A STUDY ON INCIDENCE OF RHABDOMYOLYSIS IN LIVER CIRRHOSIS AND THEIR CORRELATION WITH SERUM ALBUMIN

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CERTIFICATE

This is to certify that the dissertation titled **"INCIDENCE OF RHABDOMYOLYSIS IN LIVER CIRRHOSIS AND THEIR CORRELATION WITH SERUM ALBUMIN"** is the bonafide original work of **DR.ASWIN S KRISHNA** in partial fulfilment of the requirements for M.D.General Medicine Examination of the Tamilnadu DR. M.G.R Medical University to be held in May 2018. I forward this to the DR. M.G.R Medical University, Chennai, Tamilnadu, India.

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DECLARATION

I, **DR. ASWIN S KRISHNA**, solemnly declare that dissertation titled **"INCIDENCE OF RHABDOMYOLYSIS IN LIVER CIRRHOSIS AND THEIR CORRELATION WITH SERUM ALBUMIN"** is a bonafide work done by me at Madras Medical College & Government General Hospital, Chennai during 2015- 2018 under the guidance and supervision of Prof.Dr.S.TITO M.D.

This dissertation is submitted to Tamilnadu DR. M.G.R Medical University towards part fulfillment of requirements for the award of M.D.Degree (Branch – I) in General Medicine.

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INTRODUCTION

INTRODUCTION

Cirrhosis of liver is a parenchymal disease with multiple causes. Cirrhosis leads to liver parenchymal damage. Most common cause of cirrhosis in India is the consumption of alcohol. Various complications occur in cirrhosis patient including metabolic abnormalities and complications due to therapies which left unnoticed may lead to serious comorbidities.

Acute Rhabdomyolysis is an acute and severe form of necrotizing myopathy which occurs due to extensive muscle damage. This leads to influx of water, sodium and calcium from the extracellular component into the muscle cells leading to renal failure and hemodynamical abnormalities. Also there is efflux of potassium, uric acid, lactic acid leading to hyperuricemia, hyperphosphatemia, hyperkalemia and disseminated intravascular coagulopathy.

Rhabdomyolysis in cirrhosis may occur from vasopressin infusion,electrolyte imbalance, hyponatremia, hypokalemia and drugs. This must be managed with appropriate fluid therapy. Failing to do so leads to the serious complications like renal failure.

Not much research has been done regarding the incidence of rhabdomyolysis in cirrhosis. Keeping in the mind the above scenario and advantage of early diagnosis and reversibility of complications, we attempt to study the incidence of rhabdomyolysis in cirrhosis further relating their co-relation with serum albumin and their progression to renal failure in this study.

AIM OF THE STUDY

AIM

1. To analyse Incidence of Rhabdomyolysis in liver cirrhosis.

2. To analyse the correlation with serum albumin.

3. To find the correlation of rhabdomyolysis with renal failure in these patients.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Cirrhosis a gate way of chronic liver disease, is a term defined as diffuse hepatic fibrosis where the normal liver structure is replaced by nodules.

The main pathogenesis in liver fibrosis is the hepatic stellate cell. Stellate cells on activation are converted into myofibroblast. Stellate cells also produce fibronectin and collage 1 which inturn leads to matrix deposition in the hepatic architecture. The portal fibroblasts, which lies near the stellate cells also deposits collagen matrix and is proposed as the one of the major contributions of liver fibrosis. Other cells included in the pathogenesis of liver cirrhosis are epithelial cell injury which leads to fibrosis.

Epithelial cell injury leads to apoptosis, inflammation and necrosis. These lead to activation of stellate hepatic cells.Sinusoidal cells causes stellate hepatic cell activation through endocrine and paracrine signaling pathways.Angiogenesis is also one of the propagated mechanism that contributes to the development of stellate cell activation.

Various clinical and laboratory features help in the diagnosis of cirrhosis.

1. Reddish discoloration of palm suggest palmar erythema.
2. Pallor in the nail beds of thumb and index finger points to terry nails
3. AV shunts in the lung lead to clubbing.
4. Enlarged male breast may denote gynecomastia.
5. Dilated arterioles with prominent central arterioles with surrounding radiating cells is called spider angiomas.
6. Dilated umbilical veins called caput medusa is seen in portal hypertension due to cirrhosis.
7. Blanched dilated veins over the flanks with flow upwards suggests IVC obstruction.
8. Parotid enlargement suggests alcoholic cirrhosis.

Patient with history of chronic liver disease with symptoms of decompensations like gastrointestinal bleeding, ascites and hepatic encephalopathy are most likely to have cirrhosis. Liver biopsy is not advocated in these patients whose symptoms are suggestive of cirrhosis.

In cirrhotic patients without the signs of decompensation, clinical findings of hepatosplenomegaly along with the cutaneous markers of cirrhosis especially with supportive laboratory features like thrombocytopenia and impaired hepatic synthase functions suggests cirrhosis.

A small nodular liver with splenomegaly and ultrasound abdomen showing collaterals and ascites suggests cirrhosis. Fibroscan and MRI abdomen helps to confirm the diagnosis of cirrhosis.

In fibroscan the liver stiffness is measured. A measurement of more than 14 kpa suggests cirrhosis and a value more than 21 kpa suggests portal hypertension.

Acustic radiation forced impulse value more than 2.6 m/sec suggests cirrhosis.In cirrhosis,liver biopsy not indicated if the value is more than 5.6kpa in magnetic radiographic elastography.

Increased spleen stiffness on ultrasonography or MRE is suggestive of portal hypertension. Liver biopsy is considered as the gold standard in the diagnosis of cirrhosis but the costs, complications, limited resources are the limitations.

Bonacini discrimination score more than 7 or a serum AST/platelet ratio index more than 2 suggest cirrhosis. Bonacini score of less than 3 or

lok score less than 0.2 more are against the diagnosis of cirrhosis and an alternative diagnosis must be considered in the patients. Points in favor of cirrhosis are ascites and platelet count less than 160000 while the absence of hepatic liver or a platelet count more than 160000 makes the diagnosis of cirrhosis highly unlikely .

CIRRHOSIS is categorized as compensated and decompensated. The presence of gastro intestinal bleeding, jaundice, ascites, encephalopathy or hepatocellular carcinoma characteristics of decompensated cirrhosis. There wont be any such complications in compensated cirrhosis.

There are 4 stages of cirrhosis. Stage one and two represents compensated cirrhosis and stage three and four represents decompensated cirrhosis.

Stage 1-without as cites and cirrhosis

Stage 2 -presence of varices without bleeding and absence of ascites

Stage 3-ascitis with or without esophageal varices

Stage 4-variceal bleeding with or without ascites

Along with Clinical and histological parameters, vitals and biological data are also considered while staging of cirrhosis

CLASSIFICATION OF CIRRHOSIS

ANATOMICAL SUB TYES OF CIRRHOSIS ARE

1. Micronodular

Micro nodular cirrhosis consists of thick regular separate by regeneration small nodules differing in size and involvement of very lobule. The micronodular liver may represent impaired capacity for regrowth seen in conditions such as alcoholism malnutrition old age and anemia.

2. Macronodular

Macronodular cirrhosis consists of septae and nodules of variable sizes and has large nodules with large lobules. Juxta position in the fibrous scars of three or more portal tracts is characteristic of previous collapse. Regeneration is reflected by large cells with large nuclei and by cell plates of different thickness.

Regeneration in micronodular cirrhosis leads to macronodular or mixed appearance. The micronodular eventually evolves into macro nodular cirrhosis.

ETIOLOGY OF CIRRHOSIS

Viral hepatitis

Alcohol

Metabolic like hemochromatosis

- Wilsons
- Antitipsin deficiency
- Galactosemia
- Intestinal bypass

Prolonged cholestasis

Hepatic venous outflow obstruction

- Venoocclusive disease
- Budd chiari syndrome
- Constrictive pericarditis

Autoimmune hepatitis

Toxins

- Methotrexate
- Amiadorone

Indian childhood cirrhosis

Malnutrition

Infections

- Malaria
- Syphilis
- Schistosomiasis

Granulomatous lesions

- Brucellosis
- Tuberculosis
- Sarcoidosis

Cryptogenic cirrhosis

CLINICAL AND PATHOLOGICAL ASSOCIATIONS

1. Nutrition

Protein calorie malnutrition is the one of most common complication noticed in patients with chronic liver disease. The causes appear to be multifactorial but inadequate intake of protein and energy producing food and increased resting energy expenditure contributes.

Although gustatory and olfactory acuity is impaired in cirrhotic patients, their selection of food does not impaired when compared to normal healthy individuals. The reason for reduced intake of food may be due to humoral factors such as hyperinsulinemia. Dental and periodontal disease reflects poor oral hygiene rather than cirrhosis per se.

Several methods are formulated for estimating the REE including the composite scores of clinical observation such as skin fold thickness. Patients with chronic hepatitis C have increased consumption of energy that returns to normal when the treatment of hepatitis with antivirals have started.

Fat stored and muscle mass are reduced in many cirrhotic patients especially the alcoholics and those who are child grade C. Alcoholic cirrhotic patients will have muscle weakness that accounts to severity of

malnutrition rather than relating to severity of liver disease perse. Reduced muscle protein synthesis leads to muscle wasting.

Nutritional status of the patients also determines the prognosis of patients with cirrhosis. Malnutrition also constitutes an independent prognostic factor for first variceal bleed and survival of the patients with esophageal varices. Increased REE persisting after transplant patients is suggestive of poor prognostic factors.

2. Eye signs

Lid retraction and lid lag is significantly increased in patient with cirrhosis compared to normal population who are considered as control.There is no evidence of thyroid disease.Serum free thyroxine is not increased.

1. Alcoholic features

Parotid enlargement and dupytrens contracture is seen in many alcoholic patients with cirrhosis.

2. Clubbing

Digital clubbing and hypertrophic osteoarthropathy is seen in patients with cirrhosis especially biliary cirrhosis.These changes are due to aggregated platelets, passing peripherally through pulmonary arteriovenous shunts, plugging capillaries and releasing PDGF.

3. Muscle cramps

Muscle cramps is seen very commonly in cirrhotic patients than in patients without liver disease and correlate with the presence of ascites,low mean arterial pressure and plasma renin activity. Cramps often subsided by oral quinine sulphate, human albumin if infused weakly response to increasing effective circulate volume.

6. Steatorrhea

Steatorrhea even in absence of pancreatic patients is very common in cirrhotic patients. It is mainly due to reduced bile salt excretion.

7. Portal hypertension

Portal hypertension is usually suggested by the presence of Splenomegaly and abdominal wall venous collaterals.

8. Hernia

Abdominal hernia should not be repaired in patient with cirrhosis unless there are absolutely indicated and the cirrhosis is well compensated.

9.Gastrointestinal

Varices are seen in endoscopy of patients.A good number of cirrhotic patients showed the presence of peptic ulcerations that too most commonly in patients with coexisting hepatitis B infection.

Seventy percent are asymptomatic. Duodenal ulcers are most frequent than gastric ulcers. The prevalence of helicobacter pylori is much higher in patients with cirrhosis than in patients without cirrhosis.

Small bowel bacterial overgrowth occurs in one third of patient with cirrhosis very frequently compared to non-ascites. This condition is commonly associated with old age and administration of proton pump inhibitors.The hydrogen breath test correlates poorly with the microbial culture derived from jejunal fluid.

9. Primary liver cancer

Primary liver cancer is common in all sorts of cirrhosis except the biliary and cardiac types. An increased risk of other type of cancer has been reported but the cause has been mainly contributed to alcohol and cigarette use.

Metastatic cancer is very rare mainly due to reduced incidence of extra hepatic carcinoma in cirrhosis patients. When the incidence of

metastatic cancer was compared among the cirrhotic and noncirrhotic patients, The incidence was almost same.

10.Gall stones

Studies has shown that a good number of patient with cirrhosis has associated gall stones. The incidence is four to five times higher when compared to normal population. They do not contribute to the prognosis of patients.The low bile salt unconjugated bilirubin ration with very high biliary monoconjugated bilirubin predisposes these patients to pigmentary gall stone.

In patients with gall stones, surgery is avoided unless there is absolute indication, no eligible for transplant or patient with poor operative risk.

11. Pancreatitis

Chronic relapsing pancreatitis and pancreatic calcification are often associated with alcoholic liver disease.

12.Cardiovascular

Cirrhosis patients are less liable to coronary and aortic artheroma than the patients without cirrhosis. At autopsy of these patients, the incidence of coronary artery disease in only one forth of among the total cases examined without cirrhosis.

But cirrhosis is associated with increased cardiac output and heart rate as well as decreased systemic peripheral vascular resistance and blood pressure. Splanchnic arterial vasodilation and impaired autonomic activity play a very vital role.

Cardiac parasympathetic dysfunction was altered by captopril suggesting a defect in neuro modulation by centrally acting angiotensin 2. As a result, Qt interval is prolonged.

