholesterol, increased levels of pro-inflammatory mediators, bacterial translocation of enteric organisms, structural damage of the adrenals caused by infarction or hemorrhage, glucocorticoid resistance with exhaustion of the adrenal gland[18].

As already mentioned, cholesterol is the main source of substrate for the synthesis of steroids in the adrenal gland[19]. Nearly 80% of circulating cortisol is synthesized both at rest and during stress from plasma cholesterol (especially HDL cholesterol).

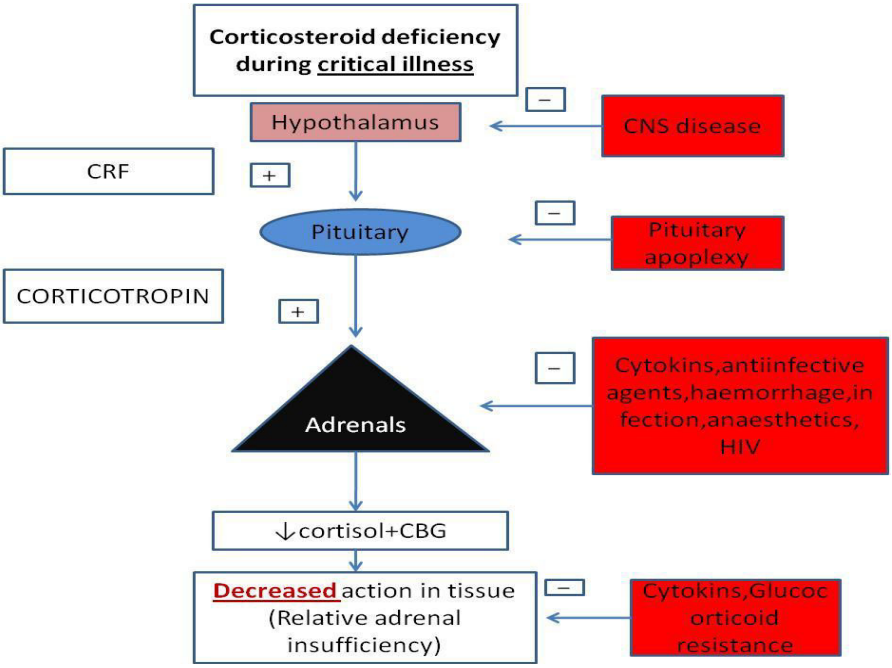
Liver diseases cause reduced synthesis of HDL, increased levels of circulating endotoxins (LPS) and TNF-α which inhibit cortisol sysnthesis.

In addition, TNF-α, IL-1 and IL-6 reduce hepatocyte synthesis of apolipoprotein A-1, the major component of HDL cholesterol[20]. The lack of substrate for steroidogenesis eventually leads to the adrenal exhaustion syndrome[21], thus contributing to adrenal insufficiency in cirrhotic patients.



Pathogenesis of Hepatoadrenal syndrome

Besides the above factors, coagulopathy which is common in liver cirrhosis can also cause adrenal hemorrhage and infarctions, causing structural damage to adrenal gland, which contributes to adrenal insufficiency[22]. Bacterial translocation of enteric organisms have also been implicated in the pathogenesis in adrenal insufficiency in cirrhosis of liver[23].



Hemodynamics of Hepato-adrenal syndrome

Cirrhosis, and liver failure have several similar hemodynamic characters in patients presenting with sepsis and septic shock like:

1. Raised cardiac output
2. Reduced peripheral vascular resistance
3. Reduced mean arterial pressure
4. Hypo responsiveness to vasopressors.

Additional unfavourable factors in critical liver disease

1. Endotoxemia
2. Increased levels of proinflammatory mediators(interleukin-6,TNF factor)
3. Decreased levels of Apo protein-A/HDL

4. Coagulopathy leading to adrenal hemorrhage
5. Decreased monocyte function and immonoparalysis

Predictors of Adrenal insufficiency in cirrhosis

Several studies have assessed the predictors of adrenal insufficiency in liver diseases[13].

1. Low HDL-C
2. High CTP and MELD score
3. High INR
4. High bilirubin
5. Renal dysfunction
6. Hypoalbuminemia

Outcome of Adrenal dysfunction in liver diseases under various clinical situations

Critically Ill patients along with liver disease

Studies report increased risk of hemodynamic instability with ventilator dependence, increased risk of mortality and increased need for liver transplantations in patients with adrenal insufficiency and hepatic diseases who are critically ill[24].

Another study by Tsai et al showed that response of cortisol to SST had inverse correlation with disease severity scores such as MELD score, SOFA, APACHE III. Studies also show that adrenal insufficiency in critically ill cirrhotic patient was associated with lower mean arterial

pressures, more requirement of vasopressors and increased hospital mortality rate[25]. Adrenal insufficiency also correlated with the progression of liver disease as reported in several studies showing higher prevalence in patients with CTP C[26].

Non critically ill Patients with liver cirrhosis

Studies report that patients with higher CTP and MELD score, ascites, INR, and lower levels of HDL - cholesterol were found to be important independent risk factors for adrenal insufficiency, irrespective of the etiology[27].

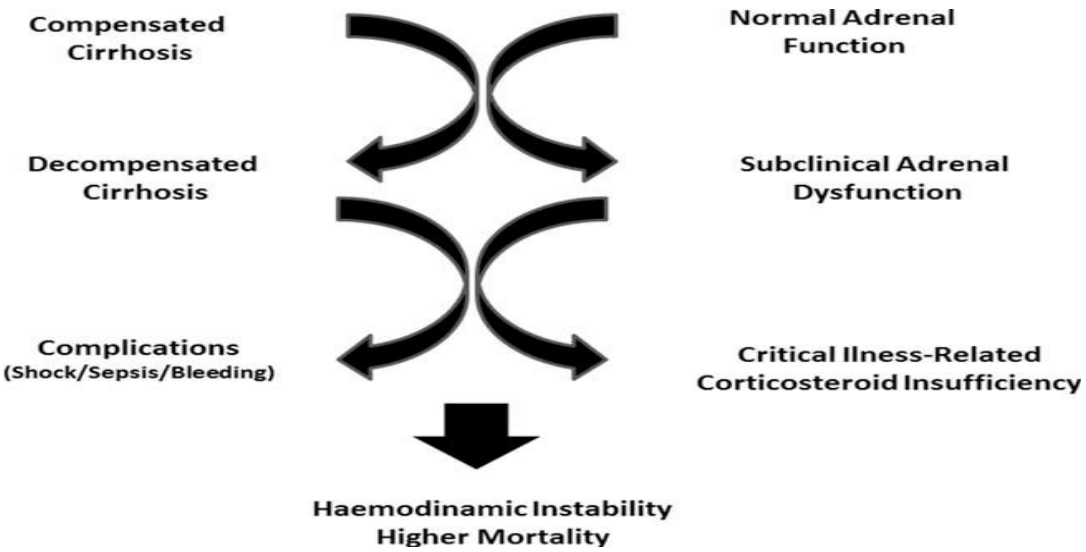
Another study by Tan et al reported that adrenal insufficiency in cirrhotic patients had higher MELD scores and higher mortality rate than in cirrhotic patients without adrenal insufficiency[28].

Most studies report more severe circulatory dysfunction, increased risk of infection, lower serum sodium levels and septic shock at the time of hospitalization with higher inhospital death rate in patients associated with adrenal insufficiency[29]. Adrenal dysfunction was associated with higher rate of failure to control variceal bleed and a lower survival in patients presenting with variceal bleed, than in non bleeders[30].

Patients with decompensated and compensated liver cirrhosis develop adrenal dysfunction both due to sepsis, and also from complications of portal hypertension like ascites and bleeding. This indicates that adrenal

insufficiency itself may be a feature of hepatic disorders per se rather than related to critical illness.

Clinical importance of adrenal dysfunction in liver disease



Outcome of Adrenal insufficiency in Liver Transplant Recipients

Adrenal insufficiency is documented in liver transplant recipients administered with steroid free immune suppression[31] or after suspension of steroids[32].

Steroids used in most of the immunosuppressive regimes following LT, prevent development of early RAI. But prolonged use of steroids leads to HPA axis suppression causing functional adrenal gland atrophy (FAGA)[33]. FAGA correlates well with the duration and also the cumulative steroid dosage. This also correlates well with total cholesterol levels and Adreno CorticoTrophic Hormone concentration.

Adrenal insufficiency can be subclinical in liver disease. Several determinants associated after liver transplant such as hypotension, infection and massive hemorrhage can cause acute adrenal dysfunction on the immediate posttransplant period. Longterm administration of steroid cause immunosuppression causing functional adrenal gland atrophy.

Intra operative administration of 1g of methylprednisolone have significantly reduced requirements for fluids, vasopressors, invasive ventilation, renal supportive therapy and Intensive Care Unit stay, in comparison to those who did not received steroids[34].

Clinical Features

Symptoms depend on the rapidity of onset, but chronic adrenal insufficiency may be asymptomatic or oligosymptomatic with fatigue, weight loss, and lassitude. Liver disease patients with adrenal insufficiency typically lack addisonian features[22]. Diagnosis of adrenal insufficiency should be made only on clinical grounds. Adrenal insufficiency in critically ill cirrhotic patients presents with hypotension refractory to vasopressors and fluid resuscitation[35]. Whereas adrenal dysfunction in stable cirrhotics is usually subclinical but can only be diagnosed by laboratory investigation.

Diagnosis of Adrenal Insufficiency

Assessment of Basal plasma cortisol levels

A basal plasma cortisol level <138 nmol/L (5μg/dl) when measured between 8.00 a.m and 9.00 a.m. highly suggests presence of adrenal insufficiency. Adrenal insufficiency is unlikely when basal plasma cortisol levels are >415 nmol/L (15 μg/dl)[36].

Assessment of Basal plasma ACTH levels

Basal plasma ACTH levels which when measured between 8.00 a.m. and 9.00 a.m., exceed 100 pg/ml (22 pmol/L) indicates primary adrenal insufficiency[37].

Insulin induced hypoglycemia test (IIHT)

Insulin-induced hypoglycemia test (IIHT) has been considered to be the gold standard to evaluate the HPA axis. The test uses injection of 0.15 IU/kg regular insulin that can achieve blood glucose level less than 40 mg/dL or until hypoglycemic symptoms develop. Blood samples are collected before and after 15, 30, 45, 60, 90 min post-stimulation. Peak cortisol cut points between 500 and 550 nmol/L (18-20 μg/dL) are used for the diagnosis of adrenal sufficiency. Contraindications to IIHT includes patients diagnosed to have cardiac diseases, central nervous system diseases including convulsive disorders[36]. In addition, the IIHT is unpleasant for the

patients and therefore it has been replaced by alternative tests (LS-SST, SD-SST) for evaluating the HPA axis.

Short synacthen test (SST)

Short Synacthen Test is the first line investigation to diagnose adrenal insufficiency. This test can be done irrespective of fasting at any time. The baseline sample is collected, followed by collection at thirty minutes and one hour after administering IV or IM 250 μg of ACTH (Synacten). The post stimulation levels of cortisol exceeding 550 nmol/L (20 μg/dl) rules out presence of primary adrenal insufficiency[36].

Currently, there are two corticotropic analogues, namely tetracosactrin (synacthen) and cosyntropin (Cortrosyn). SD-SST is not a "physiological test" since it uses supraphysiological dose of 250μg of corticotropin (which results in approximately 100 times more than normal maximal stress levels of adrenocorticotrophic hormone).

In conditions with critical illness, AI was defined by the International Task Force as a delta cortisol of <250nmol/L (<9 μg/dL) after SD-SST or a random serum total cortisol of <276 nmol/L (<10 μg/dL). No consensus or guidelines is formulated on the diagnostic criteria of AI in cirrhotic patients, although a delta cortisol under 250 nmol/L has been used by most studies to define AI in such patients.

Low dose short synacthen test

LD-SST is done by giving 1μg of synthetic ACTH (synacthen) intravenously followed by measuring cortisol level at baseline and 20 minutes and 30 minutes later. Plasma cortisol ≥500 nmol/L (18 μg/dl) denotes normal response. LD-SST is more sensitive than SST in patients not in critical illness. But LD-SST is not validated in acute hypothalamic pituitary disorders or in critically ill patients[38].

In a meta-analysis comprising the diagnostic value of SDSST and LD-SST for diagnosing AI, LD-SST was found to be superior, whereas another meta-analysis which reported similar operative characteristics for both tests. LD-SST seems to be a more physiological and sensitive test than SD-SST for the diagnosis of AI, and appropriate in non-critically ill cirrhotics.

Corticotrophin – releasing hormone test (CRH)

Corticotrophin-releasing hormone test (CRHT) evaluates the entirety of the HPA axis. The CRH test is used to differentiate primary adrenal dysfunction from secondary adrenal dysfunction. Baseline blood samples were collected for the measurement of ACTH and cortisol levels followed by collection at fifteen minutes, thirty minutes, forty five minutes and sixty minutes after administering IV 1μg/Kg of CRH. Primary adrenal

insufficiency, is suggested when high basal ACTH levels increase following CRH injection.

In secondary adrenal insufficiency, lower levels of ACTH have no response for CRH. Lower levels ACTH in association with a prolonged rise following CRH indicates hypothalamus disorders[36]. Although CRHT is free of serious side effects, it is both difficult and costly and therefore it has been used in few studies in liver disease.

Salivary Cortisol

Salivary cortisol, regardless of serum binding protein levels, correlates well with free cortisol levels [39]. Basal value of salivary cortisol levels <1.8 ng/mL or a concentration after SD-SST <12.7ng/mL, an increment <3 ng/mL are suggestive of AI.

But there are significant variations in normal salivary cortisol values reported by different studies. Other limitations of salivary cortisol are represented by oral candidiasis, low salivary flow, and contaminated salivary samples from gingival bleeding, common in cirrhotic patients.