Vasodilation is mainly due to many factors including improper response to catecholamines, increased vascular synthesis of nitric oxide and elevated circulating adreno medullin and calcitonin gene related peptide. Vascular tone is reduced accounting for blunted systemic and renal effects of volume expansion.

Cirrhotic cardiomyopathy is recognized with abnormal cardiac contractility especially seen in pharmacological and physiological strain. A reduction in myocardial beta receptor signal transduction plays a very vital role. Left ventricular wall thickness may be increased. Myocardial injury may be reflected by elevated cardiac troponin

I. cardiac dysfunction may be usually asymptomatic usually they become symptomatic after liver transplantation.

13.Pulmonary

Hepatopulmonary syndrome and portopulmonary hypertension may contribute to hypoxemia in cirrhotic patients. Alpha 1 antitrypsin deficiency may contribute to cirrhosis in childhood cirrhosis and further leads to emphysema and silent cirrhosis. Pulmonary atelectasis may eventually lead to hydrothorax due to trans diaphragmatic passage of ascites.

14.Renal

Changes in the intrarenal circulation particularly redistribution of blood flow from the cortex are found in all forms of cirrhosis further leading to the progression of hepato-renal syndrome. Intrinsic renal failure leads to hypotension and shock.

Glomerular changes including thickening of mesangial stalk and to a lesser degree of capillary walls may occur which is termed as cirrhotic glomerular sclerosis. Deposits of IgA are most frequent.These changes are especially seen in alcoholic liver disease.These changes are usually latent and associated with proliferative changes and glomerular involvement.

Chronic hepatitis C is usually associated with cyroglobinemia and membranoproliferative glomerulonephritis.

15.Infections

Altered immune defense mechanism and reduced reticulo endothelial cell phagocytic activity leads to the frequent attack of bacterial infections. Bacteremia pneumonia and urinary tract infections are most common.

Patients with ascites are more prone for spontaneous bacterial peritonitis. Spontaneous bacterial empyema in a preexisting hydrothorax may occur even in absence of SBP.In cirrhotic with febrile coma, bacterial meningitis should be the first possible differential diagnosis. Nasal carriage of staphylococcus aureus is usually seen in cirrhotic patients.

Unexplained fever or clinical decline should always make the physician to suspect the presence of sepsis. Empirical treatment with broad spectrum antibiotics should be started immediately as soon as possible once the microbial culture has been taken.

After the gastro intestinal hemorrhage, the risk of sepsis is very high in child grade C rather than child grade A/B. Prophylactic administration of ciprofloxacin and Augmentin has decreased the chance of sepsis in child grade C for a good ratio of people.

The incidence of tuberculosis and tuberculous peritonitis is not uncommon which should be always kept in mind while handling sepsis.

16.Drug metabolism

In cirrhotic patients, the effects of drugs is generally increased due to reduced elimination. There are two main patho physiological mechanism proposed,first is due to reduced hepatocyte mass rather than the enzymatic activity and the shunting of blood past the liver.

For drugs with high hepatic extraction ratio predicting the therapeutic effect after oral administration is difficult, due to the variation in the degree of shunting between patients. The clinical effect of low extraction drugs on cirrhosis is much dependent on hepatocellular function and hence the prognosis is much predictable. Overall drug usage should be reduced according to severity of degree of liver disease.

Other components of the metabolic pathway may alter the drug handling in cirrhosis including the absorptions, tissue distribution, protein binding,biliary secretion, enterohepatic circulation and target organ responsiveness.

17.Diabetes mellitus

While upto 80% of cirrhotic are glucose tolerant, only 10-20% of patients are only true diabetics. The incidence of diabetes is much higher

in patients with hepatitis C and alcohol related cirrhosis when compared to cholestatic cirrhosis.

18.sleep disturbance

Sleep abnormality is very common in patients with cirrhosis. The sleep pattern alteration varies from person to persons. Commonly they have a tendency for being active in the evening and having a delayed bedtime and wake up time. This seems part of a broader abnormality of circadian rhythm.

19.Hypergammaglobulinemia

Elevation of total serum globulins and especially the gamma level is a well-known accompanying factor of chronic liver disease. Electrophoresis shows a polyclonal gamma response but rarely a monoclonal picture seen. The increased gamma globulins may be due to increased auto immune antibodies such as smooth muscle antibodies. The major factor leading to this condition is the failure of the damaged liver to clear the antigens.

Patients with cirrhosis shows increased serum of antibodies to gastrointestinal tract antigens particularly Escherichia coli. Such antigens bypass the liver through porto-systemic channels or through the internal shunts developing around the cirrhotic nodules. Once they enter the

systemic circulation, they switch on the increased antibody response from organs such as spleen. Simultaneous systemic endotoxemia may also arise. Polymeric IgA and IgA antigen complexes that originate from the gut also reach the systemic circulation. Suppressor lymphocyte function is depressed in chronic liver disease and this would reduce the suppression of B lymphocytes band so favor antibody production.

Most common causes of mortality in cirrhosis occurs because of decompensated cirrhosis and the mortality in the compensated cirrhosis is due to cardio vascular causes, stroke, malignancy and renal diseases. Complications of portal hypertension, hepatocellular carcinoma,sepsis are the major contributors of mortality in decompensated cirrhosis.

Liver diseases are the eighth causes of mortality in the world .The patients with compensated cirrhosis have 5 fold increases risk of death when comparing to the normal population while when to comes to decompensated patients the values roles to 10 fold increase risk. The medial survival of compensated cirrhosis is 9-10 years and the medial survival of decompensated cirrhosis is only 2 years.

The presence of comorbidities contributes to assessing the prognosis of cirrhosis in additional to clinical stage of cirrhosis. The mortality risk in cirrhosis can be calculated by scores such as child Turcotte Pough sore and meld score, von Willebrand levels. The

probability of decompensation increases when the level of von Willebrand level increases more than 31.5%.

The measurement of hepatic vein pressure gradient is also an important tool in assessing the prognosis of cirrhosis.

Sepsis and renal failure is an important factor that contributes to the mortality of the patients. Infection raises the risk of mortality by 4-fold and the presence of hepatorenal syndrome increases the risk of mortality by 7-8 fold.

The assessment of conversion of compensation to decompensated stage is important because decompensated cirrhosis has increased chance of mortality.58% of patients will be converted into decompensated phase from the compensated phase in a span of 10 years. The decompensation varies with the cause of cirrhosis. The annual rate is 4% for hepatitis C related liver disease,6-10% for alcohol related liver diseases and 10% for hepatitis B related liver disease.

The other factors contributing to decompensation are serum albumin level, MELD score and hepatic venous pressure gradient. Hepatic venous pressure gradient less than 10% has a negative predictive value of 90%for the development of clinical decompensation over 4

years. An increase in MELD score and decrease in the serum albumin level are associated with decompensation.

The screening of hepatocellular carcinoma should be done in cirrhosis every 6 months. Regular screening of esophageal varices, cessation of alcohol, weight loss and other life style modification should be implicated in all cases of cirrhosis. Immunization against HAV, HBV, pneumococcal pneumonia and influenzas are recommended because of the increases suspectability of infection in cirrhotic patients.

Live vaccines can be administrated in cirrhotic patients.The treatment of the etiological factors plays a very vital role in determine the conversion of compensated to decompensated phase. some of the etiological factors to be addressed are medical management of hepatitis B and C infection, stoppage of alcohol, and weight loss.The use of low molecular weight heparin has shown to delay the decompensation in patients without portal vein cirrhosis.

Upto 2 grams of NSAIDS can be used in patients with cirrhosis. Aspirin and other NSAIDS must be avoided as much as possible in patients with decompensated cirrhosis. Especially patients with ascites statins can be advised in patients with hyperlipidemia. Aminoglycosides are contraindicated in patient with cirrhosis.

Patients of diabetes mellitus with compensated cirrhosis can be treated with oral hypoglycemic agents while patients with decompensated cirrhosis should be treated with insulin. High calorie small meals as well as bed time meals are advised in patients with cirrhosis because they are highly prone for protein energy malnutrition leading to hypoalbuminemia. Fat soluble vitamins and zinc levels should be measured and replacements must be done if required.

Fatigue, muscle cramps and sexual dysfunctions are a major issue in the management of cirrhosis. Quality of life is mainly affected in patients with cirrhosis and fatigue is a major factor reducing it.Obesity, depression and sleep apnea contributed to fatigue. SSRI and mirtazapine are used in treatment of depression in cirrhosis.

If the treatment of etiological factors is addressed, the fibrosis is almost reversible process. Angiotensin, nuclear receptors, receptor tyrosine kinases, integrins and matrix degrading proteases has been involved in research for reversal of fibrosis.

Inducing senescence, deactivation, apoptosis has been tried in aim of reversal of myofibroblast state of preclinical models. There versibility can be tried only in the early stages of fibrosis and it is no applicable in the late stages because of fixed architectural changes.

Compensated cirrhosis.

This disease may be diagnosed at a routine examination, biochemical screening or at an operation undertaken for some other condition. Firm hepatomegaly and splenomegaly are helpful diagnostic signs. Vague morning indigestion and flatulent dyspepsia may be early features in the alcoholic cirrhotics. Confirmation should be sought by biochemical tests, portal doppler, other radiological scanning and liver biopsy.

Biochemical tests may be quite normal in this group. The most common change in biochemical test is change in gamma glutyltransferase level. And the diagnosis is confirmed by the liver biopsy.

These patients are usually asymptomatic until the mortality is due to some other cause. But some patients during the course of time eventually develop hepatocellular failure. Some other patients present with portal hypertension with esophageal bleeding. These patients even have normal biochemical tests. The prognosis and progression of these patients are very difficult to predict.

Decompensated cirrhosis.

Ascites and jaundice are the two important reasons which brings the patients to physician. There will be decline of the general health, muscle wasting and weight loss. Continuing bacterial sepsis often leads to mild fever which may be also due to hepatic and complicating hepatocellular carcinoma. A liver flap may be present. Cirrhosis is the commonest cause of hepatic encephalopathy.

The sign of jaundice suggests that the regeneration capacity of the liver has exceeded and the condition is serious. The severity of liver damage is suggested by the deepness of jaundice.

There may be hyperpigmentation of the skin with clubbing of fingers. Purpura may be seen with thrombocytopenia.Spontaneous bruising and epistaxis reflects a prothrombin deficiency. They usually present with hypotension.

Ascites presents with pedal edema and hepatomegaly with firm regular edge or contracted and impalpable.The spleen may be palpable.

Laboratory finding

Mild normocytic normochromic anemia is usually seen, it may be commonly macrocytic. Gastrointestinal bleeding may be lead to hypochromic anemia. The leucocyte and platelet counts are reduced. The prothrombin time is increased which is refractory to vit K correction. The bone marrow is macro normoblastic. Plasma cells are increased in proportion to the hyper gammaglobulinemia.

Serum albumin level is depressed and gamma globulin is raised.Serum bilirubin is increased.Serum alkaline phosphate is raised, may be very high readings are seen in alcoholic cirrhosis.

Excessive urobilinogen is present, bilirubin is also present in the urine if jaundice is present. The urine sodium is diminished in presence of ascites.

Needle biopsy is advised only if there is no ascites and coagulation defect,the trans-jugular approach should be used. Serial biopsy is valuable in assessing the progress.

In cirrhosis, directed biopsies using ultrasound or CT and a truncut needle is very useful in obtaining the samples and avoiding other viscera especially gall bladder.

PROGNOSIS

Cirrhosis is usually believed to be non-reversible. But fibrosis has shown to regress in patients with hemochromatosis and wilsons disease.

Cirrhosis is not a progressive disease. Through proper therapy, the progression can be kept under check. After the discovery of liver transplantation procedure, the need of accurate prognosis has been raised.

Child classification depends on jaundice, ascites, encephalopathy, serum albumin concentration and nutrition. Child grade gives a good short-term prognostic guide. Modification of child grade replaces the nutritional status with prothrombin time. The total score classifies patient into grade A,B or C.

Poor prognosis is associated with a prolonged prothrombin time, marked ascites, gastrointestinal bleeding, advanced age, high daily consumption of alcohol, high serum bilirubin and alkaline phosphate, low albumin values and poor nutrition.

Compensated cirrhotic patients become decompensated at rate of 10% per year. Ascites is usually first sign.Decompensated patients have around a 20% 5-year survival.

The 1year survival rate of cirrhotic patients following the 1st episode of SBP is 30-45% but if 1st episode of hepatic encephalopathy occurs, then the prognosis comes around 40%.

Aminopyrine breath test add prognostic significance to child grade A and B but not contributing grade C.

The following points are useful prognostically:

1.Etiology. Alcoholic cirrhotic, if they abstain, respond better than patients with cryptogenic cirrhosis.

2.If hemorrhage, infection or alcoholism leads to decompensation, the prognosis is better than spontaneous because the precipitating factor is correctable.

3.The response to therapy: If the patients do not respond to therapy even after 1 month then the prognosis is very poor.

4. Jaundice again is a poor prognostic clinical sign.

5. Neurological complications.

The clinical significance of encephalopathy depends on the clinical circumstances. When associated with hepato cellular failure, it carries a very bad prognosis. Chronic and associated with an extensive portal systemic collateral circulation, it usually responds better to the treatment

and eventually the prognosis is better. Overall hepatic encephalopathy has a very bad prognosis. Autonomic neuropathy has very poor prognostic value.

6. Ascites worsens the prognosis, especially in case of refractory ascites.

7.Liver size: A large liver has a better prognosis when compared to shrunken liver because the large liver is likely to contain more functional cells.

8.Portal venous pressure: the prognostic value of the child pugh score increased after the addition of portal venous pressure which is derived from the hepatic venous pressure gradient.

9.Hemmohrage from the esophageal varices: if the function of liver cells is good,hemorrhage may be tolerated; if poor,hepatic coma and death are probable.

10. Biochemical tests: If serum albumin is less than25 g/l, the outlook is poor. Hyponatremia, if unrelated to diuretic therapy is grave. Serum transaminase and globulin levels gives no indicator to prognosis.

11.Persistent hypotension has serious prognostic value.

12.Hepatic histological changes. Sections are useful in evaluating the extent of necrosis and of inflammatory infiltration. A fatty liver responds well to the treatment.

Treatment

The management of well compensated cirrhosis is directed towards the maintenance of an adequate balanced diet, the avoidance of alcohol, early detection of hepato cellular failure, fluid retention and encephalopathy and prevention of variceal hemorrhage.

Nutrition

A diet of 1.0 to 1.2 g of protein per kilogram of body weight is needed in cirrhotic patients compared to normal individuals, in patients who was not on adequate nutrition then the caloric requirement increases to 1.5g/kg/day.During the acute phase of encephalopathy, the caloric requirements should be reduced.

Sip feed supplements to the standard kitchen diet are useful.The enteral route should be used. If this is not possible, paraenteral feeding must be advised with the energy provided by glucose and fat in ration of 50:50%.

The onset of hepato cellular failure with edema and ascites demands sodium restriction and diuretics; Complicating encephalopathy is an indication for a lowered protein intake and lactulose.

Portal hypertension may demand special treatment with beta blockers and other drugs.

ANTIFIBROTIC DRUGS

The treatment of cirrhosis lies in removing the damaging agent, suppressing hepatic inflammation and reducing fibrogenesis. The promotion of matrix degradation remains a theoretical than practical approach at present.

In some hepatic diseases, the cause can be removed as in alcohol, iron and copper or inhibited as in chronic viral hepatitis B and C.

Hepatic inflammation may be abolished by corticosteroids in auto immune chronic hepatitis or antiviral drugs in viral hepatitis B and C.

The components of fibrogenic pathway could be blocked or modulated. Down regulation of stellate cells is an attractive target including interferon alpha and gamma. Fibrogenesis may be reduced by antioxidants such as vitamin E cytokine blockade by receptor antagonists and inhibitors of collagen synthesis. Dietary supplementation with

phosphatidyl choline reduces. Alcohol induced fibrosis possible through a membrane stabilizing effect.

Procollagen secretion requires the polymerization of microtubules, a process that can be inhibited by microtubule disruptive drugs such as colchicine.

Surgical procedure in cirrhotic patients carry a high risk and a high mortality. Surgery in non-bleeding cirrhotic patients has an operative mortality of 30% and an additional morbidity rate of 30%. Operations on the biliary tract, for peptic ulcer disease or for colon resection have a particularly bad prognosis. The surgical risk in patients with chronic liver disease emphasizes the need for a careful pre-operative evaluation.

Upper abdominal surgery increases the difficulty and should be avoided in potential candidates for liver transplantation.

RHABDOMYOLYSIS

Rhabdomyolysis is characterized by muscle necrosis and leakage of the contents into the systemic circulation. Creatinine kinase elevation along with myalgia and myoglobinuria are the cardinal features. The clinical triad of rhabdomyolysis constitute myalgia, weakness and colored urine.

Myalgia is mostly seen in proximal muscles in patient with cirrhosis. The other symptoms are malaise, fever, tachycardia,nausea and vomiting.Muscle tenderness and swelling maybe seen. Myoglobinuria and elevated creatine kinase are the pathognomic of rhabdomyolysis.

The creatinine kinase is usually elevated. The creatine kinase is mainly of MM type or skeletal muscle. Elevation of serum aminotransferase is usually seen which brings the liver disease as one of the major differential diagnosis.

The rise in creatinine kinase rises within 2 to 12 hours following the injury and usually goes to the peak in 24 to72 hours. Creatine kinase has a half-life of 1.5 days and the value decreases about half in each day. If the creatine kinase value is not declining then the ongoing causative factor for muscle injury is still present.

Along with the creatine kinase, the myoglobulin is also released. This myoglobulin is not protein bound, so it is easily excreted in the urine giving the urine red to brown color. the half-life of myoglobulin is 1 to 3 hours.

Although the patho physiological mechanism of rhabdomyolysis related acute renal failure are unknown, several mechanism has been proposed such as tubular obstruction by myoglobulin plugs and / or urate,

renal vasoconstriction caused by inhibitory effect of myoglobulin on endothelial vasodilator production.

Toxic free radical produced by the ferrous compound a metabolite of myoglobulin. The frequency of acute renal failure in rhabdomyolysis is around 30% in the general population and the value comes around 10 in patients with cirrhosis. Thus acute renal failure seems to have a prognostic role.These finding suggests that the underlying liver functions may be the most important prognostic factor in acute causes of acute myopathy with cirrhosis.

Thedip stick method is used to detect myoglobin and hemoglobin in the bloodand the urine analysis shows myoglobinuria. Proteinuria is an another finding in the urine because of leakages of myoglobin and other proteins by the damaged myocytes.

Hypovolemia occurs due to influx of water inside the injured muscles.The release of potassium and phosphates from the injured muscles lead to hyperkalemia and hyperphosphatemia which get excreted soon.

The entry of calcium into the injured muscles lead to deficiency of calcium and further leading to deposition of calcium in the injured

muscles. Later the calcium gets effluxed from the damaged cells resulting in normal levels of calcium and sometimes even leading to hypercalcemia

Release of purines following injury leads to hyperuricemia. Metabolic acidosis with increased anion gap is often present.

Acute kidney injury is one of the important complications of rhabdomyolysis. The incidence ranges from 15 to 50%. The risk is lower in patients of 15 to 20%.The factors contributing to dehydration, sepsis and acidosis. Volume depletion leading to renal ischemia, tubular obstruction due to heme pigmentand tubular injury from the free chelatable iron all are the additional pre-disposing factor that aggravates the renal dysfunction.

Compartment syndrome specially of legs is one another important complication of rhabdomyolysis. The release of thromboplastin and other prothrombotic states makes the disseminated intravascular complication as important association with rhabdomyolysis.

Fraction of creatine kinase in addition to history and clinical evaluation will be useful not only in the diagnosis but also to exclude other differential diagnosis like stroke, myocardial infarction. The elevation of aminotransferase or lactate dehydrogenase should increase

the suspicion of associated rhabdomyolysis and there by looking for creatine kinase.

Myoglobinuria must be suspected in patient who complains of discoloration of urine. But the major disadvantage of myoglobinuria is the lack of sensitivity because of the rapid clearance of myoglobin even in renal failure patients.

Recognition and management of fluid and electrolyte imbalance should be started as quickly as possible in order to prevent metabolic disturbances and acute kidney injury. The identification of the etiological factors like metabolic cause, drugs and toxin is very important to prevent further complications of rhabdomyolysis.

Many studies have been done to establish relationship between cirrhosis and rhabdomyolysis. Martin et all described the features of rhabdomyolysis with cirrhosis who are alcoholics.

Some of the patients with cirrhosis have muscular pain and symptoms of rhabdomyolysis. Muscle cramps have been noticed in the patients with cirrhosis and it has proposed to include this symptom in one of the clinical spectrum of cirrhosis. Other symptoms seen in cirrhotic patients are weakness, aching and tenderness.

The prevalence of rhabdomyolysis is also not uncommon.But the specific entity has not yet established regarding the association of cirrhosis and rhabdomyolysis.

As discussed above, Acute rhabdomyolysis constitutes the most dangerous form of necrotizing myopathy. Some of the common causes of rhabdomyolysis in cirrhotic patients are vasopressin infusion, various infections, electrolyte imbalance consisting of hyponatremia and hypokalaemia and drugs. Infections are a major head ache in the management while treating the rhabdomyolysis in cirrhosis because a large volume of fluid is required for the treatment of infection.

But since the patient of cirrhosis with ascites have already in volume overload state, volume restriction or administration will be a real challenge. Again the patient with rhabdomyolysis whose creatine kinase are elevated must be immediately treated with large volume of fluids. Failing to do so will lead to progression of acute renal failure in this patient. Again we have limitations in liberal use of fluids in patients with ascites with cirrhosis.

ACUTE KIDNEY INJURY

AKI is characterised by sudden impairment of kidney function resulting in retention of nitrogenous and other waste products that are

normally excreted by kidney. The dominating features are increase in blood urea nitrogen and concentration, increase in creatinine concentration and decrease in urine volume. AKI can be asymptomatic and transient change in laboratory change in GFR to devastating derangements in circulating plasma volume expansion, electrolyte and acid base composition of plasma.

Patients who survive and recover from an episode of severe acute kidney injury requiring dialysis are at increased risk for later development of end stage renal disease. The most common clinical setting to induce acute kidney injury are sepsis, surgical procedures, contrasts and nephrotoxic drugs.

Prerenal azotemia occurs due to inadequate renal plasma flow and inter glomerular hydrostatic support normal glomerular filtration. It occurs mainly due to hypovolemia, decreased cardiac output and medication like NSAIDS and ACEI. Prolonged period of ischemia may predispose to acute tubular necrosis. Intra renal biosynthesis of vasodilator prostaglandins, kallikerins and kinins and nitric oxide occurs in response to low renal perfusion pressure. Renal auto regulation fails once the systolic blood pressure falls below 80 mm hg.

A very poor prognosis factor in this setting is the onset of hepatorenal syndrome without an alternative cause persists. Despite fluid

therapy and management, Inflammation, apoptosis and altered regional perfusion may contribute importantly to intrinsic AKI. Here the glomeruli tubular interstitial and vessels are most affected. Infiltrative infiltrate and peripheral eosinophilia is seen in tubule interstitial disease.

Rhabdomyolysis may result from traumatic crush injuries, muscle ischemia during vascular or orthopaedic surgery, compression during coma or immobilisations, prolonged seizure activity, excessive exercise, heat stroke or malignant hyperthermia, metabolic and other causes of myopathies.

Prerenal azotemia should be suspected in the setting of vomiting,diarrhoea, glycosuria causing polyuria and several medications including diuretics, NSAIDS,ACE inhibitors and ARBS. Physical signs of orthostatic hypotension, tachycardia, reduced JVP, decreased skin turgor and dry mucus membrane are often present in pre-renal azotemia.

A history of prostatic disease, nephrolithiasis or pelvic or para aortic malignancy would suggest the possibility of post renal azotemia. Whether or not symptoms are present during obstruction colicky flank pain radiating to the groin suggests acute ureteric obstruction. Nocturia and urinary frequency or hesitancy is usually seen in prostatic disease. Abdominal fullness and supra pubic pain can accompany massive bladder enlargement.

The low tubular flow rate and increased renal medullary recycling of urea seen in prerenal azotemia may cause a disproportion elevation of the BUN compared to creatine. Several causes of ischemia and nephrotoxin associated AKI can present with FeNa below 1%. Loss of concentrating nephropathy is common in ischemic or sepsis AKI resulting in urine osmolality below 350 but the finding is non-specific.

AKI AND RHABDOMYOLYISIS

Rhabdomyolysis is characterized by the leakage of muscle cell contents including myoglobin, electrolytes, creatine kinase, aldolase, lactate dehydrogenase and aspartate amino transaminase into the circulation. Acute kidney injury occurring mainly in severe rhabdomyolysis mainly due to vasoconstriction, proximal tubular injury from oxidant injury and intra nephronal obstruction.

Myoglobin, a heme pigment protein that mainly contains iron in the ferrous state has less nephrotoxicity in alkaline urine. Intra vascular volume contraction and acidic urine promote distal tubular obstruction from myoglobin precipitation.

Muscle injury leading to rhabdomyolysis mainly follows trauma like crush injury syndrome or limb compression from prolonged immobilization. However causes not related to trauma existed and

included increased exertion like seizure, alcohol withdraw, strenuous exercise.