Thus in the absence of a gold standard test, SD-SST remains the most used test to assess the adrenal dysfunction in critically ill cirrhotics, while LD -SST is more appropriate in patients with stable cirrhosis. At present, serum free cortisol levels and salivary cortisol levels are most accurate in

diagnosis of AI in cirrhotic patients, but cannot be used in routine clinical practice. The use of salivary cortisol needs to be validated.

Adrenal insufficiency in critical illness

An international task force definition of adrenal insufficiency in critically ill patients is as follows. Delta cortisol (which is the difference between basal and post stimulation cortisol) of 250 nmol/L (9 μg/dl) after SST or a random total plasma cortisol level of 276 nmol/L (10 μg/dl)[40].

Limitations in diagnosing adrenal dysfunction in hepatic disease patients

No clear recommendations or guidelines exists for diagnosing adrenal insufficiency in hepatic diseases. Commercially available cortisol assays measure total hormone which are not biologically active, free cortisol concentration[41]. They also suffer poor reproducibility in critically ill patients. Sensitivity and specificity of assays that are commercially available are never uniform.

Serum Cortisol

Diagnosing adrenal dysfunction based on serum total cortisol levels in cirrhosis will be inaccurate due to lower serum concentrations of albumin and Corticosteroid Binding Globulin, since the liver is the site of synthesis of both[42]. This has been already proven that low levels of CBG and albumin lead to overestimation of the diagnosis of adrenal dysfunction[43].

As already known, more than 90% of serum cortisol which are in circulation binds to CBG and albumin, and lesser than 10% is in the free biologically active form[44]. Standard laboratory assays of serum total cortisol measure the bound plus free fractions. This means that a decrease in the binding protein levels, as it often happens in cirrhosis, will reduce serum total cortisol, affecting the interpretation of SD-SST/ LD-SST[45], and this may lead to the overestimation of AI in cirrhotic patients[15]. However, most of the studies evaluating adrenal dysfunction in critically ill cirrhotics still rely on serum total cortisol levels, both at baseline and after stimulation.

Serum free cortisol assays are considered the most reliable method to assess adrenal dysfunction in critically ill patients[46]. There are several methods used to measure serum free cortisol (gel filtration, ultrafiltration, equilibrium dialysis)[46], all are expensive and inconvenient for routine clinical practice. In cirrhotics, serum free cortisol level is not altered by a reduced concentration of CBG and albumin[47] and therefore it is a better appropriate indicator for assessing adrenal dysfunction in such patients[48]. Some studies reported significant differences in diagnosis of AI using serum total cortisol level and free cortisol criteria in cirrhotics with septic shock[49] or in those with stable cirrhosis[27], while others found that assessing serumfree cortisol had limited additive diagnostic value over serum total cortisol[50].

Serum free cortisol levels under 50 nmol/L at baseline or less than 86 nmol/L after synacthen stimulation are suggestive for the diagnosis of AI (in critically ill patients[45]), although the reference range for baseline values in healthy subjects varies from 8-25 nmol/L[46] to 12-70 nmol/L[48.]

ACTH stimulation Tests

SST is first line test to diagnose adrenal insufficiency[51]. There are drawbacks in interpreting SST like variability of defining normal ranges[52], etc., In addition, there are no clear protocols on how to perform the test.

The doses of ACTH used to assess adrenal insufficiency too can influence the assessment of adrenal insufficiency in hepatic failure. This leads to variability in assessing prevalence of Adrenal Insufficiency in several studies.

Role for steroid replacement in liver disease

Few datas have been available on the role of steroid supplementation in liver disease patients.

One study compared the efficacy of 300 mg hydrocortisone per day in patients with acute liver failure or acute or chronic liver failure who are vasopressor dependent with those patients who are not on steroids and showed that steroid supplementation resulted in decrease in the requirement of vasopressor doses[53]. Meanwhile steroids did not offer any survival

benefit and also there were reports of infections in such patients with resistant organisms.

Marik et al reported that hydrocortisone therapy in patients with acute liver disease or chronic liver disease with vasopressor dependence were associated with decrease in the requirement of noradrenaline doses by 24 hours in patients with adrenal dysfunction with a reduction in the mortality rate than in patients who are not treated with hydrocortisone[13].

Another study by Fernandez et al showed that hydrocortisone therapy in cirrhotics presenting in sepsis resulted in lower mortality rate, resolution of septic shock and a better ICU and hospital survival[26].

The first RCT which evaluated the beneficial effect of lower dose of hydrocortisone in cirrhotics along with sepsis demonstrated significant decrease in the requirement of vasopressor agents and in addition increased reversal rate of shock. But there is no reduction in the 28- day mortality with more incidence of shock relapse and gastrointestinal bleeding[54].

In post liver transplant patients ,intraoperative therapy of 1g methyl prednisolone resulted in decrease in the fluid requirements, vasopressors, invasive ventilation, renal supportive therapy and intensive care unit stay than in patients who were not administered with intraoperative corticosteroids[55].

Hence preliminary studies indicates beneficial effects of supplemental steroid treatment in cirrhotics presenting with sepsis, but demands further multicenter ,randomized ,controlled trials .

Conclusion

Adrenal Insufficiency is an important part of the spectrum of both acute as well as chronic liver disease. Worsening of synthetic function of hepatic diseases predicts the presence of associated adrenal insufficiency. Such patients should be assessed periodically for adrenal insufficiency. Adrenal functions deteriorates along with the progression of liver disease. Steroid replacement in such patients may be beneficial.

In addition, presence of adrenal insufficiency may predict survival of CLD patients. This necessitates the need for largescale prospective studies to establish the role of steroid supplementation to improve the survival in patients with liver disease. Also general consensus or guidelines on the diagnostic criteria for adrenal insufficiency and the dosage and duration of steroid therapy should be established.

MATERIALS AND METHODOLOGY

The study population included consecutive patients with chronic liver diseases who were admitted in our institution, Department of Digestive Health and Diseases, Government Peripheral Hospital, Anna Nagar, Chennai-600 102.

The study was conducted from January 2013 to January 2014. Patients were included to this study after offering their willingness to undergo necessary investigations. Informed written consent was obtained from the study participants before enrollment.

Ethical Committee approval was obtained for performing the study.

Inclusion Criteria

1. Stable cirrhosis
2. Cirrhosis patients with GI bleed
3. Cirrhosis patients with hepatic encephalopathy
4. Cirrhosis patients with spontaneous bacterial peritonitis
5. Cirrhosis patients with hepato renal syndrome

Exclusion criteria

1. Patients on steroids or with history of steroids intake during last 6 months.
2. Patients with hepatocellular carcinoma
3. Patients with portal venous thrombosis

Methodology

All the patients satisfying the exclusion and inclusion criteria were enrolled in to the study. Age, sex and etiology of liver disease were documented.

All the participants were subjected to history taking, clinical evaluation, blood investigations, ascitic fluid analysis, ultrasonogram and UGI scopy.

Chronic liver disease was diagnosed on the basis of evidence of deranged liver function of more than 6 months duration with evidence of portal hypertension and cirrhosis in ultrasonography and upper gastrointestinal endoscopy.

Ascites was graded as Grade 1, Grade 2 and Grade 3 by USG. Hepatic encephalopathy was graded according to West Haven criteria from grade I to IV.

Clinical evaluation

Detailed history regarding present and past history of jaundice, ascites, gastrointestinal bleeding, pedal edema, hepatic encephalopathy, blood transfusion, tattooing, surgeries, extra marital sexual exposure, alcohol intake, and associated co-morbidities, were entered.

Clinical examination done to check presence of evidence of chronic liver disease such as jaundice, spider angioma, duputyrens contracture, palmar erythema, gynaecomastia, ascites, splenomegaly, caputmedusae and asterixis.

Ascites is graded according to International Ascites Club 2010.

Grade 1 : Only detected on ultrasound examination

Grade 2 : Manifested by symmetric distention of the abdomen

Grade 3 : Gross ascites with marked distension of abdomen

Laboratory investigations

Blood investigations like hemoglobin, WBC count, platelet count, prothrombin time, INR, S.bilirubin, T.protein, albumin, alanine aminotransferase, aspartate aminotransferases, HBSAg, Anti HCV, urea, creatinine, total cholesterol, HDL cholesterol, LDL cholesterol and Fasting serum cortisol were done for all patients. Child pugh score was calculated using the various parameters.

A basal plasma cortisol level <138 nmol/L (5 μg/dl) is taken as a cut off value to define adrenal insufficiency.

Ascites

Presence of ascites is assessed by clinical examination and confirmed by ultrasound examination. Ascitic fluid analysis is done to calculate serum ascites albumin gradient, cell count, polymorphs, ascitic fluid culture.

Spontaneous bacterial peritonitis is diagnosed when the ascitic fluid Polymorphonuclear count is more than 250 cells / cumm with positive culture of the ascitic fluid.

Upper Gastrointestinal Endoscopy

All the patients underwent oesophagogastro duodenoscopy. Oesophageal varices were graded using Pacquet's grading system from grades I to IV. Gastric varices if present were graded according to Sarin's classification. Presence of portal hypertensive gastropathy or duodenopathy were also noted. Endotherapy (Endoscopic variceal legation or endoscopic sclerotherapy) were done if required.

Hepatic Encephalopathy

Hepatic Encephalopathy was graded using West Haven's criteria from Grade I to IV, based on the level of consciousness, intellectual functions, behavior and neuromuscular functions.

Hepatorenal Syndrome

Hepatorenal syndrome was diagnosed using the International Ascites club diagnostic criteria.

Serum Cortisol

Serum Cortisol was done in all patients after a overnight fasting. Blood sample for measuring serum cortisol was collected between 8.00 a.m.

and 9.00 a.m. Serum cortisol level <5 μg/dl is highly suggestive of adrenal insufficiency.

For comparison, 20 healthy age matched control subjects were included and their health status was validated by clinical examination and routine laboratory investigations. Informed consent was obtained from all participants.

STATISTICAL ANALYSIS

Statistical analysis was done using the statistical software package SPSS for window version for analyzing the data. The statistical methods used are Chi Square tests.

- p.value 0.000 to 0.010 is highly significant.
- p.value 0.000 should be considered as <0.001 (statistically highly significant).
- p.value 0.011 to 0.050 is significant.
- p.value 0.051 to 1.000 is not significant.

RESULTS

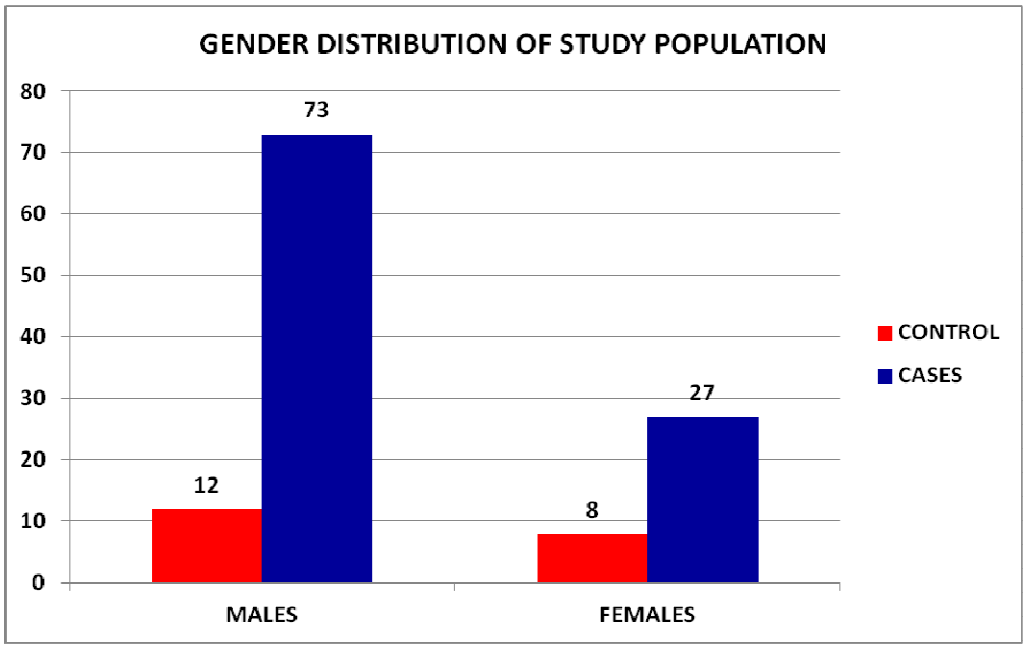
Patient characteristics

A total of 100 patients were included in the study. Among the 100 patients, 73(73%) were males and 27(27%) were females. 20 healthy control subjects were included in this study for comparison. Among the 20 controls, 12(60%) were males and 8(40%) were females.

Table 1 : GENDER DISTRIBUTION OF STUDY POPULATION

GENDER	GROUP		TOTAL
	CONTROL	CASES	
MALES	12 (60%)	73 (73%)	85
FEMALES	8 (40%)	27 (27%)	35
TOTAL	20	100	120

The preponderance of males in this study may be attributed to the etiology of the liver diseases, the most common being ethanol induced chronic liver disease.



Prevalence of Adrenal Insufficiency in the study population

On comparing serum cortisol level between cases and controls, 29(29%) cases had serum cortisol level <5 µg/dl and 71(71%) cases had serum cortisol level >5 µg/dl.