The other condition are genetic defects e.g., disorder of glycolysis or gluconeogenesis, disorder of lipid metabolism, and mitochondrial disorders, infections like influenzas A and B, body temperature changes like heat stroke, neuroleptic malignant syndrome and hypothermia and drug or toxin exposure like lipid lowering drugs, alcohol, cocaine and heroin.

Patients with acute rhabdomyolysis often present with muscle pain and reddish-brown urine. The presence of pigmented granular casts and the lack of RBCs on urine microscopy coupled with a blood positive urinary dipstick are important laboratory clues for rhabdomyolysis related acute kidney injury. However the diagnosis must be confirmed by elevated serum creatinine kinase and the presence of urinary myoglobin.

A very weak correlation exists between creatinine kinase values and the incidence of acute kidney injury and the probability of acute kidney injury is lower when the creatinine kinase level at admission are less than twenty thousand. Rhabdomyolysis may contribute to acute kidney injury with CPK levels as low as 5000 U/L , when coexisting conditions such as sepsis, intravascular volume contractions and acidosis are present.

In the prevention of myoglobin induced nephropathy after crush syndrome, intra venous hydration should be initiated with isotonic saline before the crushed limb is relived to prevent precipitation of the pigment in the tubular lumen. A solution of 0.27% sodium bicarbonate should be given every second or third litre to maintain urinary ph above 6.5 and to prevent intratubular deposits of myoglobin and uric acid. The urinary output should be maintained around 300 ml/ h, which may require infusion of 12 litre of fluid per day. The volume administered may be needed to be higher than the urinary output.

The accumulation of fluid in the injured muscles may exceed 4 litres. This protocol should be continued until clinical or biochemical evidence of myoglobinuria disappears by day 3.It is proposed that mannitol is beneficial because of its diuretic property, antioxidant and also vasodilatory properties. Mannitol could prevent renal tubular cast deposition, expand extra cellular volume and reduced intra compartmental pressure, muscle oedema and pain.

However, mannitol may exuberate congestive heart failure and nephrotoxicity, requires close monitoring and is not used or contraindicated in oliguria, hypervolemia, hypertension and heart failure. Mannitol administration is considered if the urinary flow is sustained

above 20 ml/h given at the rate of 5 g/h added to each litre of infusate and not exceeding1 to 2 g/kg/day.

Muscle damage induces stretch activated ion channels, allowing for the influx of calcium ion channels into cells after reperfusion. The hypocalcaemia occurring due to this is asymptomatic but if left untreated can lead to dangerous arrhythmias which can go vital.

Hence care must be taken to avoid sodium bicarbonate induced decrease in ionized calcium channels caused by metabolic alkalosis which can trigger tetany, seizures and cardiotoxicity and worsen the existing muscle damage.

During the acute kidney injury recovery phase, hypocalcaemia is present mainly in patient who receive calcium infusion as a result of mobilization of previously precipitated calcium in muscles. Thus, the hypocalcemia if symptomatic must be treated at the movement they show symptoms.

The importance of early fluid administration and the most important aspects of the treatment of crush victims have been recently summarized.

In non-traumatic rhabdomyolysis prevention of acute kidney injury involves vigorous fluid expansion to maintain renal perfusion pressure

and to dilute myoglobin and other toxins.A urinary output of 200 to 300 ml/hour is desirable until the myoglobinuria disappears.

Urine alkalinisation may help prevent tubular pigment cast formation. However, there is no clinical evidence that mannitol and bicarbonate are more effective than saline solution. But there is potential risk to bicarbonate therapy include precipitation of calcium phosphate and hypocalcaemia.

In treating patient with rhabdomyolysis, it is important to consider when to stop the fluid resuscitation. Although the fluid expansion is the main therapeutic intervention to reduce the haemoglobin precipitation in the tubular lumen, the risk of fluid accumulation and compartmental expansion should always be the part of clinical judgement.

Frequent assessment of renal functional parameters associated with uric acid and creatine kinase level help the clinician decide how intense the volume expansion must be.

LATEST RECOMMENDATIONS IN CIRRHOSIS INCLUDE:

1. Diagnostic abdominal paracentesis should be performed and ascitic fluid should be obtained from all those patients with clinically presenting with new onset ascites. Fluid due to portal hypertension should be readily differentiated from other causes of ascites also. Due to high

prevalence of ascetic fluid infection at the time of admission in the hospital set up, tapping may detect unexpected infection.

2. Since bleeding is not common, the routine prophylactic use of FFP or platelets before paracentesis is not recommended. Routine test of coagulations also doesn’t reflect the risk of bleeding complications in patient with cirrhosis. The plasma products are used in cirrhotic patient only if the INR is more than 2.5.

Coagulopathy should preclude paracentesis only when there is evidence of hyperfibrinolysis. Epsilon amino caprioc acid can be used to treat hyperfibrinolyisis. In most of the cases there is no bleeding manifestations, even if there are no prophylactic transfusions, platelet count less than 20000 and even if the INR is higher than 8.

3. The initial laboratory investigation of the ascitic fluid include an ascitic fluid cell count and differential, ascitic fluid total protein and SAAG. If SAAG is greater than or equal to 1.1, the patient has portal hypertension. The SAAG retains accuracy despite fluid infusion and diuretic use.

4.If the ascetic fluid infection is suspected the culture for aerobic and anerobic infection should be sent before the initiation of antibiotics in this patient. When the ascitic fluid is analysed if the PMN is greater than

or equal to 250*10 ^{3} cells /mm3 then the presence of bacterial infection is suspected.

5.Other studies of ascetic fluid can be ordered based on the pre-test probability of the disease. If the patient present with uncomplicated ascites due to cirrhosis, then the screening test like cell count and differential albumin and total protein concentration is performed. Additional test like LDH and glucose to assist in differentiating the spontaneous from secondary bacterial peritonitis.

The most expensive test are cytology and smear and culture for mycobacteria. The ascitic fluid cytology is only positive only for peritoneal carcinamatosis. Polymerase chain reactions testing for mycobacteria or laparoscopy with biopsy and culture for mycobacteria are the most rapid and accurate method of diagnosing tuberculous peritonitis.

Testing serum for CA125 is not helpful in the differential diagnosis of ascites. Its use is not recommended in patients of any type.

6. Patients with ascites who are suspected to have alcohol as the main culprit of the cause of cirrhosis must abstained from alcohol consumption. In such patient with alcohol craving, baclofen can be used to reduce the alcohol craving and further alcohol consumption.

7.1st line treatment of patient with cirrhosis and ascites consist of sodium restriction and diuretics. Usual maximum doses of spironolactone 400 mg and 160 mg of furosemide can be used. Amiloride can be used as a good substitute for spironolactone. triamterene, metalazone and hydrochlorothiazide are also used for the treatment of ascites.

Epleneroneis a newer aldosterone antagonist that has been used in heart failure. Fluid restriction is not recommended unless the sodium levels falls below 125.Vaptans improve generally serum sodium in patient with cirrhosis and ascites. The high cost of the drug and lack of evidence of efficiency in meaningful outcomes have limited the use of the drugs.

8. An initial therapeutic Paracentesis should be performed in patient with tense ascites. Sodium restriction and oral diuretics should be initiated. A volume of upto 5 litres of fluid can be tapped in patient with diuretic resistant ascites. But the diuretic sensitive patient can be treated with fluid and sodium restriction rather than serial paracentesis. In this setting, the stopping consumption from alcohol shouldn't be forgotten.

9. Use of angiotensin receptor blockers and angiotensin converting enzyme inhibitor is very harmful in patient with cirrhosis and should be

used very carefully in the view of the blood pressure monitoring and renal function in the patient.

The use of non-steroidal anti-inflammatory drugs should be very limited in patient with cirrhosis except in few unavoidable conditions like ischemic cardiac events and neurological events. Liver transplantation should be considered in patient with cirrhosis and ascites.

The use of beta blockers in the patient should be carefully weighed in patient with liver cirrhosis and the risk of hypotension should be always kept in the mind while using beta blockers.

Oral midodrine is very useful drug used in cirrhosis especially in patient with diuretic resistant ascites and this drug also useful in converting the diuretic resistant to diuretic sensitive ascites.

Post paracentesis albumin infusion may not necessary if the fluid tapping is less than 5 litres. For large volume paracentesis, an albumin infusion of 6-8 gram per litre of fluid removed appears to improve the survival of patient and the setting is recommended.

Patient with ascites infection in community acquired setting in the absence of recent beta lactam antibiotic exposure should receive an

empirical antibiotic therapy mainly a third-generation antibiotic most probably ceftriaxone.

In nosocomial setup, the patient treatment must be adjusted according to the suspectability of antibiotic to the organism in the local setup. Oral Ofloxacin should be considered a substitute for intravenous cefotaxime is in patients without prior exposure to quinolones, vomiting, shock or serum creatinine greater than 3 mg/dl.

Even if the patient has symptoms suggestive of infections like fever, abdominal tenderness or pain in absence of reduced PMN, the prophylactic antibiotic can be started in those patients. Patient who have survived one episode of spontaneous bacterial peritonitis should receive life long term prophylaxis with daily norfloxacin or septran.

In patient with cirrhosis and ascites long term treatment of oral ciprofloxacin is suggested if the ascetic protein is less than < 1.5 g/dl along with impaired renal function that include creatine more than equal to 1.2, blood urea nitrogen more than equal to 25 or serum Na less than or equal to 130 or liver failure with child score more than or equal to 9 or bilirubin more than or equal to 34.

Intermittent dosing of antibiotic is found inferior to the daily dosing in preventing the incidence of secondary bacterial peritonitis in the

patient with cirrhosis, urinary biomarkers such as NGAL may assist in the differential diagnosis of azotemia in Patient with cirrhosis.

Albumin infusion with vasoactive drugs like somatostatin and midodrine has found to be effective in prevent the incidence of hepatorenal syndrome. But when the patient is in intensive care unit, hepatorenal syndrome can be prevented with the use of albumin with non-epinephrine.

Patient with hepatorenal syndrome, ascites and cirrhosis should be immediately referred for liver transplantation. Chest tube insertion should be contraindicated in patient with hepatic hydro thorax.

Elective repair of a hernia in a patient with cirrhosis is best performed after the ascites is controlled by medical treatment, first line treatment of hepatic hydrothorax should consist of dietary sodium restrictions and diuretics the amount of sodium to be restricted is less than 2000 mg/ day.

This can be more effective if the patient is having a reversible component to their liver injury like alcohol. The therapeutic thoracocentesis should be performed in the patient with dyspnoea. TIPS can be considered as the second line treatment for hydrothorax once it become refractory.

Fluid passes from the peritoneal cavity to the pleural space through a small defect in the diaphragm. TIPS is the most common used second line treatment.

Cellulitis can explain pain and fever in patient with cirrhosis and should be treated with diuretics and antibiotics. Percutaneous endoscopic gastrostomy should be avoided in patient with cirrhosis and ascites.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY DESIGN

Observational study

STUDY CENTRE

All patients are enrolled in Institute of Internal Medicine, Madras medical college, Chennai.

SAMPLE

60 patients with clinical evidence of cirrhosis were enrolled in this study. All patients had documented evidence of liver cirrhosis and were on cirrhosis treatment for at least one month. Informed consent was obtained from all patients.

INCLUSION CRITERIA

Diagnosed cases of liver cirrhosis through portal doppler.

EXCLUSION CRITERIA

- History of Trauma
- History of hypothyroidism
- History of hyperthyroidism
- History of statin therapy
- History of seizure disorder
- History of HIV patients
- Laboratory evidence of acidosis
- Laboratory evidence of anemia
- Laboratory evidence of thrombocytopenia
- Laboratory evidence of hematological disorders

PROCEDURE

Patients diagnosed as liver cirrhosis who are on follow up in Institute of internal medicine, madras medical college or on presentation to the Emergency Department in Rajiv Gandhi Government General Hospital are analysed.

The age and sex of the patient is noted. Absence of comorbities like hyperthyroidism, seizure disorder, hypothyroidism, trauma is noted. Absence of drug history such as antiretroviral therapy, statin therapy is noted. Personal history such as alcohol and smoking is noted. Patients with laboratory evidence of anemia, thrombocytopenia, acidosis and other hematological disorders are excluded. The history of comorbidities like diabetes mellites, hypertension, chronic kidney disease is noted.

The serum level of creatine phosphokinase, whole blood counts are noted. Serum albumin, urea and serum creatinine is noted. Parameters of liver function tests like total bilirubin levels and alkaline phosphatase level is noted. Patients presented with liver cirrhosis are staged clinically.

A detailed physical examination was conducted in this patient in order to stage the patient with liver cirrhosis. Portal vein doppler was conducted in these patients to confirm the presence of cirrhosis in the radiology department of Rajiv Gandhi hospital. Patients has undergone

upper oesophageal endoscopy to visualise the presence of varices in the patients in the gastroenterology department.

The incidence of rhabdomyolysis in liver cirrhosis is analysed. The correlation with serum albumin is noted. Serum creatinine is compared with rhabdomyolysis to analyse the correlation of rhabdomyolysis in cirrhosis patient as a risk factor for renal failure.

INSTRUMENTS

1.PORTAL DOPPLER

All the patients were undergone portal vein doppler study using duplex ultra sound system and looked for the coarse echoes, portal pressure and the presence of portal hypertension mainly to confirm the presence of liver cirrhosis.

2.OGD SCOPY

Upper esophageal endoscopy was done in all the patients in order to stage the grade of patients with liver cirrhosis. The presence of variceal bleeds along the esophagus and stomach is noted. The presence of variceal bleeding in the endoscopy is an important indicator of portal hypertension.

The esophageal varices identified during the endoscopy are graded according to their size as:

1.grade1: small straight esophageal varices

2. grade 2:enlarged tortuous esophageal varices occupying less than one third of the lumen

3.grade 3:large coiled varices occupying more than one third of the lumen.

LABORATORY METHODS

The whole blood count is calculated by auto analyser from the venous anti coagulated sample. The normal reference range value in adults is 4000-10000 cells/mm^3 .

Creatinine phosphokinase is measured in venous sample collected in red bottom tube. The creatinine phosphokinase is taken as the laboratory marker for rhabdomyolysis. The cut off value taken for rhabdomyolysis is around 773 as per the articles cited below. The creatinine kinase levels are enormously elevated in cases of rhabdomyolysis.

Liver function test was carried out with serum level of bilirubin, albumin, total protein and alkaline phosphatase has been measured. The normal reference range for

Serum total Bilirubin: 0.3-1.2 mg/dl

Serum albumin: 3.5-5.0 g/dl

Serum alkaline phosphatase:40-140 IU/L

Total protein:6.0-8.0 g/l

The renal parameters like serum urea and serum creatinine is also calculated. The normal reference range for

Serum urea: 15-40 mg/d

Serum creatinine: 0.8-1.0 mg/dl

DEFINITON

STAGE OF LIVER CIRRHOSIS

Stage of liver cirrhosis is determined by the presence of cirrhosis, ascites and variceal bleeding and is classified as

Stage 1-without ascites and cirrhosis

Stage 2 -presence of varices without bleeding and absence of ascites

Stage 3-ascitis with or without esophageal varices

Stage 4-variceal bleeding with or without ascites

ACUTE KIDNEY INJURY

The reference range of acute kidney injury is set as more than1.5 mg/dl as per KDIGO guidelines.

STATISTICAL ANALYSIS

STATISTICAL ANALYISIS

(If P-Value is <0.05 then statistically significant)

To compare two mean values independent samples is applied. To compare three or more mean values one way ANOVA is applied followed by Tamhane's post hoc tests for multiple pair wise comparisons. To compare proportions between study and control groups Chi-Square test is applied, if any expected cell frequency is less than five then Fisher's exact test is used. Trend Chi-Square is applied when there is a linear trend in the independent variable. To analyse the data SPSS (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp. Released 2013) is used. Significance level is fixed as 5% ($\alpha = 0.05$).

RESULTS

RESULTS

Age group	Rhabdomyolysis					
	No		Yes		Total	
	N	%	N	%	N	%
≤ 40 yrs	13	86.7%	2	13.3%	15	100.0%
41 – 50 yrs	15	78.9%	4	21.1%	19	100.0%
51 – 60 yrs	14	82.4%	3	17.6%	17	100.0%
> 60 yrs	5	55.6%	4	44.4%	9	100.0%
Total	47	78.3%	13	21.7%	60	100.0%

Totally out of 60 patients studied, 13 patients had increased levels of creatinine kinase suggesting the evidence of rhabdomyolyisis. That is 21% of the population had evidence of rhabdomyolysis.

The study was analysed based on gender sex, comorbities like DM, HTN, CKD, habits like smoking, alcohol and also laboratory parameters like WBC, Total bilirubin, albumin and with creatinine.

Independent samples t-t to compare mean CPK value between two categories

P value less than 0.05 is considered statistically significant. Values are rounded up to two decimals. SD denotes standard deviation.

Gender	N	Mean CPK	Std. Error	t-Value	P-Value
Male	56	457.43	90.778	0.008	0.994
Female	4	454.75	232.605		

The mean value was less in female group. There was no statistical significance between the two groups in CPK levels.

DM	N	Mean CPK	Std. Error	t-Value	P-Value
No	59	463.88	86.956	-	-
Yes	1	66.00	.		

SHI	N	Mean CPK	Std. Error	t-Value	P-Value
No	59	461.51	87.109	-	-
Yes	1	206.00	.		

CKD	N	Mean CPK	Std. Error	t-Value	P-Value
No	57	459.96	89.689	0.137	0.892
Yes	3	405.67	239.810		

The mean value was less in non CKD group. There was no statistical significance between the two groups in CPK levels.

CAD	N	Mean CPK	Std. Error	t-Value	P-Value
No	60	457.25	85.751	-	-
Yes	0	.	.		

Drug	N	Mean CPK	Std. Error	t-Value	P-Value
No	60	457.25	85.751	-	-
Yes	0	.	.		

Smoking	N	Mean CPK	Std. Error	t-Value	P-Value
No	51	433.63	88.907	0.653	0.517
Yes	9	591.11	280.976		

The mean value was less in SMOKERS group. There was no statistical significance between the two groups in CPK levels.

Alcohol	N	Mean CPK	Std. Error	t-Value	P-Value
No	22	432.05	123.746	0.222	0.825
Yes	38	471.84	116.045		

The mean value was less in alcoholic group. There was no statistical significance between the two groups in CPK levels.

Oneway ANOVA to compare mean CPK values between stages

Stage	N	Mean CPK	Std. Error	F-Value	P-Value
Stage-2	19	288.74	75.441	5.156	0.009
Stage-3	32	387.22	110.763		
Stage-4	9	1062.00	331.782		

The mean value was less in stage 2group. There was no statistical significance between the two groups in CPK levels.

Tamhane's Post Hoc Tests for Multiple Comparisons

Stage		Mean Difference	Std. Error	P-Value
Stage-2	Stage-3	98.482	134.014	0.848
	Stage-4	773.263	340.250	0.042
Stage-3	Stage-4	674.781	349.782	0.229

Pearson Correlations coefficient between CPK and other variables

		CPK
Age (yrs)	Correlation value	0.059
	P-Value	0.656
	N	60
WBC	Correlation value	0.074
	P-Value	0.576
	N	60
S.Bilirubin	Correlation value	-0.098
	P-Value	0.455
	N	60
Albumin	Correlation value	0.030
	P-Value	0.818
	N	60
Alt	Correlation value	0.066
	P-Value	0.618
	N	60
Protein	Correlation value	-0.004
	P-Value	0.977
	N	60
Urea	Correlation value	0.154
	P-Value	0.241
	N	60
Creatinine	Correlation value	0.088
	P-Value	0.503
	N	60

All the laboratory values such as WBC, bilirubin, protein, creatinine and albuminwere reviewed .there was no statistical difference of CPK levels among the two groups.

T-Test to compare mean values of parameters between Rhabdomyolysis Present and Absent cases

Parameters	Rhabdo-myolysis	N	Mean	Std. Error	t-Value	P-Value
WBC	No	47	6119.15	380.523	0.077	0.939
	Yes	13	6184.62	851.006		
S.Bilirubin	No	47	4.174	.6841	1.122	0.266
	Yes	13	2.677	.5088		
Albumin	No	47	2.989	.1197	0.743	0.460
	Yes	13	3.169	.1521		
Alt	No	47	78.745	8.3141	0.830	0.410
	Yes	13	93.769	16.8185		
Protein	No	47	5.994	.1859	0.126	0.900
	Yes	13	6.046	.4222		
Urea	No	47	39.511	4.0489	1.263	0.211
	Yes	13	53.346	15.0609		
Creatinine	No	47	1.317	.0967	0.212	0.833
	Yes	13	1.362	.1923		

All the laboratory values such as WBC, bilirubin, protein, creatinine and albumin were reviewed .there was no statistical difference of CPK levels among the two groups.

Chi-Square test to compare proportions

Age group	Rhabdomyolysis					
	No		Yes		Total	
	N	%	N	%	N	%
≤ 40 yrs	13	86.7%	2	13.3%	15	100.0%
41 – 50 yrs	15	78.9%	4	21.1%	19	100.0%
51 – 60 yrs	14	82.4%	3	17.6%	17	100.0%
> 60 yrs	5	55.6%	4	44.4%	9	100.0%
Total	47	78.3%	13	21.7%	60	100.0%

Chi-Square Test	Value	P-Value
Trend Chi-Square Test	2.057	0.151

Analysing the patients based on the age group , age group more than 60 has highest incidence of rhabdomyloysis.

Gender	Rhabdomyolysis					
	No		Yes		Total	
	N	%	N	%	N	%
Male	44	78.6%	12	21.4%	56	100.0%
Female	3	75.0%	1	25.0%	4	100.0%
Total	47	78.3%	13	21.7%	60	100.0%

Chi-Square Test	Value	P-Value
Fisher's Exact Test	-	0.995

The percentage of rhabdomyolysiswas 21.4% among males and 25.0% among the females in the study group.

DM	Rhabdomyolysis					
	No		Yes		Total	
	N	%	N	%	N	%
No	46	78.0%	13	22.0%	59	100.0%
Yes	1	100.0%	0	0.0%	1	100.0%
Total	47	78.3%	13	21.7%	60	100.0%

Chi-Square Test	Value	P-Value
Fisher's Exact Test	-	0.994

The percentage of rhabdomyolysis was 22.2 % among non diabetic and no one in the diabetic group.

Smoking	Rhabdomyolysis					
	No		Yes		Total	
	N	%	N	%	N	%
No	41	80.4%	10	19.6%	51	100.0%
Yes	6	66.7%	3	33.3%	9	100.0%
Total	47	78.3%	13	21.7%	60	100.0%

Chi-Square Test	Value	P-Value
Fisher's Exact Test	-	0.392

The percentage of rhabdomyolysis was 19.6% among non smoker and 33.3% among the smokers in the study group.

Alcohol	Rhabdomyolysis					
	No		Yes		Total	
	N	%	N	%	N	%
No	18	81.8%	4	18.2%	22	100.0%
Yes	29	76.3%	9	23.7%	38	100.0%
Total	47	78.3%	13	21.7%	60	100.0%

Chi-Square Test	Value	P-Value
Fisher's Exact Test	-	0.751

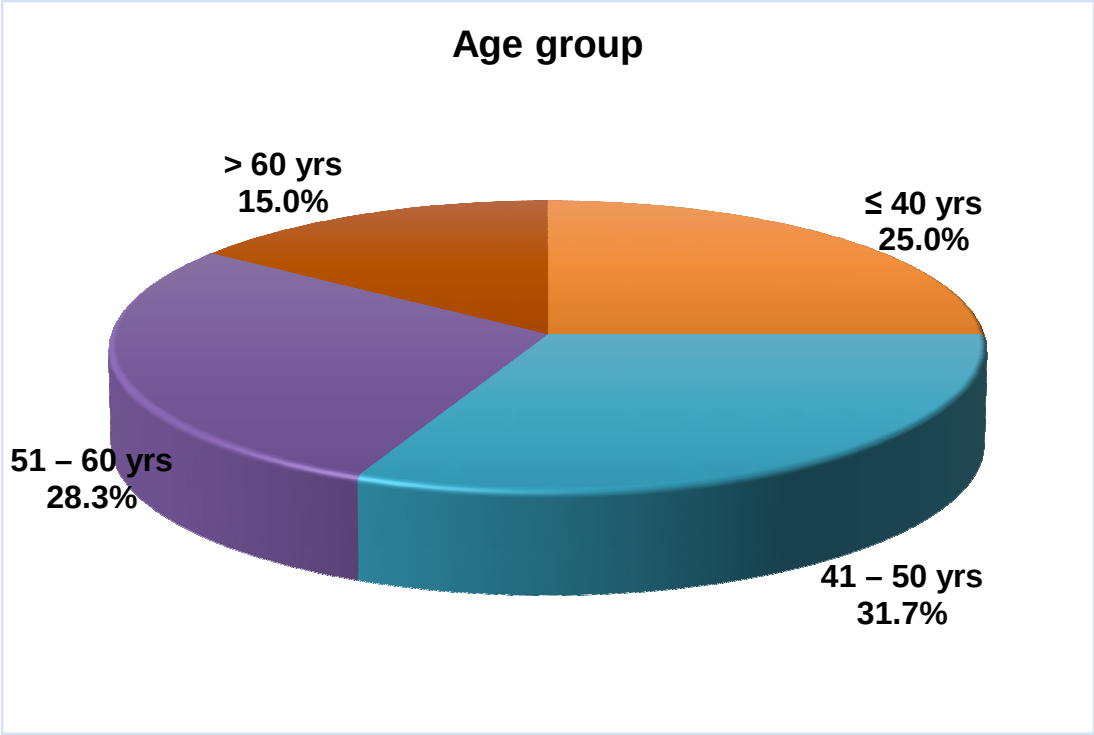
The percentage of rhabdomyolysis was 18.2% among non alcoholics and 23.7% among the alcoholic in the study group.