Table 2 : PREVALENCE OF ADRENAL INSUFFICIENCY IN THE STUDY POPULATION AMONG CASES

S.Cortisol	Frequency	Percent	Valid percent	Cumulative percent
<5	29	29%	29%	29%
>5	71	71%	71%	71%
Total	100	100%	100%	100%

In our study, out of 100 cases, 29 patients (29%) demonstrated adrenal insufficiency with a highly significant p.value (<0.001)

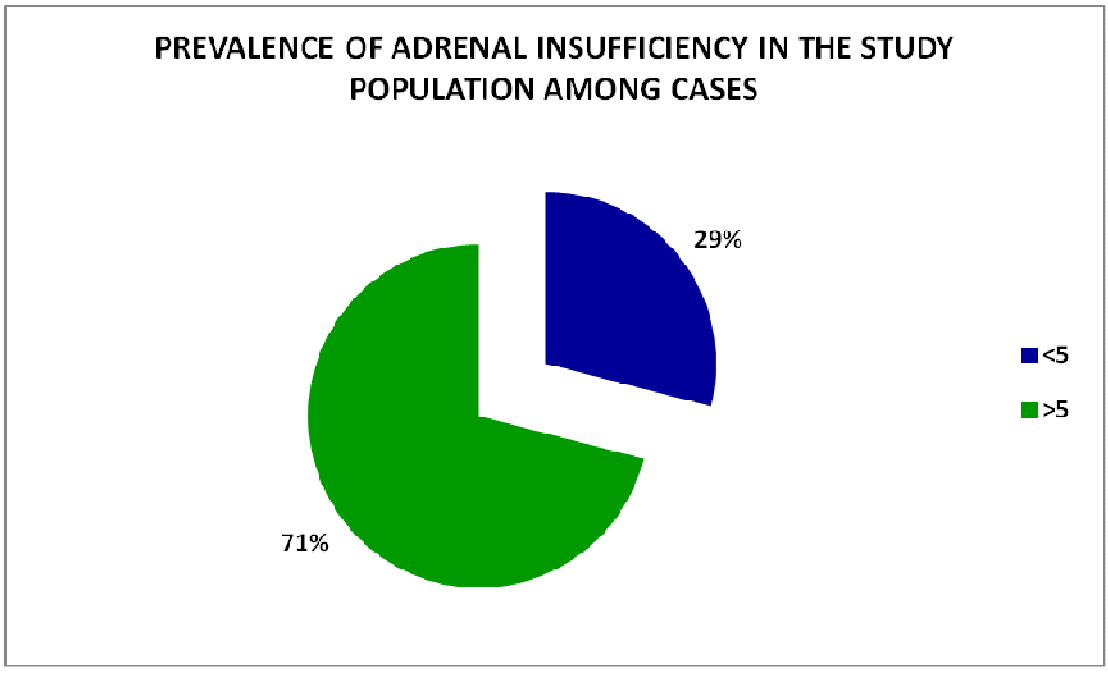


Table 3 : GENDER DISTRIBUTION OF ADRENAL INSUFFICIENCY AMONG CASES

Gender	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
Male	28	96.6	45	63.4	73	0.001
Female	01	3.4	26	36.6	27	
Total	29		71		100	

Among the 29 patients with adrenal insufficiency, 28 cases (96.6%) were males and 01 (3.4%) case was female.

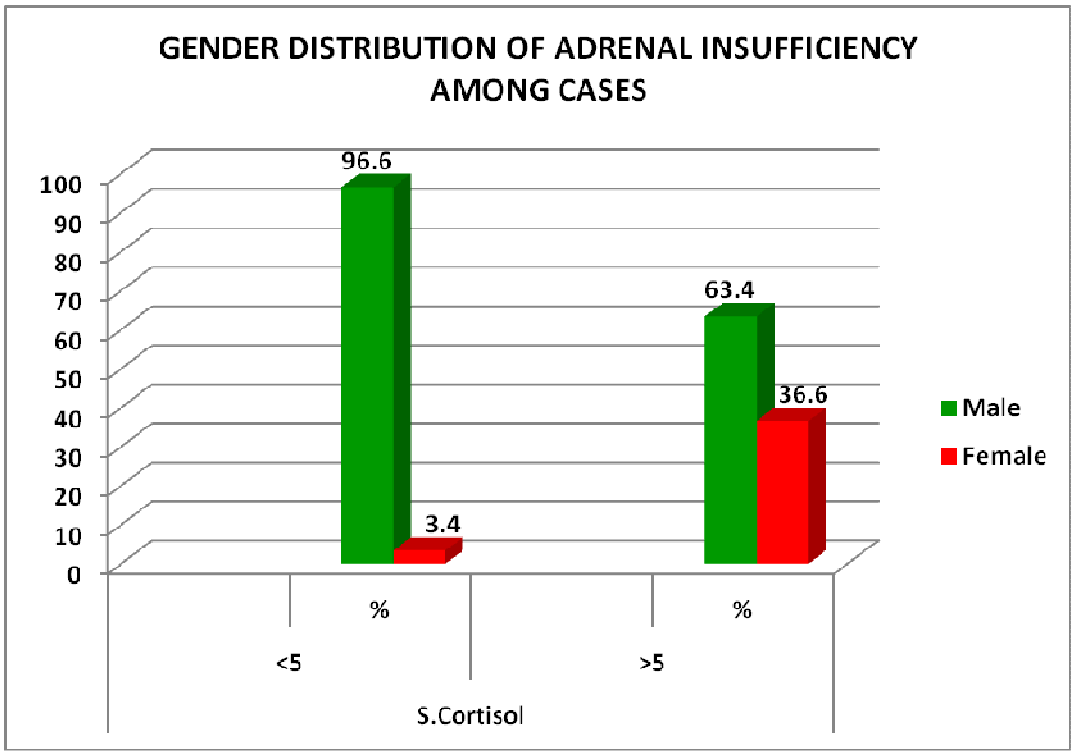


Table 4 : AGE DISTRIBUTION OF PATIENTS WITH ADRENAL INSUFFICIENCY AMONG CASES

Age	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
<40	03	10.3	25	35.2	28	0.011
40 – 50	20	69	27	38	47	
>50	06	20.7	19	26.8	25	
Total	29		71		100	

Among cases who were less than 40 years, only 3(10.3%) had adrenal insufficiency. 20 (69%) cases in the age group between 40 – 50 years were found to have adrenal insufficiency. In cases >50 years, only 6(20.7%) were found to have adrenal insufficiency.

Table 5 : CORRELATION BETWEEN ADRENAL INSUFFICIENCY AND ETIOLOGY OF THE LIVER DISEASE AMONG CASES

Etiology	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
Ethanol	21	72.5	31	43.7	52	0.019
HBV	3	10.3	28	39.4	31	
Metabolic	3	10.3	10	14.1	13	
HCV	2	6.9	2	2.8	4	
Total	29		71		100	

21 cases (72.5%) with Ethanol related chronic liver disease had adrenal insufficiency. Only 3 cases (10.3%) with HBV related chronic liver disease and 2 (6.9%) with HCV related chronic liver disease had adrenal insufficiency. 3 patients (10.3%) with chronic liver disease due to metabolic cause showed adrenal insufficiency.

.Table 6 : CORRELATION BETWEEN S.CORTISOL AND S.BILIRUBIN AMONG CASES

	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
<1.5	0	0	17	23.9	17	0.004
>1.5	29	34.9	54	65.1	83	
Total	29		71		100	

In our study, out of total 100 cases 17(17%) cases had serum bilirubin <1.5mg/dl and 83 (83%) cases had serum bilirubin >1.5mg/dl. Among the 83 patients with hyperbilirubinemia, 29(34.9%) patients had adrenal insufficiency with high statistical significance (p.value 0.004).

Table 7: CORRELATION BETWEEN S.CORTISOL AND CTP SCORE AMONG CASES

	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
A	0	0	30	100.0	30	<0.001
B	10	28.6	25	71.4	35	
C	19	54.3	16	45.7	35	
Total	29		71		100	

Among 100 study patients, 30 patients belong to CTP-A, 35 in CTP-B and 35 patients in CTP-C. Among the 30 patients in CTP-A, none of the patients had adrenal insufficiency. Out of 35 patients in CTP-B (28.6%), 10 patients had adrenal insufficiency. Among 35 patients with CTP-C, 19 (54.3%) patients had adrenal insufficiency.

Among 29 patients with adrenal insufficiency, 10 patients (34.5%) belonged to CTP-B and 19 patients (65.5%) belonged to CTP-C.

Our study shows highly significant statistical correlation (p.value <0.001) between serum cortisol and CTP score.

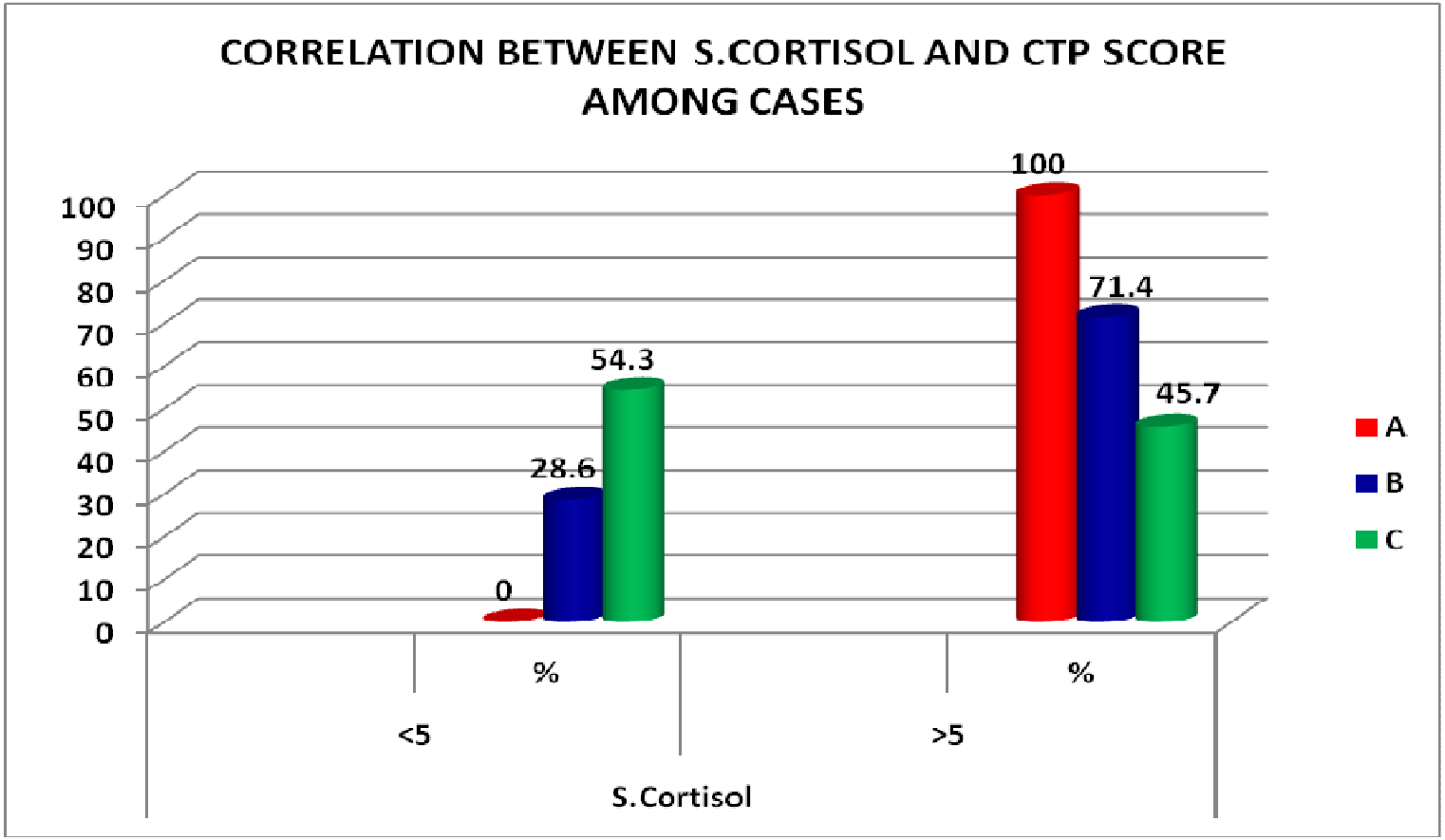

CORRELATION BETWEEN S.CORTISOL AND CTP SCORE AMONG CASES
100
90
80
70
60
50
40
30
20
10
0
0
28.6
54.3
100
71.4
45.7
%
%
<5
>5
S.Cortisol
A
B
C

Table 8 : CORRELATION BETWEEN S.CORTISOL AND S.ALBUMIN AMONG CASES

	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
<2.0	11	84.6	02	15.4	13	<0.001
2.0 – 2.5	15	48.4	16	51.6	31	
2.5 – 3.0	01	4.5	21	95.5	22	
>3.0	02	5.9	32	94.1	34	
Total	29		71		100	

Out of 100 study cases, 13 patients (13%) had serum albumin <2.0 g/dl, 31 patients (31%) had serum albumin between 2.0 – 2.5 g/dl, 22 patients (22%) had serum albumin between 2.5 – 3.0 g/dl and 34 patients (34%) had serum albumin >3.0 g/dl.

Among 13 patients with S.Albumin <2.0 g/dl, 11 patients (84.6%) had adrenal insufficiency.

Among 31 patients with S.Albumin <2.0 – 2.5 g/dl, 15 patients (48.4%) had adrenal insufficiency.

Among 22 patients with S.Albumin <2.5 – 3.0 g/dl, 1 patient (4.5%) had adrenal insufficiency.

Among 34 patients with S.Albumin >3.0 g/dl, 2 patients (5.9%) had adrenal insufficiency.

Among 29 patients with adrenal insufficiency, 11(37.93%) patients had S.Albumin <2.0 g/dl, 15(51.72%) patients had S.Albumin <2.0 – 2.5 g/dl ,1(3.44%) patient had S.Albumin <2.5 – 3.0 g/dl and 2(6.89%) patients had S.Albumin >3.0 g/dl.