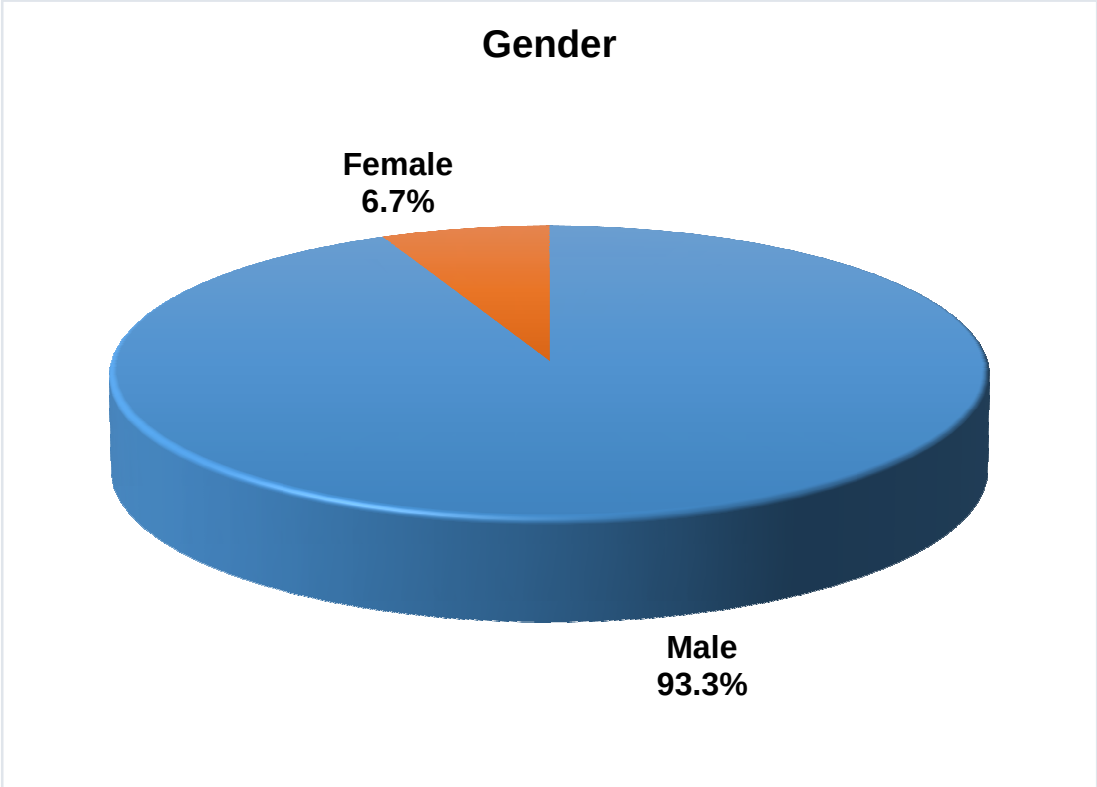
Stage	Rhabdomyolysis					
	No		Yes		Total	
	N	%	N	%	N	%
Stage-2	16	84.2%	3	15.8%	19	100.0%
Stage-3	27	84.4%	5	15.6%	32	100.0%
Stage-4	4	44.4%	5	55.6%	9	100.0%
Total	47	78.3%	13	21.7%	60	100.0%

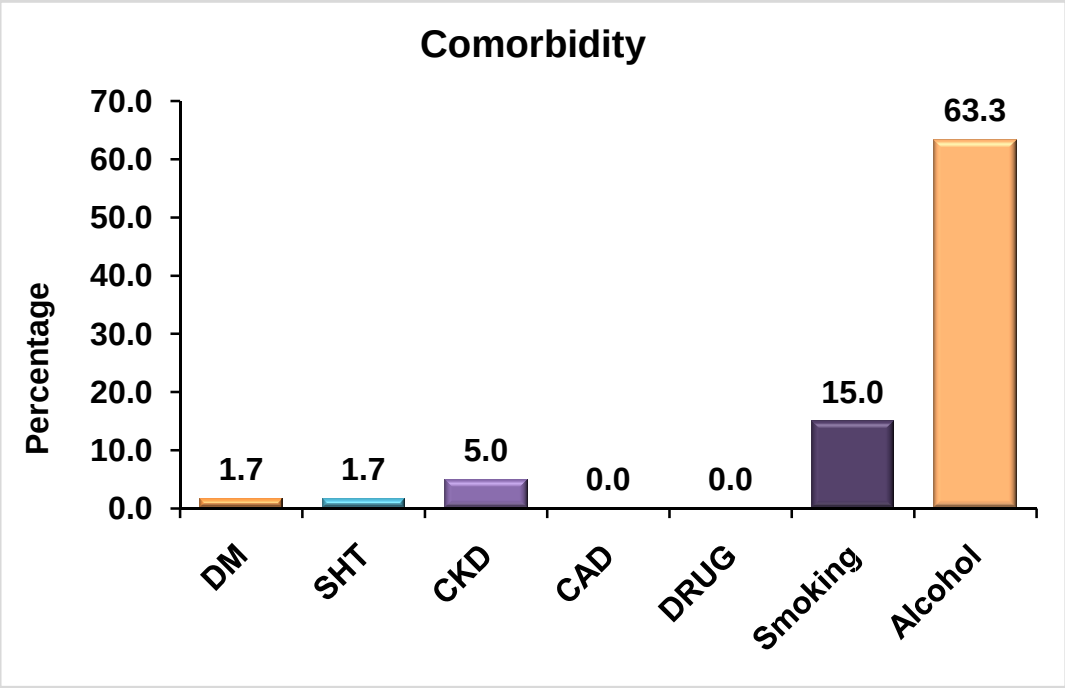
Chi-Square Test	Value	P-Value
Trend Chi-Square Test	3.820	0.051

Analysing the patients based on the stage of cirrhosis, stage 4 of cirrhosis has highest incidence of rhabdomyloysis.

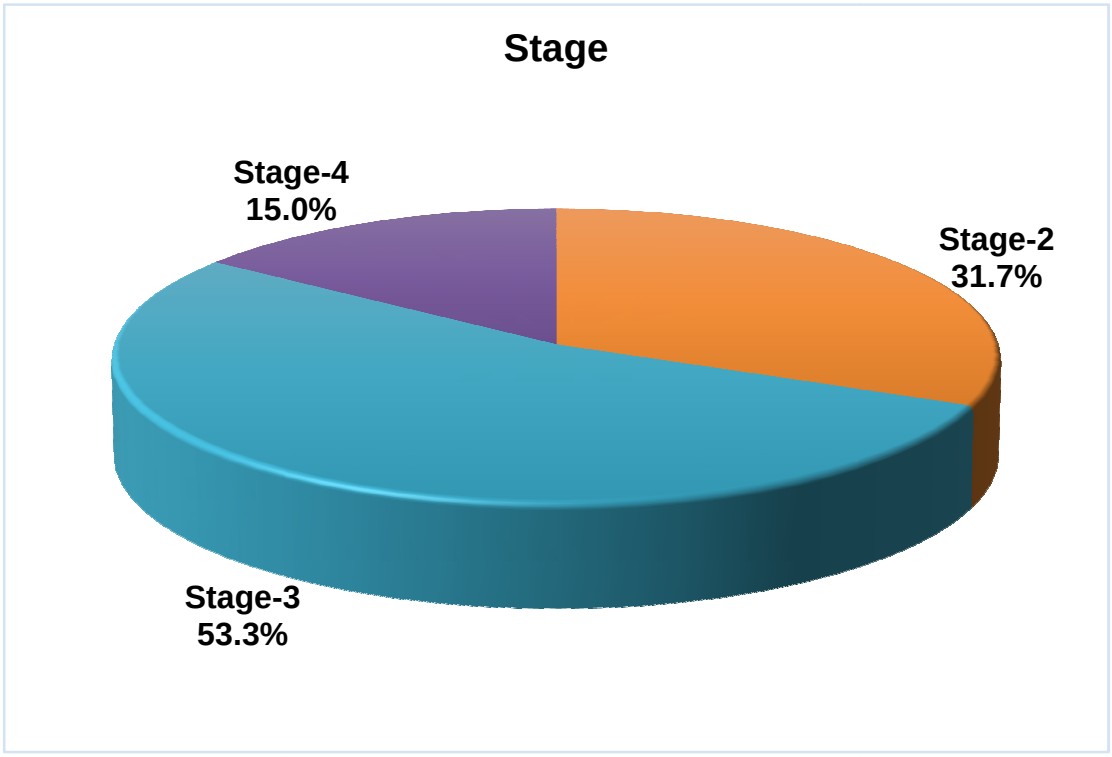
CHARTS

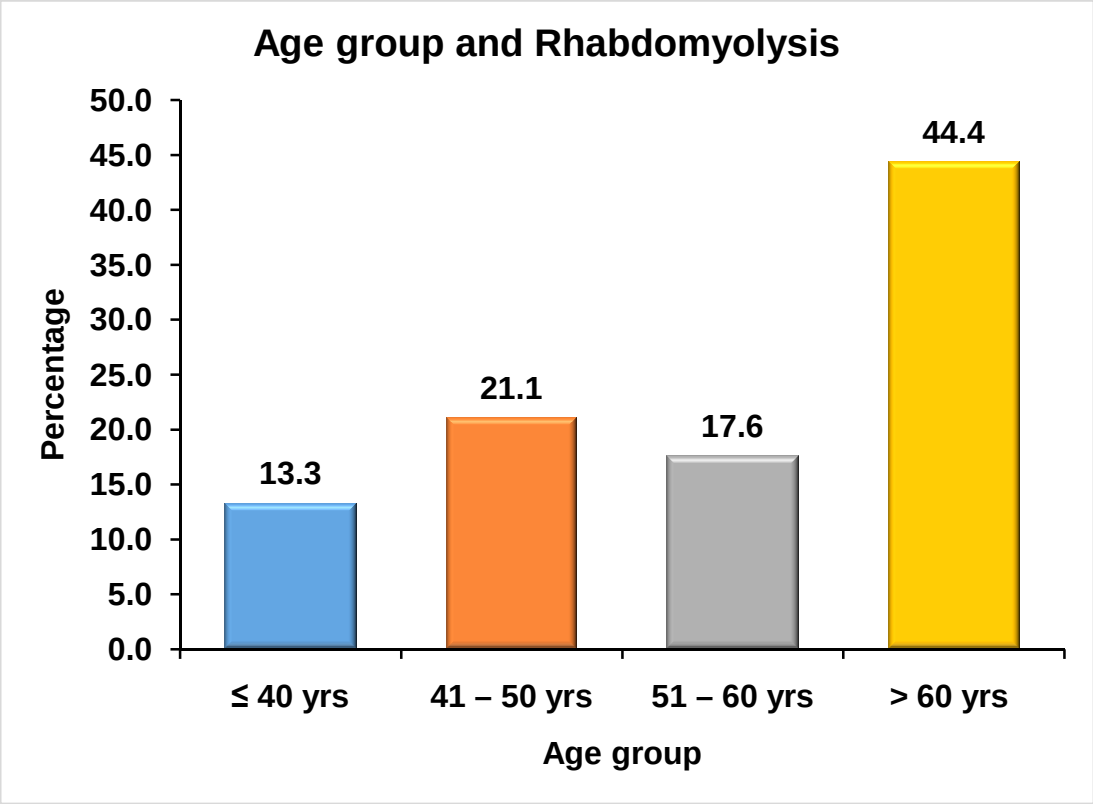



Gender
Female
6.7%
Male
93.3%

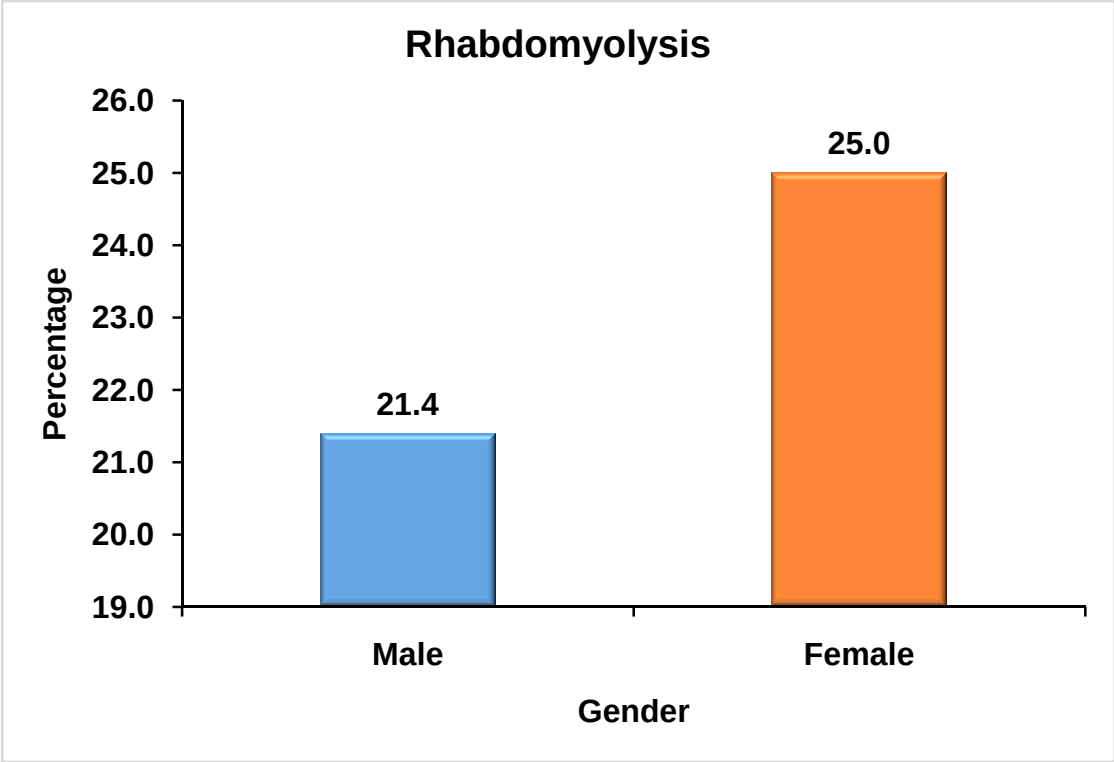


Among the comorbidities, rhabdomyolysis was seen in 63.3% of alcoholics. The percentage was around 0 when associated with comorbidities such as CAD and drug usage.

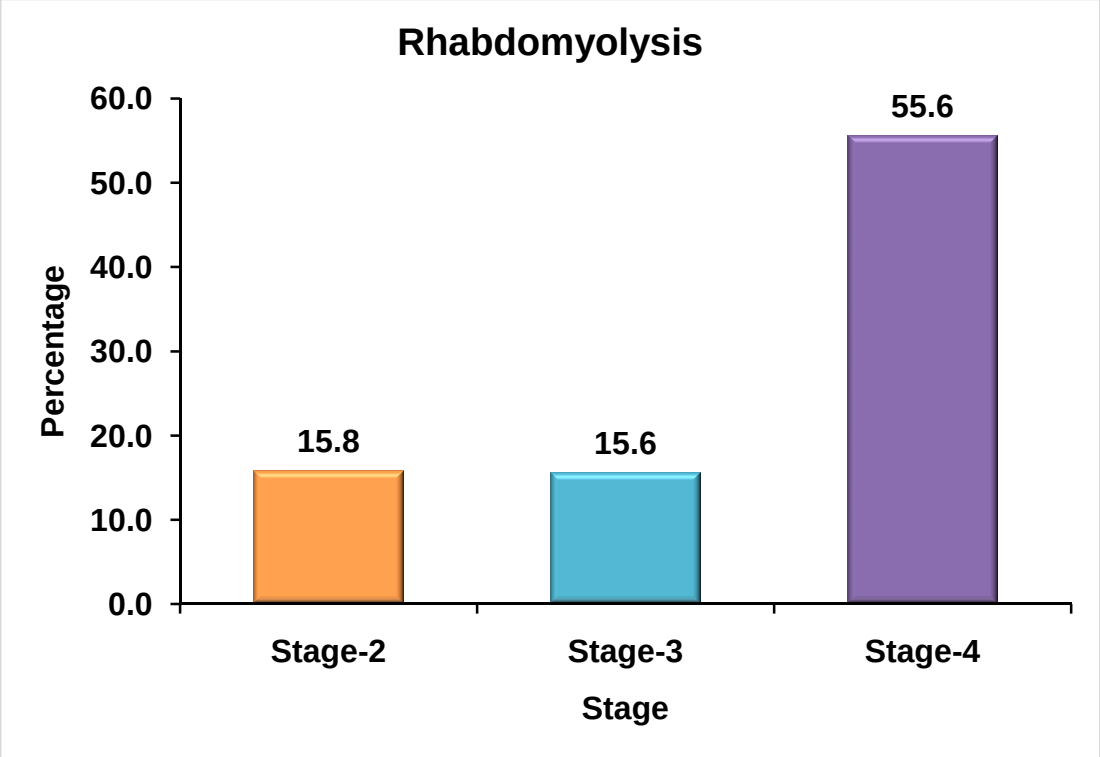

Stage
Stage-4
15.0%
Stage-2
31.7%
Stage-3
53.3%



The incidence of rhabdomyolysis was around 21.1% in 41 -50 age group and it was around 44.4% in more than 60 group. The incidence was around 17.6% in 51-60 age group.



The incidence of rhabdomyolysis was around 21.4% in males and almost 25% in females. The percentage was higher in females when compared to females.



The incidence of rhabdomyolysis was around 55.6% in stage 4 ,15.6% in stage 3 and 15.8% in stage 2 among the study group. The percentage was quite higher in stage 4 group when compared to others.

Pearson Correlations coefficient between CPK and other variables

		CPK
Albumin	Correlation value	0.030
	P-Value	0.818
	N	60
Creatinine	Correlation value	0.088
	P-Value	0.503
	N	60

The correlation between CPK and Albumin; CPK and Creatinine are weak and statistically not significant.

DISCUSSION

DISCUSSION

Many researchers has been reported on the high prevalence of rhabdomyolysis in liver cirrhotic patients. Konikoff Et all found an 88% incidence of rhabdomyolysis in 22 cirrhotic patients, as compared to 21% in a matched population without liver cirrhosis. In their research, they found high prevalence and uniformity of the phenomenon mist justify the inclusion of rhabdomyolysis among the patients with cirrhosis.

Abrams et al suggested that muscle cramps are specifically related to the development of cirrhosis than in the controls and it was related to the duration of recognized cirrhosis and to the severity of liver function impairment. Moreover, they concluded that the patho physiological link between cirrhosis and rhabdomyolysis may associate with a reduced effective circulating volume and also indicated that reports focused upon muscle cramps as a symptom observed in liver cirrhosis patients and not on the clinical and laboratory finding with muscular symptoms.

Moreover, in addition to muscular cramps, weakness, acting and tenderness, rhabdomyolysis can also occur in liver cirrhosis patients. However, no systemic investigation has been conducted on rhabdomyolysis development in cirrhosis patients.

We found that rhabdomyolysis occurs in the cirrhosis patients. We investigated here cirrhotic patients with elevated muscle enzyme concentrations to rule out rhabdomyolysis

We observed that almost many cirrhotic patients with rhabdomyolysis had poor liver function stage 4 rather than stage 3 and 2. therefore the patients with advanced cirrhosis has to monitored for acute myopathy and rhabdomyolysis in addition to better known complications of hepatic encephalopathy, gastro intestinal bleeding or hepatorena syndrome.

Comparing with the rhabdomyolysis of the general population, in which drug response and septicemia are the most common etiological factors, it is identified that the predisposing factor to myopathy development in cirrhosis was infection including respiratory, spontaneous bacterial peritonitis and urinary tract infection.

By our study, it has been very difficult to identify the presence of rhabdomyolysis by analysing the elevated value of enzymes because of the statistical insignificance. Since the patients with cirrhosis can develop many complications the complication of muscle enzymes should be used for detection of acute myopathy.

The patients with decompensated liver disease had a higher plasma levels of enzymes than the patients with compensated liver disease. This finding represents the natural course of acute myopathy development in cirrhotic patients.

Increased levels of muscle enzymes and serum myoglobulin are more sensitive marker for the diagnosis of rhabdomyolysis especially creatine kinase which is a very important marker.

Many case reports has mentioned the usefulness of technicium scan bone scintigraphy for early diagnosis and for determining the location and extent of muscle injury in rhabdomyolysis. In the current study, Technicium scans could not be used due to the unavailability of the scan in our set up. Such patients may show increased uptake of the dye if evaluated within few days of admission. But not every patients who are symptomatically improving will show an increased uptake of the radionucleotide scan.

Through this study we tried to correlate the levels of CPK levels and level of albumin and creatinine. But our study revealed that the correlation between CPK and Albumin; CPK and Creatinine are weak and statistically not significant.

CONCLUSION

CONCLUSION

The end points of our study are

- Rhabdomyolysis is seen in patients suffering from liver cirrhosis.
- The correlation between rhabdomyolysis and liver cirrhosis are weak and statistically not significant
- In our study, rhabdomyolysis was seen more common in males.
- In our study, rhabdomyolysis was more common inn more than 60 years age group.
- In our study, rhabdomyolysis was more common in stage 4 disease.
- The correlation between CPK and Albumin; CPK and Creatinine are weak and statistically not significant

SCOPE FOR FUTURE

STUDIES

SCOPE FOR FUTURE STUDIES

- Large-scale studies are needed to evaluation of the role of Rhabdomyolysis in liver cirrhosis. If beneficial results could be demonstrated this could be a cost effective measure to reduce the high mortality and morbidity associated with this condition.

- Frequent estimating CPK levels at various stages of cirrhosis can help in better understanding of the role of rhabdomyolysis in cirrhosis and further correlation should be made out.

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BIBLIOGRAPHY

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ANNEXURES

PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

IP/OP NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

CARE GIVER :

PAST HISTORY :

1. Diabetes mellitus :
2. Systemic hypertension :
3. Chronic Kidney Disease :
4. Coronary artery disease :

TREATMENT HISTORY:

1. Antiepileptic therapy :
2. Antiretroviral therapy :
3. Treatment for cirrhosis :
4. Vasopressin therapy :

PERSONAL HISTORY

Smoking :

Alcohol :

INVESTIGATIONS:

WBC :

Creatine Phosphokinase :

Serum urea :

Serum creatinine :

Total bilrubin :

ALT :

SERUM PROTIEN :

SERUM ALBUMIN :

STAGE OF CIRRHOSIS:

MASTER CHART

s no	NAME	AGE	SEX	DM	SHT	CKD	CAD	DRU	SMO	ALC	WBC	CPK	BIL	ALB	ST	alt	pro	ur	crea
1	NANDHI	24	M	NO	NO	NO	NO	NO	NO	NO	1800	47	4.4	3.9	3	80	7.3	21	0.9
2	KALI	51	M	YES	NO	NO	NO	NO	NO	YES	4500	66	1.9	3.9	2	66	7.3	29	1
3	VIJAY	55	M	NO	NO	NO	NO	NO	YES	YES	2600	1170	3.3	3.4	4	74	5.5	27	0.8
4	DURAI	42	M	NO	NO	NO	NO	NO	NO	YES	11000	74	5.1	3.3	2	15	6.3	33	1.1
5	ARU	46	M	NO	NO	YES	NO	NO	NO	YES	5100	107	6.1	3.2	4	29	6.3	21	1.3
6	SAKTHIVEL	62	M	NO	NO	YES	NO	NO	YES	YES	3300	880	1	3.5	2	38	7.1	21	1.1
7	SEKAR	65	M	NO	NO	NO	NO	NO	NO	NO	4300	121	8.9	3.7	2	28	4	29	0.9
8	JEBASINGH	47	M	NO	YES	NO	NO	NO	NO	NO	4100	206	4.1	2.9	3	10	4.2	31	1
9	PRABHU	31	M	NO	NO	NO	NO	NO	NO	YES	3600	113	3.7	3.1	2	21	3.9	27	0.8
10	RAJESH	40	M	NO	NO	NO	NO	NO	NO	YES	4200	420	3.9	2.6	2	46	4.5	31	1.2
11	RAVI	42	M	NO	NO	NO	NO	NO	YES	NO	15100	2560	4.7	3.5	4	48	7	86	1.6
12	JEEVA	31	M	NO	NO	NO	NO	NO	NO	NO	6100	56	24	2.1	3	69	5.5	36	1.4
13	PORKODI	35	F	NO	NO	NO	NO	NO	NO	NO	4600	82	1.2	3.8	3	65	7.7	29	0.9
14	RAM	56	M	NO	NO	NO	NO	NO	YES	YES	5400	68	1.8	3.2	2	21	7	42	1.2
15	RAJESH	39	M	NO	NO	NO	NO	NO	NO	YES	4900	123	1.3	3.7	3	62	705	29	1
16	SELVAM	30	M	NO	NO	NO	NO	NO	NO	NO	4300	254	1.6	3.6	4	26	7.7	31	1.1
17	PANDYAN	41	M	NO	NO	NO	NO	NO	YES	YES	5100	79	5.4	3	3	94	8.4	36	1
18	GOPI	52	M	NO	NO	NO	NO	NO	NO	YES	9200	32	1	2.8	3	78	4.1	39	2.8
19	PRAKASH	55	M	NO	NO	NO	NO	NO	NO	YES	8600	840	1.9	2.8	2	115	5.3	24	1