The correlation between adrenal insufficiency and hypoalbuminemia was found to be high statistical significance (p <0.001).

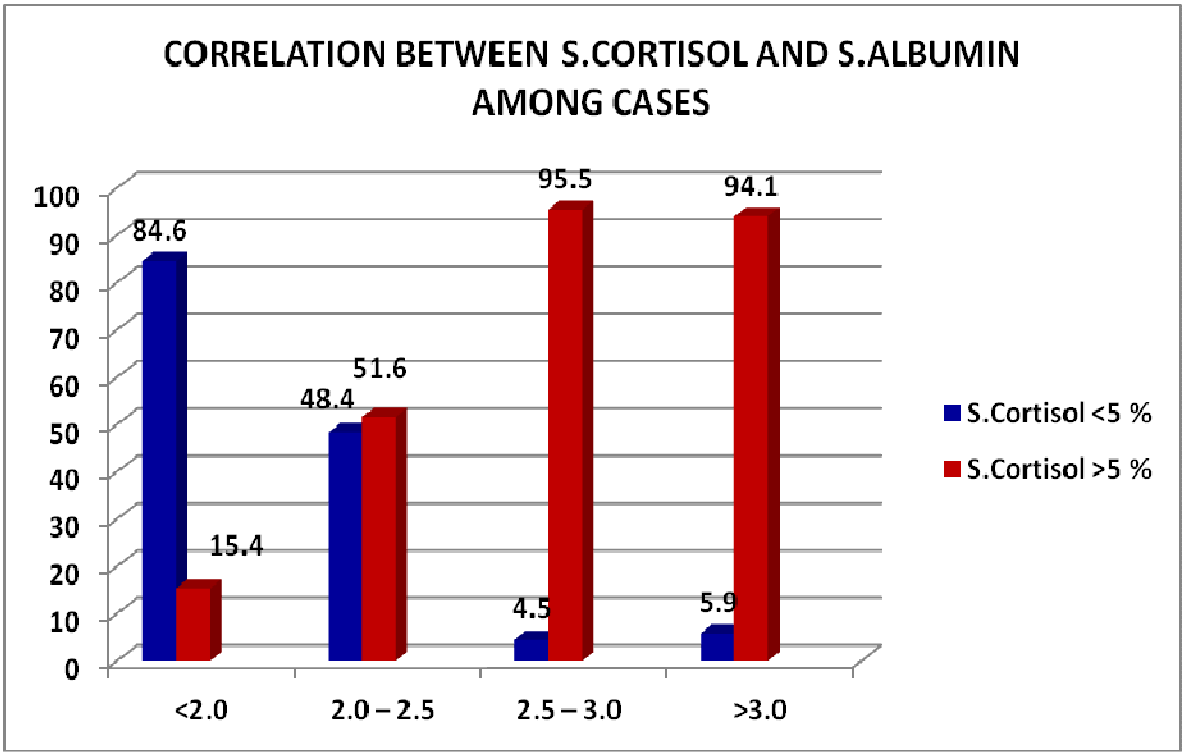


Table 9 : CORRELATION BETWEEN ADRENAL INSUFFICIENCY AND UGI BLEED AMONG CASES

	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
Present	14	45.2	17	54.8	31	0.017
Absent	15	21.7	54	78.3	69	
Total	29		71		100	

Out of 100 study cases, 31(31%) patients had UGI bleed. Among these 31 patients, 14 patients (45.2%) had adrenal insufficiency.

Among 29 patients with adrenal insufficiency 14 (48.27%) patients had UGI bleed.

The correlation between adrenal insufficiency and UGI bleed was found to be statistically significant (p. 0.017).

Table 10

CORRELATION BETWEEN ADRENAL INSUFFICIENCY AND HEPATIC ENCEPHALOPATHY AMONG CASES

	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
Present	**15**	**38.5**	**24**	**61.5**	**39**	**0.095**
Absent	**14**	**23.0**	**47**	**77.0**	**61**	
Total	**29**		**71**		**100**	

Out of 100 study patients, 39(39%) patients had hepatic encephalopathy. Among 39 patients with hepatic encephalopathy, 15 patients (38.5%) had adrenal insufficiency.

The correlation between adrenal insufficiency and hepatic encephalopathy is not statistically significant (p. 0.095).

Table 11: CORRELATION BETWEEN ADRENAL INSUFFICIENCY AND SPONTANEOUS BACTERIAL PERITONITIS AMONG CASES

	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
Present	09	42.9	12	57.1	21	0.115
Absent	20	25.3	59	74.7	79	
Total	29		71		100	

In our study, 21(21%) patient had spontaneous bacterial peritonitis. Among 21 patients with SBP, 9 (42.9%) patients had adrenal insufficiency. Among 29 patients with adrenal insufficiency, 9(31.03%) patients had SBP.

But the correlation was not statistically significant (p. 0.115).

Table 12: CORRELATION BETWEEN ADRENAL INSUFFICIENCY AND HEPATORENAL SYNDROME AMONG CASES

	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
Present	16	55.2	13	18.3	29	<0.001
Absent	13	44.8	58	81.7	71	
Total	29		71		100	

Totally 29 (29%) patients had hepatorenal syndrome in our study. Among the 29 patients with HRS, 16(55.2%) reported adrenal insufficiency.

Among the 29 patients with adrenal insufficiency, 16(55.2%) patients had hepatorenal syndrome.

The above correlation between adrenal insufficiency and hepato renal syndrome is statistically highly significant (p.<0.001).

Table 13 : CORRELATION BETWEEN S.CORTISOL AND TOTAL CHOLESTEROL AMONG CASES

	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
<150	19	65.5	0	0	19	<0.001
150 – 250	7	24.1	10	14.1	17	
>250	3	10.4	61	85.9	64	
Total	29		71		100	

In our study, 19 patients (19%) had total cholesterol <150 mg/dl, 17 patients (17%) had total cholesterol between 150 – 250 mg/dl and 64 patients (64%) had total cholesterol >250 mg/dl.

Among the 29 patients with adrenal insufficiency, 19 patients (65.5%) had total cholesterol <150 mg/dl, 7 patients (24.1%) had serum cholesterol between 150 – 250 mg/dl and 3 patients (10.4%) had total cholesterol >250 mg/dl

Among 19 cases with total cholesterol <150 mg/dl, all 19 patients (100.0%) had adrenal insufficiency.

Out of 17 patients with total cholesterol between 150 – 200 mg/dl, 7 patients (41.2%) had adrenal insufficiency.

Among the 64 patients with total cholesterol >250 mg/dl, only 3 patients (4.7%) had adrenal insufficiency.

The correlation between adrenal insufficiency and total cholesterol was highly significant (p.<0.001).

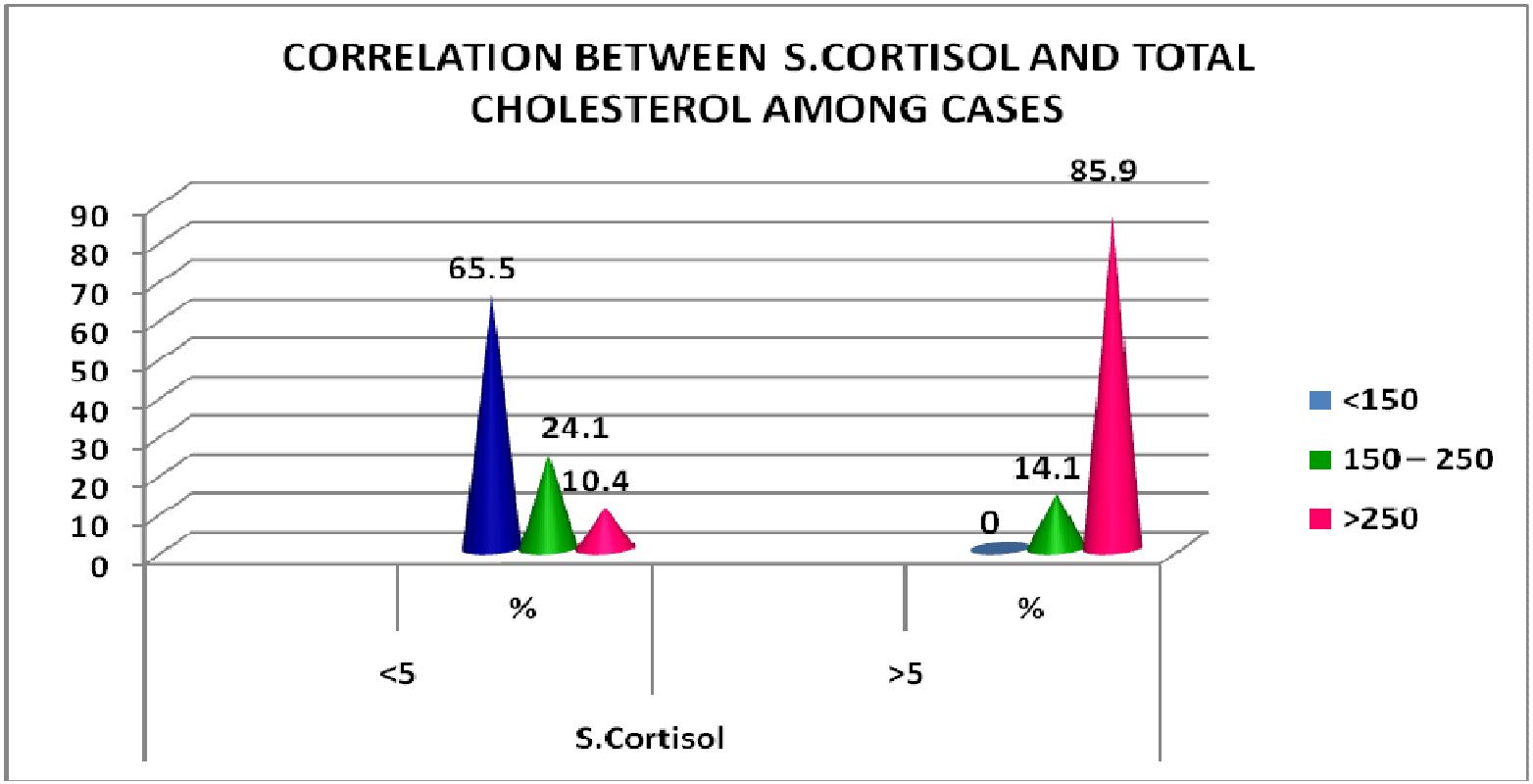

CORRELATION BETWEEN S.CORTISOL AND TOTAL CHOLESTEROL AMONG CASES
90
80
70
60
50
40
30
20
10
0
65.5
24.1
10.4
0
14.1
85.9
%
%
<5
>5
S.Cortisol
<150
150 – 250
>250

Table 14 : CORRELATION BETWEEN S.CORTISOL AND HDL AMONG CASES

	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
30 – 40	26	89.7	3	4.2	29	<0.001
40 – 50	3	10.3	57	80.3	60	
>50	0	0	11	15.5	11	
Total	29		71		100	

Among the 100 cases, 29 patients (29%) had HDL between 30 – 40 mg/dl. 60 patients (60%) had HDL between 40 – 50 mg/dl. 11 patients (11%) had HDL >50 mg/dl. Among controls, 18(90%) patients had HDL level 40-50mg/dl , and 2(10%) patients had HDL levels >50mg/dl.

Among the 29 patients with HDL between 30 – 40 mg/dl, 26 (89.7%) patients had adrenal insufficiency.

Out of 60 patients with HDL between 40 – 50 mg/dl, 3 patients (10.3%) patients had adrenal insufficiency.

Among the 11 patients with HDL >50 mg/dl, none of the patients had adrenal insufficiency.

Among the 29 patients with adrenal insufficiency, 26 patients (89.7%) had HDL between 30 – 40 mg/dl, and 3 patients (5.0%) had HDL between 40-50mg/dl.

The above correlation between adrenal insufficiency and HDL levels was found to be highly significant (p.<0.001).