20	VAIDYAN	47	M	NO	NO	NO	NO	NO	NO	NO	8500	672	1.9	2.9	4	36	6.9	14	1
21	SADIQ	47	M	NO	NO	YES	NO	NO	NO	NO	12700	230	4.8	2.5	3	90	6.3	8.7	3
22	KUMAR	38	m	NO	NO	NO	NO	NO	NO	NO	10600	890	2.5	2.6	3	52	2.6	44	0.9
23	RAMU	45	M	NO	NO	NO	NO	NO	NO	YES	8800	212	2.2	3.2	3	72	4.5	38	1.1
24	ANBU	55	M	NO	NO	NO	NO	NO	YES	YES	7600	182	1	4.2	3	77	7.9	97	2.9
25	MURUGAN	40	M	NO	NO	NO	NO	NO	NO	YES	4100	2781	2.1	3.2	4	164	5.9	68	1.9
26	ASHOK	32	M	NO	NO	NO	NO	NO	NO	YES	6000	43	2.7	3.7	2	88	6.2	34	1.2
27	PARASU	52	M	NO	NO	NO	NO	NO	NO	YES	11700	2877	7.1	2.4	3	46	4.2	123	1.9
28	ELANGO	52	M	NO	NO	NO	NO	NO	NO	YES	5200	21	11	2.1	2	76	4.8	112	2.8
29	RAM	63	M	NO	NO	NO	NO	NO	NO	YES	4400	74	4.9	1.7	4	112	6.5	16	0.9
30	IRAEL	54	M	NO	NO	NO	NO	NO	NO	YES	6500	563	4.3	2	3	75	4.8	24	2.2
31	MOORTHY	32	M	NO	NO	NO	NO	NO	NO	NO	2500	650	4.2	2.4	3	76	4.4	42	0.8
32	KUMAR	39	M	NO	NO	NO	NO	NO	NO	YES	3700	38	8	2.9	3	110	6.1	33	2.4
33	RAJKUMAR	34	M	NO	NO	NO	NO	NO	NO	YES	2800	56	0.6	2.5	2	73	5.3	45	1.2
34	RANGAN	53	M	NO	NO	NO	NO	NO	NO	YES	4800	86	6.4	2.9	3	29	5.4	91	1.5
35	KUMAR	41	M	NO	NO	NO	NO	NO	NO	NO	9600	1070	4.1	3	2	102	6.6	28.5	0.5
36	GANGAYAN	48	M	NO	NO	NO	NO	NO	NO	YES	6500	510	2.6	1.8	3	52	6.4	112	2.1
37	BASKAR	57	M	NO	NO	NO	NO	NO	NO	NO	3600	68	2.1	2.2	2	112	5.4	18	0.3
38	MANO	52	M	NO	NO	NO	NO	NO	NO	YES	6500	70	13	1.8	3	289	4.2	93	2.1
39	RANI	60	F	NO	NO	NO	NO	NO	NO	NO	4000	65	3.2	2.5	3	29	5.1	16	1.6
40	VALLI	43	F	NO	NO	NO	NO	NO	NO	NO	5400	1020	0.5	3.9	4	146	7.9	209	2.7
41	IQBAL	42	M	NO	NO	NO	NO	NO	NO	YES	9700	48	4.7	2.5	3	30	5.5	58	1.6
42	PITVHAI	60	M	NO	NO	NO	NO	NO	NO	YES	7400	368	1	3.5	2	292	4	23	0.9

43	NATHAN	53	M	NO	NO	NO	NO	NO	NO	NO	5600	45	0.4	3.1	3	122	6.1	15	0.9
44	MUTHU	68	M	NO	NO	NO	NO	NO	NO	YES	5800	46	0.5	2.9	3	84	5.8	22	1
45	ANBU	48	M	NO	NO	NO	NO	NO	NO	YES	6700	65	2.1	2.5	2	85	7.5	12	0.8
46	SENGALINI	43	M	NO	NO	NO	NO	NO	NO	YES	6300	109	1.8	3.1	3	156	62	22	0.7
47	PANDYAN	40	M	NO	NO	NO	NO	NO	NO	NO	5600	149	4.4	6	2	60	7.8	28	0.7
48	VENKI	65	M	NO	NO	NO	NO	NO	NO	NO	5400	258	2.3	1.5	2	43	7.1	29	0.9
49	MOHAN	47	M	NO	NO	NO	NO	NO	NO	YES	6300	1800	3.1	2.5	3	53	6.5	48	0.4
50	BABU	45	M	NO	NO	NO	NO	NO	NO	YES	4400	154	2.1	2.9	2	128	5.6	1.7	1
51	SYED	49	M	NO	NO	NO	NO	NO	NO	NO	5300	178	3	3.3	3	98	6.2	40	0.6
52	RAGMA	45	F	NO	NO	NO	NO	NO	NO	NO	13600	652	1.1	4.6	2	45	8.7	29	1.1
53	DHANDA	67	M	NO	NO	NO	NO	NO	NO	YES	6600	920	0.6	4.1	4	42	6.8	19	1
54	KUMARAN	48	M	NO	NO	NO	NO	NO	NO	NO	5500	172	1.6	3.3	3	128	6.6	24	1.1
55	GOPAL	57	M	NO	NO	NO	NO	NO	YES	YES	8800	34	1	2.5	3	62	6.3	112	2.3
56	SRINIVAS	61	M	NO	NO	NO	NO	NO	YES	YES	8600	289	2.5	2.9	3	34	6.2	18	1
57	ANCHAAN	62	M	NO	NO	NO	NO	NO	NO	YES	12600	1300	1.6	2.7	3	242	11.1	56	2.2
58	RAHIM	51	M	NO	NO	NO	NO	NO	NO	NO	4600	60	0.3	3.6	3	100	5.2	24	0.7
59	GANESAN	40	M	NO	NO	NO	NO	NO	YES	YES	12000	58	21	2.2	3	128	5	48	1.9
60	RAMU	66	M	NO	NO	NO	NO	NO	NO	YES	13000	1254	2.3	3.6	3	97	5.1	46	1.7

PATIENT CONSENT FORM

Study Detail	:	INCIDENCE OF RHABDOMYOLYSIS IN LIVER CIRRHOSIS AND THEIR CORRELATION WITH SERUM ALBUMIN
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination , biochemical and radiological tests ❑

Signature of Investigator
Study Investigator's Name:
DR. ASWIN S KRISHNA

Signature/thumb impression
Patient's Name and Address:

INFORMATION SHEET

We are conducting a study on **"INCIDENCE OF RHABDOMYOLYSIS IN LIVER CIRRHOSIS AND THEIR CORRELATION WITH SERUM ALBUMIN"** among patients attending Rajiv Gandhi Government General Hospital, Chennai

The purpose of this study is to assess **"INCIDENCE OF RHABDOMYOLYSIS IN LIVER CIRRHOSIS AND THEIR CORRELATION WITH SERUM ALBUMIN"**

We are selecting certain cases and if you are found eligible, we may be using clinical profile, lab test reports and radiological reports for study purposes which does not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant / Guardian

Place:
Date:

PLAGIARISM DIGITAL REPORT

URKUND

Urkund Analysis Result

Analysed Document: THESIS.docx (D31042081)
Submitted: 10/5/2017 2:35:00 PM
Submitted By: aswinkrishna1@gmail.com
Significance: 1 %

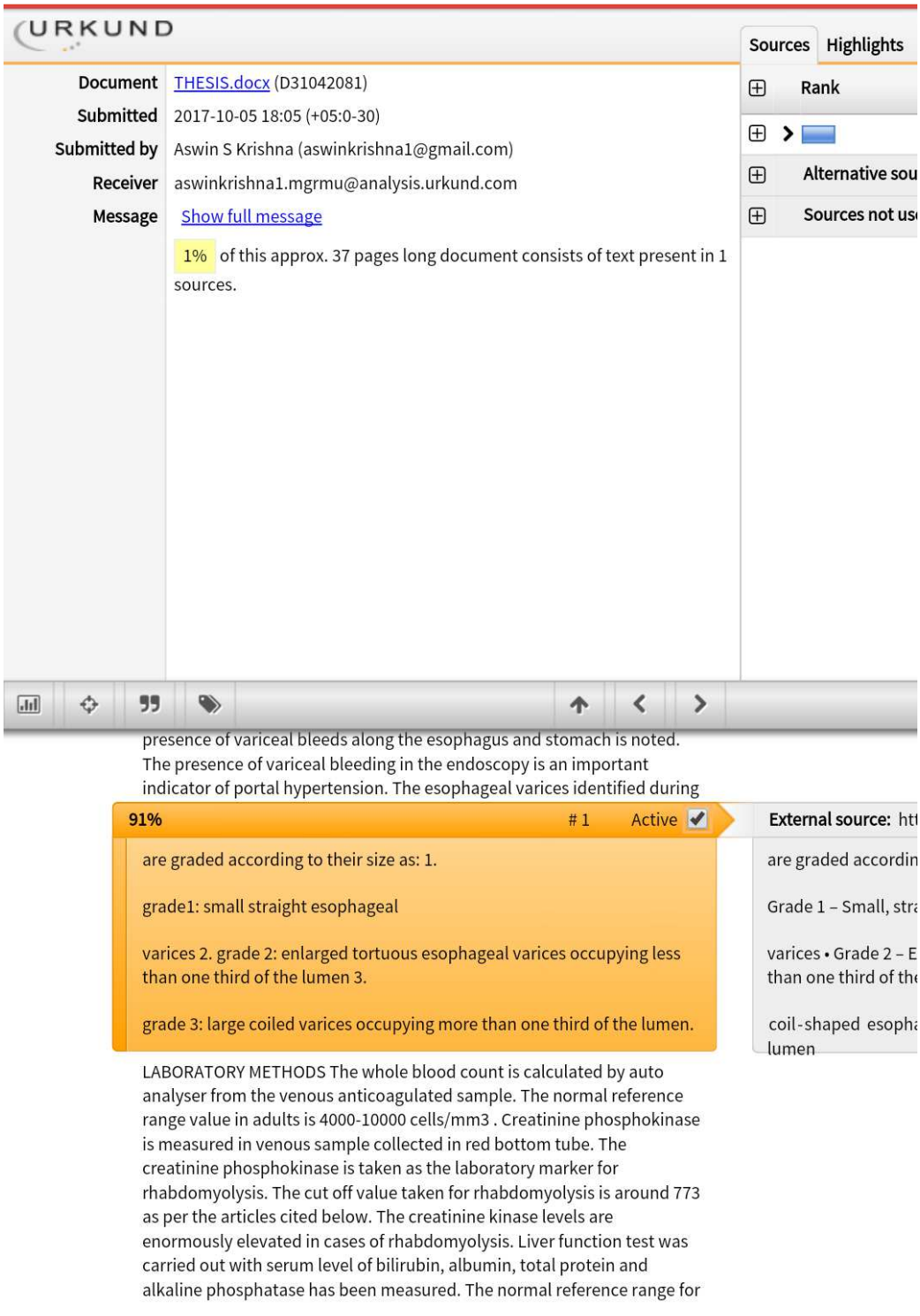
Sources included in the report:

http://emedicine.medscape.com/article/367986-overview

Instances where selected sources appear:

1

PLAGIARISM CERTIFICATE



INSTITUTIONAL ETHICS COMMITTEE APPROVAL

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Aswin S.Krishna
Post Graduate in MD General Medicine
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.Aswin S.Krishna

The Institutional Ethics Committee has considered your request and approved your study titled **"INCIDENCE OF RHABDOMYOLYSIS IN LIVER CIRRHOSIS AND THEIR CORRELATION WITH SERUM ALBUMIN " - NO.18012017 (II).**

The following members of Ethics Committee were present in the meeting hold on **19.01.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.A.Rajendran,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
8.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
9.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
10.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

ABBREVIATIONS

DM	-	DIABETES MELLITUS
SHT	-	SYSTEMIC HYPERTENSION
CKD	-	CHRONIC KIDNEY DISEASE
CAD	-	CORONARY ARTERY DISEASE
SMO	-	SMOKING
ALC	-	ALCOHOLIC
WBC	-	WHITE BLOOD COUNT
CPK	-	CREATININE PHOSPHOKINASE
BIL	-	BILIRUBIN
ALB	-	ALBUMIN
ST	-	STAGE
ALT	-	ALKALINE TRANSAMINASE
PRO	-	PROTIEN
URE	-	UREA
CR	-	CREATININE