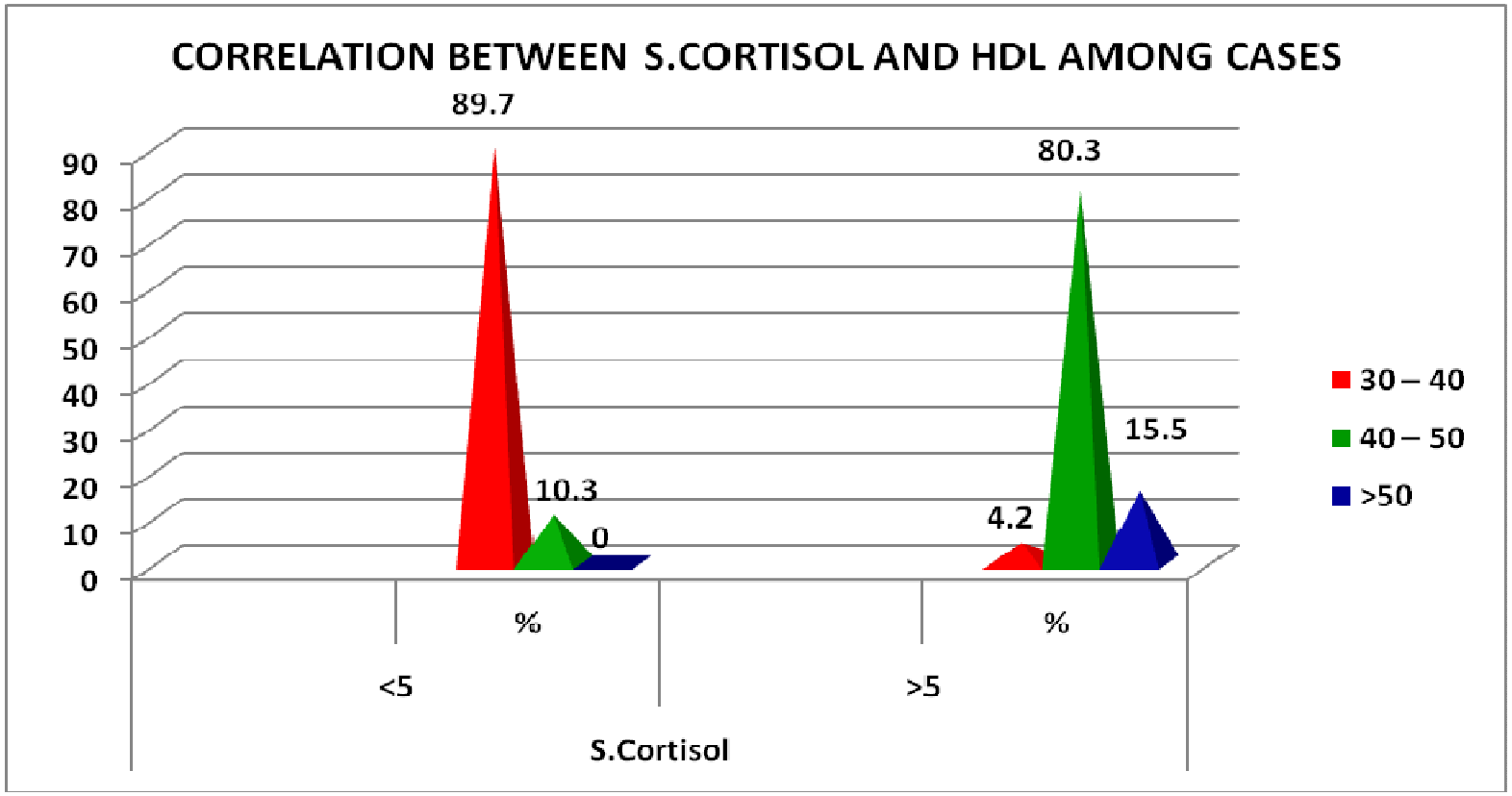

CORRELATION BETWEEN S.CORTISOL AND HDL AMONG CASES
89.7
80.3
10.3
0
4.2
15.5
90
80
70
60
50
40
30
20
10
0
%
%
<5
>5
S.Cortisol
30 – 40
40 – 50
>50

Table 15 : CORRELATION BETWEEN S.CORTISOL AND LDL AMONG CASES

	S.Cortisol				Total	p.value
	<5		>5			
	Frequency	%	Frequency	%		
<100	26	96.3	01	3.7	27	<0.001
100 – 150	01	2.8	35	97.2	36	
>150	02	5.4	35	94.6	37	
Total	29		71		100	

In our study population, 27 patients (27%) had LDL <100 mg/dl, 36 patients (36%) had with LDL between 100 – 150 mg/dl and 37 patients (37%) had LDL >150 mg/dl.

Among controls, 12(60%) patients had LDL level <100 mg/dl, and 8 (40%) patients had LDL levels between 100- 150mg/dl.

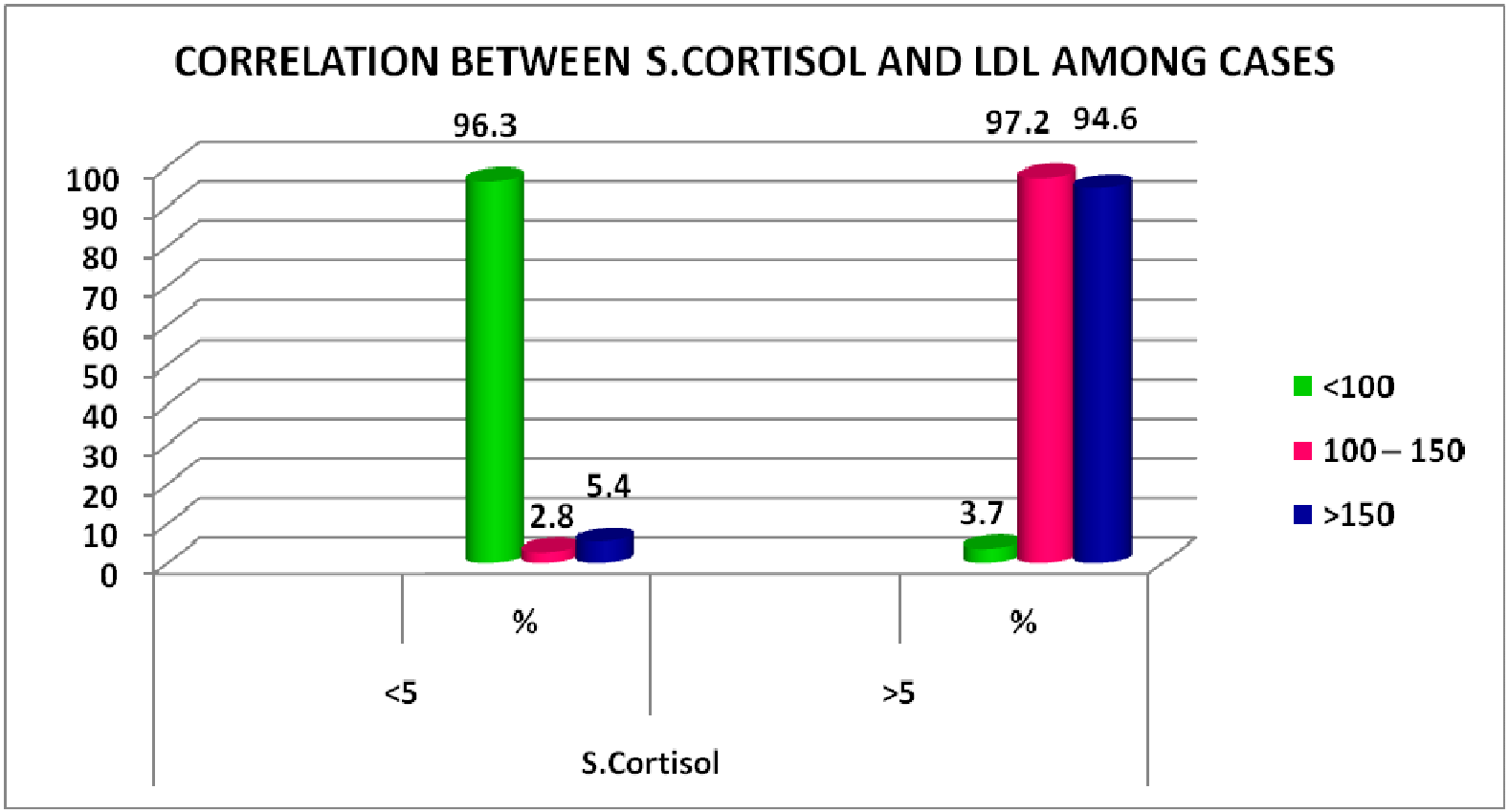
Among 27 patients with LDL <100 mg/dl, 26 patients (96.3%) patients had adrenal insufficiency.

Out of 36 patients with LDL between 100 – 150 mg/dl, 1 patient (2.8%) had adrenal insufficiency.

Among 37 patients with LDL >150 mg/dl, 2 patients (5.4%) had adrenal insufficiency.

Among 29 patients with adrenal insufficiency, 26 patients (89.7%) had LDL <100 mg/dl, 1 patient (3.4%) had with LDL between 100 – 150 mg/dl and 2 patients (6.9%) had LDL >150 mg/dl.

The above correlation between adrenal insufficiency and LDL levels was found to be highly significant (p.<0.001).


CORRELATION BETWEEN S.CORTISOL AND LDL AMONG CASES
96.3
97.2
94.6
100
90
80
70
60
50
40
30
20
10
0
2.8
5.4
3.7
%
%
<5
>5
S.Cortisol
<100
100 – 150
>150

DISCUSSION

Adrenal dysfunction or insufficiency (AI) is surging as one of vital cause of increasing morbidity and mortality in seriously ill patients[3]. Activation of the hypothalamic pituitary adrenal axis leading to the release of cortisol is an important component of adaptation to stress and illness thus contributing to the maintenance of cellular and organ homeostasis[56].

Since liver failure and sepsis are both associated with increased levels of circulating endotoxin and pro-inflammatory mediators, along with reduced levels of apolipoprotein II and HDL, adrenal failure was proposed to prevail in patients with hepatic diseases also[57]. Increasing occurrence of adrenal dysfunction in critically ill patients with liver disease has lead to a new term Hepatoadrenal syndrome[13].

This is a prospective study done to evaluate the prevalence of adrenal insufficiency in patients with chronic liver disease, both compensatory cirrhosis and decompensated cirrhosis and to assess the correlation between adrenal dysfunction and the complications of cirrhosis.

The prevalence of Adrenal Insufficiency varies widely, depending on the population of patients studied and the diagnostic criteria used. Fede et al studied the prevalence of adrenal insufficiency in stable cirrhotics and demonstrated that the overall prevalence of adrenal dysfunction was 38% with a higher prevalence in patients with advanced liver disease[59]. Various studies have shown that prevalence of adrenal dysfunction varies in

different stages of liver disease, with about (34.6%)[62] in acute liver disease, 10-87 %[13] in compensated cirrhosis, 7-83 %[60] in decompensated cirrhosis and 61-92 %[13] in post liver transplant patients.

Our study reflects similar results in various studies with a prevalence of 29% (p value highly significant <0.001).

The prevalence of Adrenal Insufficiency is more common in males than the females (96.6% Vs 3.4%), the reasons being alcoholic liver disease which is the commonest etiology of chronic liver disease in India, and is also commoner in males than females.

Ziets et al have reported that there was no significant correlation between adrenal dysfunction and the etiology of the liver disease[61]. But our study showed that adrenal dysfunction is more common in ethanol related chronic liver disease (72.4%), for the simple reason that ethanol being the commonest etiology of liver disease in our part of the country as already mentioned.

Adrenal Insufficiency and severity scores

Mohamed et al showed statistically significant relationship between serum cortisol and the CTP score[12]. Tsai et al had shown that the severity of adrenal insufficiency correlates with the disease severity scores such as MELD and APACHE scores and a negative correlation with CTP score[25].

Fernandez et al also reported that adrenal dysfunction was more prevalent in patients with advanced liver disease. (CTP C 76% Vs CTP B 25%)[26].

Our study also demonstrates similar results with adrenal dysfunction being reported in 10(28.6%) of patients with CTP B and 19(54.3%) of patients with CTP C and none of the patients in CTP A.

Adrenal Insufficiency and Hyperbiliruminemia

Previous studies have shown the correlation between adrenal dysfunction and serum bilirubin. Tsai et al reported a significant correlation between adrenal dysfunction and serum bilirubin and also had demonstrated that serum bilirubin was an independent predictor of AI in citically ill patients with cirrhosis and severe sepsis[25]. Our study also shows highly significant statistical correlation between serum cortisol and serum bilirubin (p.0.004).

Adrenal Insufficiency and Hypoalbuminemia

On evaluating the correlation of serum albumin to that of serum cortisol, our study showed that serum albumin levels are lower in patient with adrenal dysfunction. 11(37.9%) patients with serum albumin <2.0 g/dl and 15(51.7%) patients with serum albumin 2.0 – 2.5 g/dl had adrenal dysfunction. Only one patient (3.4%) with serum albumin 2.5 – 3.0 g/dl and two patients with serum albumin >3 g/dl had adrenal insufficiency. Thus,

our study shows a highly significant statistical correlation between serum cortisol and serum albumin (p. <0.001).

Kharbe et al showed that serum albumin was one of the predictor of adrenal insufficiency in CLD[62] whereas Marik et al found no correlation between serum albumin and serum cortisol[13].

Adrenal Insufficiency & Upper Gastro intestinal bleed

Our study evaluated the correlation between adrenal insufficiency and variceal bleeding and found that adrenal dysfunction was significantly higher in bleeders than in non bleeders. Among the total bleeders (31), 14 patients (45.2%) had been found to have adrenal insufficiency with a statistically significant p value (p. 0.017).

Similar results were also shown by Triantos et al who reported higher prevalence of Adrenal Insufficiency in bleeders (60%) than in non bleeders[14]. Hamrahian et al had reported that coagulopathy, which is commoner with liver disease patients, can result in adrenal infarction due to adrenal hemorrhage and AI[45]. Graupera et al reports high chances of failure to control bleed in patients with AI[30].

Adrenal Insufficiency & Hepatorenal syndrome

In this present study, we analyzed the correlation between Adrenal Insufficiency and hepatorenal syndrome. Overall 29(29%) patients had HRS in the study population among which 16 patients (55.2%) had adrenal

insufficiency with a high statistical significance [p value (p.<0.001)]. This result is similar to previous studies by Acevedo et al who reported a high prevalence of (16% Vs 3%) of AI in patients with type I hepatorenal syndrome[29]. In addition, he showed that patients with AI have greater impairment of circulatory and renal function, increased rate of severe sepsis and Type I HRS and higher short term mortality than in patients with normal adrenal function.

Hepatic Encephalopathy and Adrenal Insufficiency

We evaluated the correlation between Adrenal Insufficiency and hepatic encephalopathy. Totally 39(39%) patients had hepatic encephalopathy among the study population. Among the 39 patients with hepatic encephalopathy, 15(38.5%) patients had associated adrenal insufficiency, which is not statistically significant (p.0.095).

But previous studies shows significant correlation between hepatic encephalopathy and adrenal insufficiency. Arafa et al had reported that serum cortisol concentration in cirrhotic patients with hepatic encephalopathy were significantly decreased compared to those in patients without hepatic encephalopathy[46]. The same study also showed that serum cortisol concentration decreased with progression of hepatic encephalopathy from Grade I to IV.

AI & spontaneous bacterial peritonitis

In our study, 21 patients (21%), out of 100 study patients, had spontaneous bacterial peritonitis. Among the 21 patients, 9 patients (42.9%) had AI, but this was not statistically significant (p value 0.115). Tsai et al in his study had reported a significant prevalence of AI in patients with spontaneous bacterial peritonitis (8.91%)[25].

AI & Serum cholesterol

In our study, we analysed the correlation between serum cortisol and total cholesterol, HDL & LDL, which showed that lower levels of total cholesterol, HDL and LDL were found to be associated with AI in chronic liver disease patients. Among 29 cases with AI, 19 (65.5%) patients had hypocholesterolemia with high statistical significance ($p < 0.001$).

Similarly, out of 29 patients with AI, 26(89.7%) patients had lower HDL levels with high statistical significance ($p < 0.001$). As already mentioned, out of 29 patients with AI, 26(89.7%) had lower LDL levels with high statistical significance ($p < 0.001$).

Similar results were reported in most of the previous studies. Marik et al found that reduced levels of total cholesterol, HDL and LDL were associated with AI[17]. Kharb et al also reflects similar results and found that low LDL and HDL were one of the predictors of AI[62].

This can be explained by direct decrease in substrate supply since cortisol synthesis requires cholesterol as a substrate. Cicognani et al demonstrated a marked decrease in the level of serum HDL in cirrhotic patients which was associated with the severity of liver disease (child class)[63].

Habib et al showed that HDL cholesterol less than 30 mg/dl in cirrhotic patients were found to have 3 – 4 fold increase in the rate of death due to cirrhosis or transplantation at 6 or 12 months[64].

Predictions of Adrenal Insufficiency

Our study analysed the various predictors in chronic liver disease patients presenting with adrenal dysfunction. Among several parameters, most important predictors of AI in chronic liver disease are:

1. Serum bilirubin
2. CTP score
3. Variceal bleed
4. Serum albumin
5. Hepato renal syndrome
6. Low total cholesterol, HDL and LDL.

Several studies have reported the predictors of AI in chronic liver disease. Elfaramawy reports that the presence of ascites, high temperature, high CRP, neutrophilia, high AST, ALT, high total bilirubin, prolonged INR and liver albumin were all factors associated with AI[66].

Tsai et al reported that serum bilrubin was an independent factor in predicting AI in critically ill patients with cirrhosis and sepsis. Fede et al reported that advanced liver disease (CTPC), high MELD score, ascites and basal cortisol were independently associated with adrenal insufficiency[25].

Kharb et al reports that AI was predicted by higher total biliruin INR, CTP scores and lower basal total cortisol, albumin, total cholesterol and LDL and HDL[62]. Marik et al study found that the HDL level was the only predictor of AI ($p < 0.001$)[3].

CONCLUSION

1. Adrenal Insufficiency occurs frequently in patients with liver cirrhosis both during critical illness and in stable disease.

2. Adrenal insufficiency occurs more frequently in patients with more advanced liver disease and correlated with disease severity scores.

3. Adrenal function worsens with progression of liver disease and such patients should be periodically assessed for adrenal insufficiency.

4. Significant correlation was found between serum cortisol and serum bilirubin, variceal bleeding, CTP score and hepatorenal syndrome.

5. Significant predictors of adrenal insufficiency in patients with chronic liver disease were found to be serum bilirubin, serum albumin, total cholesterol, HDL and LDL.

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ABBREVIATIONS

1. AI	:	Adrenal Insufficiency
2. CTP	:	Child-Turcotte-Pugh score
3. ALT	:	Alanine Aminotransferase
4. AST	:	Aspartate Aminotransferase
5. HRS	:	Hepato-renal Syndrome
6. SBP	:	Spontaneous Bacterial Peritonitis
7. HPA axis	:	Hypothalamo-Pituitary-Adrenal axis
8. HE	:	Hepatic Encephalopathy
9. ACTH	:	Adreno Corticotrophic Hormone
10. CRH	:	Corticotrophin releasing hormone
11. HDL – C	:	High Density Lipoprotein – cholesterol
12. LDL – C	:	Low Density Lipoprotein – cholesterol

PROFORMA

NAME : AGE/SEX :

DDHD No:

HISTORY:

Haemetemesis: Malena: Haematochezia: Abdominal pain: Abdominal distension: Vomiting: Altered sleep pattern: Jaundice:

PAST HISTORY

GI Bleed: Jaundice: Ascites: Blood transfusions:

DM: SHT: TB: IHD :

Drug/ NSAID intake:

PERSONAL HISTORY:

Smoking: Alcohol : Premarital / extramarital sexual exposure : Inravenous drug abuse :

FAMILY HISTORY:

GENERAL EXAMINATION:

CONSCIOUS/ORIENTED: PALLOR: ICTERUS: CYANOSIS: CLUBBING: EDEMA;

OTHER SIGNS:

VITALS: HT: WT: BMI:

PULSE: BP: TEMP: URINE OUTPUT:

SYSTEMIC EXAMINATION:

ORAL CAVITY: P/A: P/R: R.S: CVS: CNS:

INVESTIGATIONS:

Hb : ESR: TC : DC: P L E M

BT: CT: PLATELET COUNT:

PT/INR:

RBS: UREA: CREATININE:

LFT: TOTAL BILIRUBIN: DIRECT:

INDIRECT:

SGOT : TOTAL PROTEIN:

SGPT : ALBUMIN:

HBsAg: Anti-HCV:

CTP SCORE: MELD SCORE:

FASTING LIPID PROFILE : TOTAL CHOLESTEROL

LDL CHOLESTEROL

HDL CHOLESTEROL

BASAL SERUM CORTISOL:

USG ABDOMEN:

ASCITIC FLUID ANALYSIS : CELL COUNT: DIFFERENTIAL COUNT:

PROTEIN: SAAG:

ALBUMIN: CULTURE:

OGD REPORT:

ECG:

CHEST X RAY:

MASTER CHART - CASES

S.No	Age/Sex	Hb	Platelets	S.Bilirubin	AST/ALT	T.Protein	S.Albumin	PT/INR	B.Urea	S.Creatinine	S.Cortisol	T.Cholesterol	HDL	LDL	SAAG	A.F.PMN	A.F.Culture	UGIB	Ascites	HE	SBP	HRS	OGD	CTP	Etiology
1	45/M	11.4	2,20,000	2.2	48/57	5.9	2.4	14/1.68	22	0.9	22.1	298	51	164	1.8	320	P	-	P	-	P	_	No o.v.	B	Ethanol
2	38/M	12.8	1,88,000	1.1	23/34	7.2	3.9	17/1.3	19	1	20.4	286	49	171	-	-	-	-	-	-	-	-	No o.v.	A	HBV
3	44/F	9.8	98,000	4.1	97/114	5.7	2.3	20/1.8	59	2.9	19.84	314	52	181	1.4	-	-	P	P	P	-	P	Gr11/red signs	C	Metabolic
4	51/F	8.9	76,000	6.8	112/134	6.1	2.4	16/1.7	68	3.1	16.72	288	49	172	1.6	-	-	P	P	P	-	P	Gr11/red signs	C	Ethanol
5	54/M	9.1	80,000	3.4	84/68	6.3	1.9	17/1.58	17	1	4.1	292	50	174	-	-	-	-	-	-	-	-	No o.v.	B	Metabolic
6	49/F	8.9	88,000	8.4	98/74	5.8	3.9	17/1.3	82	3.8	4.9	138	36	71	2.1	350	P	P	P	P	-	P	Gr111/red signs	C	Ethanol
7	55/M	12	2,40,000	1.2	31/42	6.9	2.1	11/1.3	20	0.9	17.84	282	44	162	-	-	-	-	-	-	-	-	No o.v.	A	HBV
8	36/M	7.4	54,000	3.2	64/41	6.7	2.3	16/1.7	74	4.2	3.8	239	32	72	1.8	330	P	P	P	-	P	P	Gr111/red signs	C	Ethanol
9	42/M	9.8	98,000	1.8	64/72	6.3	3.6	20/1.8	19	0.8	19.13	279	49	164	1.4	280	P	-	P	-	P	-	No o.v.	B	Ethanol
10	55/M	8.8	74,000	2.3	32/46	6.4	3.9	16/1.7	23	0.9	21.14	312	51	172	1.3	300	P	P	P	-	P	-	Gr11/red signs	B	Metabolic
11	25/F	12.2	2,10,000	1.4	28/38	6.9	2.2	17/1.52	18	1	20.36	272	48	162	-	-	-	-	-	-	-	-	No o.v.	A	HBV
12	22/F	10.2	1,86,000	4.6	56/66	6.1	2.6	17/1.3	61	3.2	18.46	278	49	159	1.6	-	-	-	P	P	-	P	Gr1 o.v.	C	Ethanol
13	50/F	11.4	1,72,000	2.3	37/49	5.8	3.6	16/1.7	17	0.7	19.32	311	51	172	1.4	280	P	-	P	-	P	-	No o.v.	B	Metabolic
14	38/M	12.6	1,24,000	1.8	18/24	6.6	3.9	20/1.8	16	0.8	21.44	276	47	156	-	-	-	-	-	-	-	-	No o.v.	A	HBV
15	44/M	7.6	76,000	5.2	71/59	6.2	2.2	17/1.4	79	4.6	4.6	139	32	70	2.2	320	P	P	P	-	-	P	Gr111/red signs	C	Ethanol
16	51/M	9.8	2,40,000	1.3	18/29	6.4	3.6	21/1.68	21	1	22.36	282	49	162	-	-	-	-	-	-	-	-	No o.v.	A	HBV
17	48/M	9.6	1,80,000	2.3	39/47	5.8	2.4	14/1.6	23	0.9	3.7	138	31	81	-	-	-	-	-	-	-	-	No o.v.	B	HBV
18	26/M	11.6	1,98,000	1.2	24/32	6.3	3.5	12/1.9	18	0.8	21.48	282	47	152	-	-	-	-	-	-	-	-	No o.v.	A	HBV
19	38/M	7.4	66,000	2.2	35/48	5.9	2.9	17/1.3	17	0.7	19.38	266	44	138	1.6	300	P	P	P	-	P	-	Gr11/red signs	B	HCV
20	49/M	8.1	72,000	5.9	62/74	6.2	2.1	15/1.4	72	4.2	4.2	139	33	71	1.8	330	P	P	P	P	-	P	Gr11/red signs	C	Ethanol
21	51/M	10.1	2,50,000	0.9	24/34	6.8	3.9	11/1.8	17	0.9	16.84	283	47	141	-	-	-	-	-	-	-	-	No o.v.	A	HBV
22	39/M	9.8	3,25,000	2.1	49/58	5.9	3.1	12/1.9	21	1	14.32	314	49	154	1.4	-	-	-	P	P	-	-	No o.v.	B	Metabolic
23	48/M	11.4	1,85,000	6.4	98/112	5.8	1.9	16/1.68	71	3.2	4.2	145	31	71	2.2	320	P	-	P	P	P	P	Gr1 o.v.	C	HCV
24	56/M	12.3	1,91,000	8.2	114/132	6.1	2.9	21/1.68	62	2.9	18.46	298	46	141	1.2	350	P	-	P	P	P	P	Gr11 o.v.	C	Ethanol
25	52/M	11.8	1,60,000	2.4	62/84	6.8	2.4	17/1.3	23	0.9	3.2	144	31	80	1.4	-	-	-	P	P	-	-	No o.v.	B	Ethanol
26	50/M	7.2	86,000	5.9	96/72	6.3	2.3	20/1.8	68	4.5	2.9	139	31	73	2.1	300	P	P	P	P	P	P	Gr111/red signs	C	Ethanol
27	42/F	12.8	1,12,000	0.8	32/41	7.6	3.9	16/1.7	16	0.8	17.32	284	49	141	-	-	-	-	-	-	-	-	No o.v.	A	HBV
28	49/M	10.9	1,84,000	1.9	66/74	6.4	2.1	10/1.2	21	0.7	2.6	149	32	76	1.9	-	-	-	P	-	-	-	Gr1 o.v.	B	Ethanol

S.No	Age/Sex	Hb	Platelets	S.Bilirubin	AST/ALT	T.Protein	S.Albumin	PT/INR	B.Urea	S.Creatinine	S.Cortisol	T.Cholesterol	HDL	LDL	SAAG	A.F.PMN	A.F.Culture	UGIB	Ascites	HE	SBP	HRS	OGD	CTP	Etiology
29	46/F	11.1	1,38,000	0.9	19/21	6.7	3.4	21/1.72	19	1	22.84	309	54	169	-	-	-	-	-	-	-	-	No o.v.	A	Metabolic
30	57/M	12.2	2,26,000	2.1	34/48	6.2	2.1	17/1.3	16	0.9	4.6	139	32	79	1.4	-	-	-	P	-	-	-	Gr11 o.v.	B	Ethanol
31	39/F	8.4	98,000	4.8	72/58	6.4	2.9	11/1.3	54	2.7	19.32	320	53	176	1.6	-	-	P	P	P	-	P	Gr11/red signs	C	Metabolic
32	48/F	10.2	2,40,000	4.9	38/49	5.9	2.3	22/2.0	15	1	20.82	298	49	162	-	-	-	-	-	-	-	-	No o.v.	B	HBV
33	49/M	7.8	82,000	6.8	54/68	5.6	1.8	20/1.8	83	3.9	3.9	131	30	71	2.1	350	P	P	P	P	-	P	Gr11/red signs	C	Ethanol
34	34/F	10.4	1,94,000	0.8	32/42	6.8	3.9	16/1.7	22	0.8	16.54	289	49	154	-	-	-	-	-	-	-	-	No o.v.	A	HBV
35	48/M	11.4	2,10,000	8.4	54/66	5.3	1.7	17/1.52	76	4.1	4.1	128	32	76	1.9	300	P	-	P	-	-	P	Gr11/red signs	C	Ethanol
36	39/M	12.2	2,66,000	0.7	21/32	7.2	3.9	17/1.3	17	0.7	22.32	276	46	162	-	-	-	-	-	-	-	-	No o.v.	A	Ethanol
37	51/M	7.2	88,000	2.2	43/54	6.7	2.9	16/1.7	58	2.8	19.46	282	47	166	1.8	-	-	P	P	P	-	P	Gr11 o.v.	B	Ethanol
38	44/M	10.1	1,60,000	1.3	36/48	6.9	1.9	15/1.4	79	0.6	18.32	278	46	159	-	-	-	-	-	-	-	-	No o.v.	A	Ethanol
39	39/M	8.1	94,000	4.8	63/58	6.1	2.4	18/1.68	19	3.7	3.8	146	34	81	2.2	320	P	P	P	-	P	P	Gr111/red signs	C	Ethanol
40	42/M	7.4	76,000	2.1	52/68	6.3	2.6	19/2.0	21	0.8	17.46	316	52	76	1.6	-	-	P	P	P	-	-	Gr11 o.v.	B	Metabolic
41	33/F	12	1,40,000	5.3	50/67	6.1	2.6	17/1.4	16	1.1	19.68	284	48	142	-	-	-	-	-	-	-	-	No o.v.	A	HBV
42	48/M	11.4	2,36,000	4.2	56/62	5.4	2.4	11/1.4	22	0.9	4.61	324	49	168	1.4	80	-	-	P	-	-	-	Gr1 o.v.	B	Ethanol
43	29/M	10.8	1,90,000	4.1	60/38	6	2.7	10/1.2	19	1	21.34	296	44	154	-	-	-	-	-	-	-	-	No o.v.	B	Ethanol
44	41/F	8.1	86,000	17	158/87	6.2	3.5	29/2.76	21	0.8	19.24	264	46	132	1.6	350	P	P	P	P	P	-	Gr11/red signs	C	Ethanol
45	39/M	7.6	68,000	2.7	86/34	6.4	1.8	11/1.4	82	3.8	3.81	161	32	74	2.1	-	-	P	P	P	-	P	Gr111/red signs	C	Ethanol
46	57/M	9.4	1,52,000	7.4	185/75	5.2	1.6	11/1.3	79	4.2	2.91	156	33	71	1.8	400	P	_	P	P	P	P	Gr11 o.v.	C	Ethanol
47	44/F	11.5	2,13,000	3.6	32/45	5.2	2.2	11/1.3	56	2.8	18.69	256	48	116	1.6	-	-	-	P	P	_	P	Gr1 o.v.	B	Ethanol
48	56/M	10.6	1,96,000	1.9	50/24	7.6	3	18/1.68	23	0.9	17.34	273	49	132	-	-	-	-	-	-	-	-	No o.v.	A	HBV
49	46/F	7.2	94,000	5.2	126/110	6.1	2.9	16/1.7	19	1.1	19.82	269	45	134	1.8	-	-	P	P	P	-	-	Gr11/red signs	B	Ethanol
50	49/M	6.9	76,000	7.2	236/142	6.2	1.9	21/2.03	69	3.9	4.11	164	36	78	2.1	-	-	P	P	P	-	P	Gr111/red signs	C	HBV
51	51/M	9.8	1,30,000	0.9	28/22	7	3.6	10/1.2	17	0.9	18.64	259	42	141	-	-	-	-	-	-	-	-	No o.v.	A	HBV
52	38/F	11.2	2,30,000	1.9	50/24	7.6	3	18/1.68	20	1.1	15.42	286	51	148	-	-	-	-	-	-	-	-	No o.v.	A	HBV
53	52/M	10.8	3,82,000	6.5	24/30	6.1	3.2	11/1.4	22	0.7	4.39	141	34	84	1.4	-	-	-	P	-	-	-	Gr1 o.v.	B	Ethanol
54	39/M	10.1	2,40,000	2.3	42/54	6.4	3.2	18/1.68	61	3.2	19.32	288	44	136	1.8	-	-	-	P	P	-	P	Gr1 o.v.	B	Ethanol
55	46/M	9.3	1,98,000	7.1	66/84	5.9	1.7	16/1.7	20	0.8	3.93	296	46	148	2.2	300	P	-	P	P	P	-	Gr11 o.v.	C	Metabolic
56	49/M	8.2	1,12,000	6.2	56/72	5.1	2.2	17/1.3	72	4.6	4.14	138	33	79	1.6	-	-	P	P	-	-	P	Gr11/red signs	C	Ethanol

S.No	Age/Sex	Hb	Platelets	S.Bilirubin	AST/ALT	T.Protein	S.Albumin	PT/INR	B.Urea	S.Creatinine	S.Cortisol	T.Cholesterol	HDL	LDL	SAAG	A.F.PMN	A.F.Culture	UGIB	Ascites	HE	SBP	HRS	OGD	CTP	Etiology
57	43/M	8.8	98,000	0.8	24/29	6.8	3.9	20/1.8	17	1.1	20.34	274	41	156	-	-	-	-	-	-	-	-	No o.v.	A	HBV
58	39/M	9.4	1,10,000	1.1	32/44	6.6	3.8	21/1.9	19	0.9	22.12	283	45	132	-	-	-	-	-	-	-	-	No o.v.	A	HBV
59	46/M	10.3	1,56,000	6.5	132/121	5.9	1.8	14/1.7	21	0.7	4.72	162	36	79	2.1	380	P	-	P	P	P	-	Gr11 o.v.	C	HCV
60	51/F	7.4	84,000	2.4	39/51	6.1	3.6	11/1.4	18	0.8	18.46	278	42	156	1.2	-	-	P	P	P	-	-	Gr11 /red signs	B	HBV
61	39/M	10	1.65.000	5.3	50/67	6.1	3.1	17/1.58	20	0.8	12.39	212	44	108	-	-	-	-	-	-	-	-	No o.v.	A	Ethanol
62	37/M	12	1,10,000	4.2	56/42	5.4	2.5	11/1.4	24	0.6	23.14	208	41	141	-	-	-	-	-	-	-	-	No o.v.	B	Ethanol
63	48/M	10	91,000	8.4	88/64	5.7	2.3	34/3.1	85	3.8	3.89	151	32	89	1.9	100	-	P	P	P	-	P	Gr111/red signs	C	Metabolic
64	46/F	11	1,90,000	6.8	114/88	6.4	3	18/1.68	74	2.9	15.18	256	49	141	2.1	150	-	P	P	P	-	P	Gr11/red signs	C	HBV
65	51/M	11	2,20,000	1.9	40/24	7.6	3	15/1.4	35	0.8	19.23	284	41	136	-	-	-	-	-	-	-	-	No o.v.	A	Ethanol
66	39/F	9.8	1,20,000	3.6	30/45	5.2	2.2	11/1.3	21	0.9	16.84	239	42	114	-	-	-	-	-	-	-	-	No o.v.	B	Ethanol
67	51/M	10.1	1,50,000	16	68/42	6.3	2.3	16/1.7	79	4.1	18.14	259	44	131	1.8	400	P	-	P	P	P	_	Gr1 o.v.	C	Ethanol
68	59/M	11.1	2,40,000	7.6	112/74	5.2	2.8	11/1.3	19	0.9	21.32	219	41	124	-	-	-	-	-	-	-	-	No o.v.	B	HBV
69	48/M	12	3,12,000	12	24/30	6.1	2.4	10/1.2	27	0.9	4.25	144	31	78	-	-	-	-	-	-	-	-	No o.v.	B	HBV
70	38/F	10.8	2,36,000	5.2	64/30	6.1	3.4	20/1.8	61	2.8	22.41	226	43	112	2.1	40	-	P	P	P	-	P	Gr11/red signs	C	Ethanol
71	44/M	10.8	1,90,000	4.3	82/114	6.8	2.7	19/1.59	31	0.8	19.65	283	40	135	2.4	-	-	P	P	-	-	-	Gr11/red signs	B	Ethanol
72	41/M	11.2	2,10,000	0.9	28/22	7	3.6	10/1.2	28	1.1	17.34	272	44	141	-	-	-	-	-	-	-	-	No o.v.	A	HBV
73	48/M	9.8	1,84,000	11.2	84/98	5.7	2.4	34/3.1	89	3.6	13.45	269	43	136	1.9	60	P	-	P	P	P	_	Gr11 o.v.	C	Metabolic
74	36/F	9.6	2,14,000	4.3	28/22	6.8	2.7	19/1.59	19	0.9	18.42	273	40	136	1.7	90	-	-	P	-	-	-	Gr1 o.v.	B	Ethanol
75	49/M	11.1	2,36,000	1.9	40/24	7.6	3	15/1.4	23	0.8	17.36	279	41	135	-	-	-	-	-	-	-	-	No o.v.	A	HBV
76	51/M	10.1	1,86,000	5.3	50/67	6.1	2.9	17/1.58	17	0.7	19.19	268	42	131	-	-	-	-	-	-	-	-	No o.v.	A	HBV
77	48/M	10.6	2,12,000	17	148/77	6.8	2.1	24/2.76	98	4.2	2.81	149	33	81	2.4	400	P	P	P	P	P	P	Gr11/red signs	C	Ethanol
78	37/F	9.8	3,10,000	7.4	52/64	5.2	2.8	11/1.3	27	1	21.56	248	42	124	1.9	60	-	-	P	-	-	-	Gr1 o.v.	B	Ethanol
79	47/M	10.2	2,10,000	1.9	28/32	7.6	3.1	15/1.4	33	0.8	18.32	236	40	121	-	-	-	-	-	-	-	-	No o.v.	A	HBV
80	52/M	9.6	1,40,000	1.6	68/42	6.3	2.3	16/1.7	73	3.4	16.15	266	41	132	2.2	45	-	P	P	P	-	P	Gr11/red signs	C	Ethanol
81	34/F	9.8	1,36,000	4.2	50/67	5.4	2.5	11/1.4	28	1	16.28	278	46	141	1.4	40	-	-	P	P	-	-	Gr 1 o.v.	B	HBV
82	39/M	10.1	1,80,000	1.6	34/42	6.1	3.2	17/1.58	19	1.1	16.64	246	43	156	-	-	-	-	-	-	-	-	No o.v.	A	Ethanol
83	42/F	7.9	67,000	7.8	88/92	5.7	2.3	11/1.4	29	3.2	18.32	228	44	134	1.6	65	-	P	P	P	-	P	Gr 111 /red signs.	C	Metabolic
84	49/M	9.2	88,000	4.7	66/48	5.2	2.9	21/1.93	23	0.9	3.21	151	39	78	-	-	-	-	-	-	-	-	No o.v.	B	Ethanol

S.No	Age/Sex	Hb	Platelets	S.Bilirubin	AST/ALT	T.Protein	S.Albumin	PT/INR	B.Urea	S.Creatinine	S.Cortisol	T.Cholesterol	HDL	LDL	SAAG	A.F.PMN	A.F.Culture	UGIB	Ascites	HE	SBP	HRS	OGD	CTP	Etiology
85	48/F	8.4	92,000	5.9	39/24	5.7	2.4	13/1.4	16	1.1	17.04	268	46	142	2.4	400	P	P	P	P	P	-	Gr11/ red signs	C	HCV
86	51/M	11.4	1,56,000	1.9	28/36	6.4	3.8	16/1.48	18	0.9	14.98	239	48	124	-	-	-	-	-	-	-	-	No o.v.	A	HBV
87	32/F	9.4	1,79,000	2.9	44/68	5.8	2.4	17/1.58	25	1.1	14.36	268	47	134	1.6	40	-	P	P	-	-	-	Gr11/red signs	B	HBV
88	48/M	8.7	96,000	4.2	112/88	6.3	1.8	16/1.7	85	3.8	2.45	142	38	82	2.1	80	-	P	P	P	P	P	Gr111/red signs	C	Ethanol
89	54/M	9.8	1,48,000	3.8	82/64	6.4	3.8	13/1.4	19	1.1	15.24	274	47	156	1.4	50	-	-	P	-	-	-	Gr1 o.v	B	Ethanol
90	41/M	11.4	2,10,000	1.9	24/38	6.9	4.2	11/1.	20	0.7	17.32	309	52	165	-	-	-	-	-	-	-	-	No o.v.	A	HBV
91	49/M	10.6	88,000	2.2	56/48	6.1	2.4	17/1.52	26	1.1	3.45	138	38	81	1.2	45	-	-	P	-	-	-	Gr.11 o.v	B	Ethanol
92	48/F	10.1	1,54,000	4.9	73/66	5.8	2.9	21/2.03	29	0.9	15.81	296	49	154	2.6	350	P	-	P	P	P	-	Gr11 o.v	C	Ethanol
93	56/M	8.4	92,000	7.4	112/84	5.1	1.9	17/1.3	27	1.1	3.98	147	37	76	2.2	70	-	P	P	P	-	-	Gr11/red signs	C	Ethanol
94	44/M	11.1	,86,000	1.8	25/32	6.8	4.2	11/1.4	19	0.9	14.98	308	52	172	-	-	-	-	-	-	-	-	No o.v.	A	Ethanol
95	49/M	12.3	2,34,000	3.1	53/68	6.1	3.5	16/1.7	18	0.8	21.34	294	48	166	-	-	-	-	P	-	-	-	Gr 1 o.v,	B	Ethanol
96	39/M	10.9	1,66,000	0.9	22/33	6.9	4.5	10/1.2	23	0.8	23.64	312	49	174	-	-	-	-	-	-	-	-	No o.v.	A	Metabolic
97	42/M	9.8	84,000	5.3	78/94	6.1	2.6	14/1.3	26	0.9	21.22	303	51	168	1.9	350	P	-	P	P	P	-	Gr 11 o.v,.	C	Ethanol
98	53/M	10.6	1,36,000	2.6	38/49	6.4	3.2	18/1.68	18	1	19.68	288	49	152	-	-	-	-	-	-	-	-	No o.v.	B	Ethanol
99	56/M	10.9	1,79,000	5.8	112/94	5.1	1.7	36/3.13	77	3.6	18.64	294	47	161	2.2	50	-	-	P	P	-	P	Gr11 o.v	C	Ethanol
100	48/M	11.2	1,82,000	0.8	24/34	7.6	4.8	15/1.4	19	0.8	19.18	266	48	158	-	-	-	-	-	-	-	-	No o.v.	A	HBV

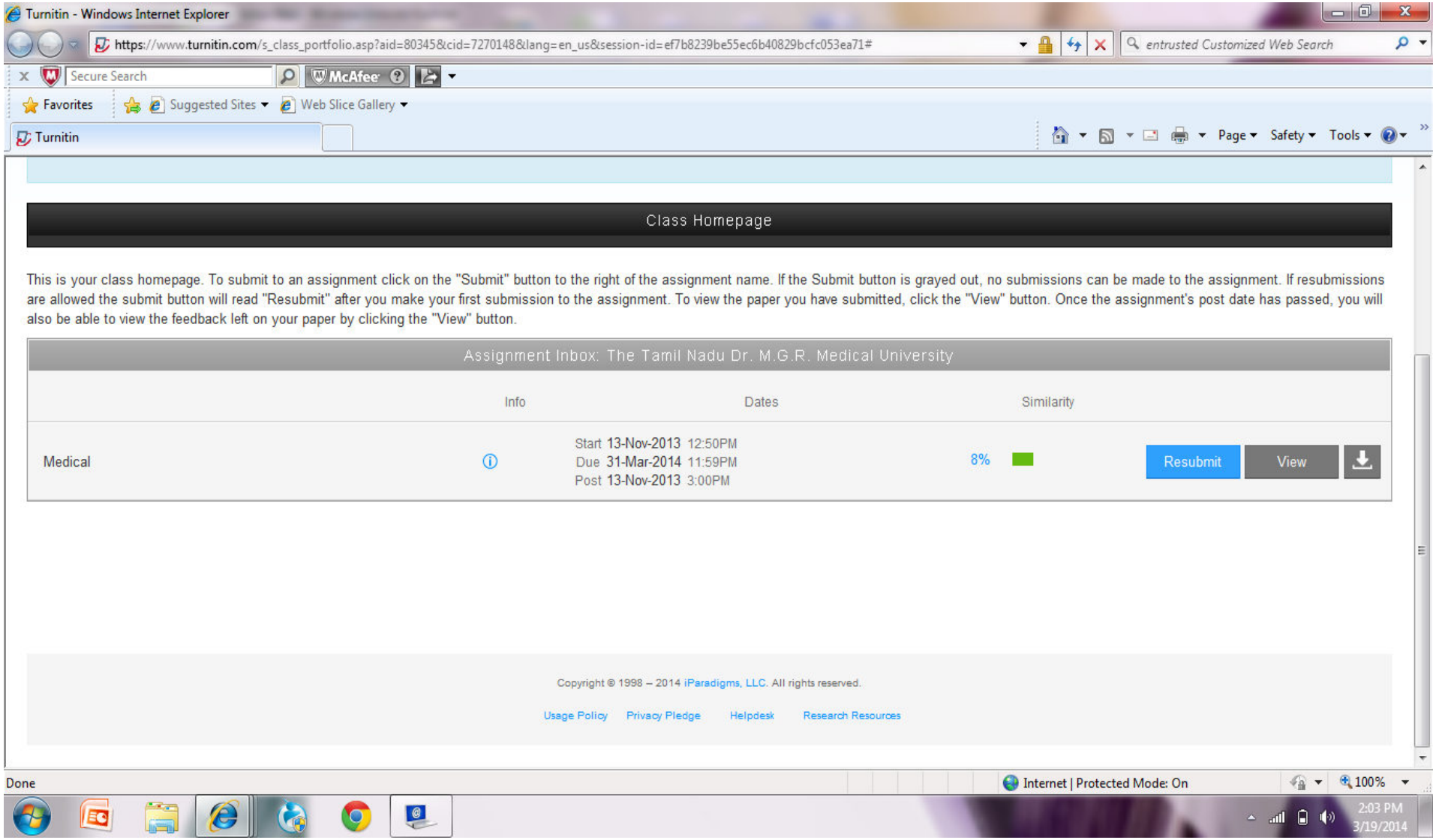
Abbreviations:

Hb	**Haemoglobin**	**LDL**	**Low Density Lipoprotein**
AST	**Aspartate Aminotransferase**	**OV**	**Oesophageal Varices**
ALT	**Alanine Aminotransferase**		
PT	**Prothrombin Time**		
SBP	**Spontaneous Bacterial Peritonitis**		
HRS	**Hepatorenal syndrome**		

HE	**Hepatic Encephalopathy**
UGI bleed	**Upper Gastrointestinal bleed**
HBV	**Hepatitis B Virus**
HCV	**Hepatitis C Virus**
HDL	**High Density Lipoprotein**

MASTER CHART - CONTROLS

S.No	Age/Sex	Hb	Platelets	S.Bilirubin	AST/ALT	T.Protein	S.Albumin	PT/INR	B.Urea	S.Creatinine	S.Cortisol	T.Cholesterol	HDL	LDL	SAAG	A.F.PMN	A.F.Culture	UGIB	Ascites	HE	SBP	HRS	OGD	CTP	Etiology
1	48/M	12.1	2,44,000	0.9	14/21	7.2	3.4	_	19	0.9	25.48	184	51	111	-	-	-	-	-	-	-	-	-	-	-
2	38/M	11.9	3,12,000	0.8	15/22	6.9	3.6	_	21	0.8	26.34	169	49	103	-	-	-	-	-	-	-	-	-	-	-
3	49/M	11.2	2,26,000	1.1	22/24	6.8	3.8	_	23	0.8	27.46	198	50	98	-	-	-	-	-	-	-	-	-	-	-
4	29/F	12.4	2,98,000	0.9	21/24	7.4	3.9	_	22	1	25.34	187	48	112	-	-	-	-	-	-	-	-	-	-	-
5	38/M	13.1	2,34,000	0.7	16/18	6.9	3.4	_	15	0.9	26.24	179	47	124	-	-	-	-	-	-	-	-	-	-	-
6	31/F	12.8	2,46,000	0.8	14/19	7.1	3.7	_	24	0.8	24.18	176	47	98	-	-	-	-	-	-	-	-	-	-	-
7	28/M	11.3	3,22,000	1	13/20	7.4	3.5	_	16	0.8	25.32	169	48	97	-	-	-	-	-	-	-	-	-	-	-
8	34/F	11.1	3,78,000	1.1	15/21	6.7	3.6	_	17	0.9	26.19	178	46	102	-	-	-	-	-	-	-	-	-	-	-
9	37/M	13.4	2,68,000	0.9	14/17	7.2	3.8	_	20	0.7	27.34	184	49	113	-	-	-	-	-	-	-	-	-	-	-
10	28/M	12.6	3,09,000	0.7	16/19	6.8	3.5	_	22	1	20.98	168	50	102	-	-	-	-	-	-	-	-	-	-	-
11	35/F	12.8	2,78,000	0.8	15/19	7.3	3.8	_	25	0.9	22.86	172	49	105	-	-	-	-	-	-	-	-	-	-	-
12	41/F	11.8	2,45,000	0.8	16/19	6.8	3.4	_	22	0.8	23.84	175	51	98	-	-	-	-	-	-	-	-	-	-	-
13	44/F	11.2	2,89,000	0.9	14/18	6.9	3.6	_	23	0.9	22.14	182	48	99	-	-	-	-	-	-	-	-	-	-	-
14	47/M	12.6	2,54,000	0.7	16/21	7	3.2	_	20	0.8	23.86	178	47	92	-	-	-	-	-	-	-	-	-	-	-
15	42/F	11.3	3,14,000	0.8	14/22	7.2	3.8	_	18	0.7	24.67	185	49	98	-	-	-	-	-	-	-	-	-	-	-
16	38/F	11.7	2,86,000	1.1	17/19	6.8	3.7	_	21	0.8	25.87	188	47	99	-	-	-	-	-	-	-	-	-	-	-
17	28/M	13.2	2,58,000	0.9	18/22	7.3	3.9	_	20	0.9	26.16	178	46	96	-	-	-	-	-	-	-	-	-	-	-
18	43/M	12.8	2,96,000	1	15/21	6.9	3.6	_	16	0.8	25.78	168	49	98	-	-	-	-	-	-	-	-	-	-	-
19	46/M	12.4	2,78,000	0.7	18/21	6.6	3.8	_	21	0.9	24.76	174	48	93	-	-	-	-	-	-	-	-	-	-	-
20	44/M	11.6	2,46,000	0.8	17/22	7.1	3.6	_	23	0.7	24.34	168	48	94	-	-	-	-	-	-	-	-	-	-	-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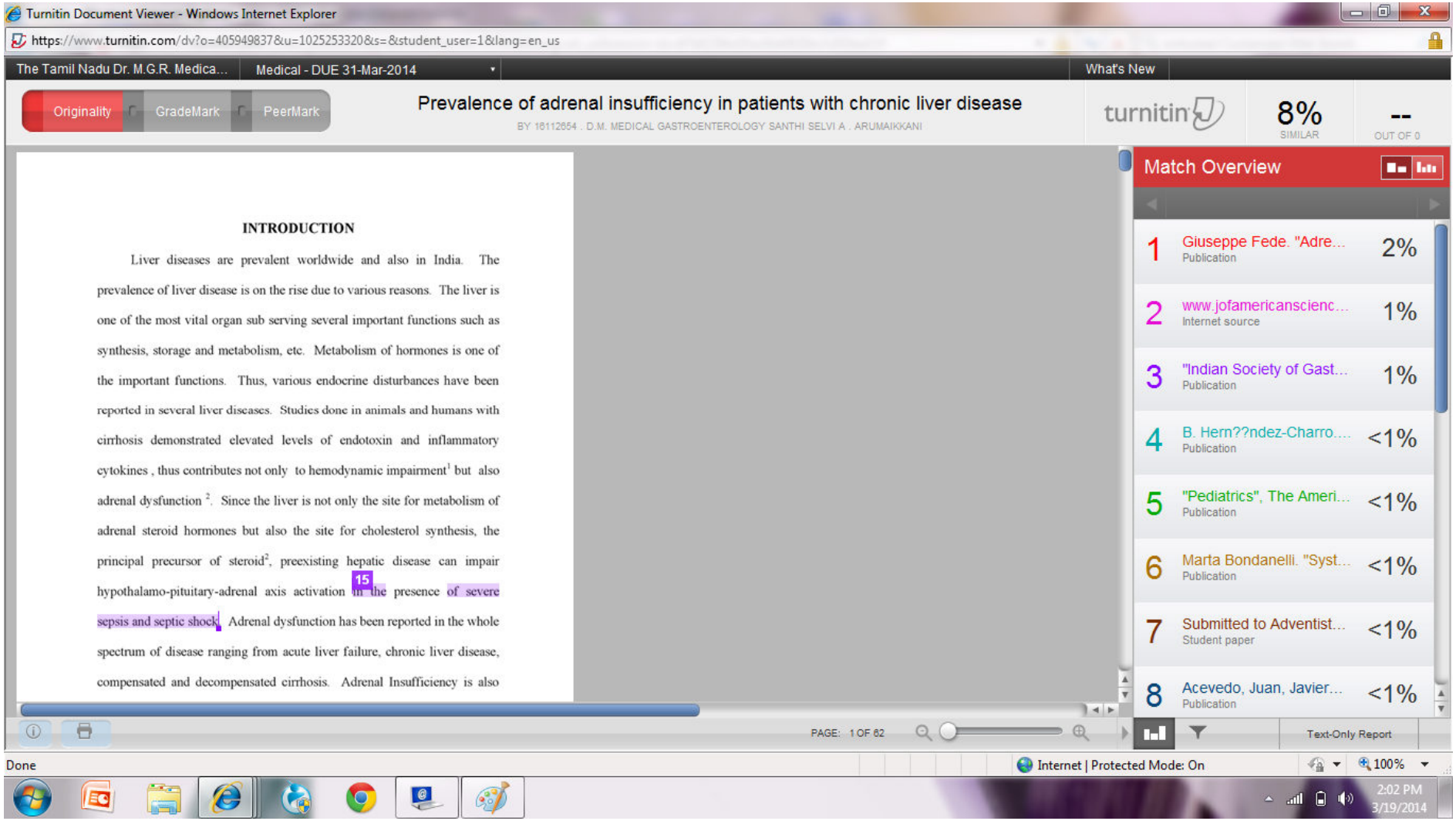
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INTRODUCTION
Liver diseases are prevalent worldwide and also in India. The prevalence of liver disease is on the rise due to various reasons. The liver is one of the most vital organ sub serving several important functions such as synthesis, storage and metabolism, etc. Metabolism of hormones is one of the important functions. Thus, various endocrine disturbances have been reported in several liver diseases. Studies done in animals and humans with cirrhosis demonstrated elevated levels of endotoxin and inflammatory cytokines , thus contributes not only to hemodynamic impairment[1] but also adrenal dysfunction [2]. Since the liver is not only the site for metabolism of adrenal steroid hormones but also the site for cholesterol synthesis, the principal precursor of steroid[2], preexisting hepatic disease can impair hypothalamo-pituitary-adrenal axis activation in the presence of severe sepsis and septic shock. Adrenal dysfunction has been reported in the whole spectrum of disease ranging from acute liver failure, chronic liver disease, compensated and decompensated cirrhosis. Adrenal Insufficiency is also
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