# DISSERTATION ON

# A STUDY ON RENAL FAILURE IN CHRONIC LIVER DISEASE PATIENTS

**Dissertation Submitted To**

**THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY,**

**In partial fulfillment of the**

**Rules and regulations, for the award of the**

**M.D. DEGREE IN GENERAL MEDICINE**

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**THANJAVUR – 613004**

**THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY**

**CHENNAI – 600032**

**APRIL - 2017**

## CERTIFICATE

This is to certify that dissertation entitled A **STUDY ON RENAL FAILURE IN CHRONIC LIVER DISEASE PATIENTS** is the bonafide record of work done by **Dr BONDADA RAMA ABHISHEK** in the Department of General Medicine , Thanjavur Medical College, Thanjavur during his Post Graduate Course from 2014 – 2017 . This is submitted as partial fulfillment for the requirement of M.D. Degree Examinations – Branch I (General Medicine) to be held in April 2017. The period of study was from January 2016 to June 2016.

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## DECLARATION

I , **Dr.BONDADA RAMA ABHISHEK**, solemnly declare that dissertation titled **A STUDY ON RENAL FAILURE PATIENTS IN CHRONIC LIVER DISEASE PATIENTS** is a bonafide work done by me at Thanjavur Medical College Hospital during Jan 2016 – May 2016 under the guidance and supervision of **Prof**. **Dr. C. GANESAN, M.D** .HOD., Department of Internal Medicine.

The dissertation is submitted to **THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY, CHENNAI, TAMILNADU** as partial fulfillment for the requirement of M.D. Degree Examinations – Branch I (General Medicine) to be held in April 2017.

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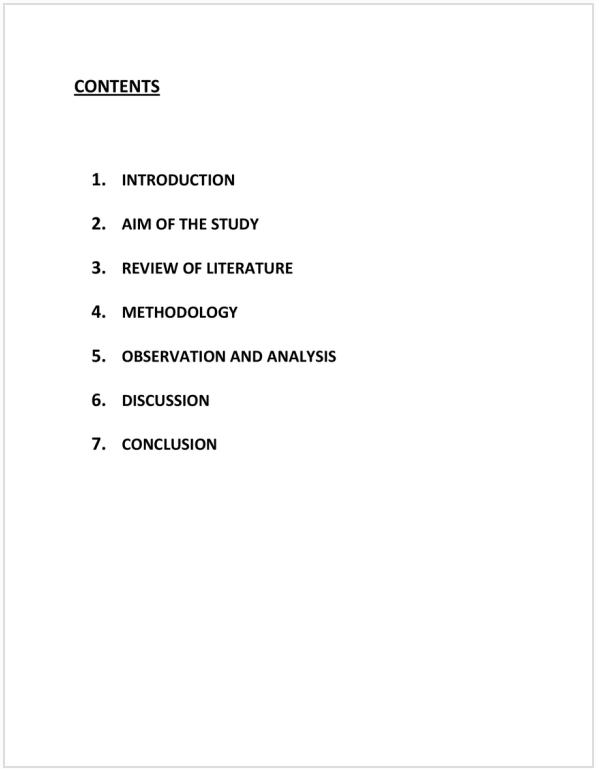

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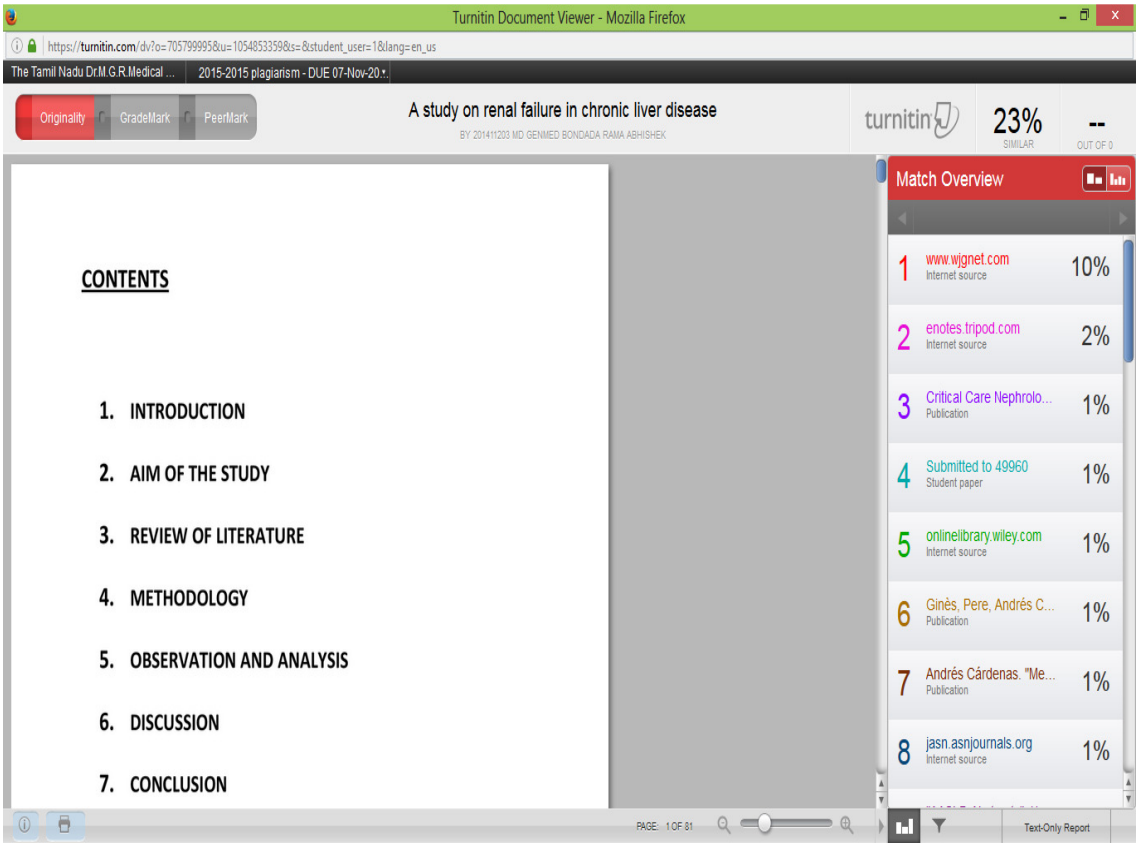
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**CONTENTS**

# INTRODUCTION

Renal failure is a major challenging complication in patients with chronic liver disease patients and is one of the most important risk factor associated with mortality and liver transplantation is considered.

Patients with cirrhosis are susceptible to develop renal failure due to persistent vasodilatory state, reduced effective blood volume and stimulation of vasoconstrictor hormones.

Infection is a major risk factor precipitating renal failure in liver disease

Renal parameters should be monitored routinely in all patients with cirrhosis due to potiential risk of renal failure during hospitalisation

Patients with cirrhosis and renal failure are at higher risk for death

# AIM OF THE STUDY

1. To identify the precipitating /risk factors associated with the renal failure in patients with chronic liver disease

2. To study the clinical profile in patients with cirrhosis who developed the renal failure

3. To assess the outcome of renal failure on mortality in a period of two weeks of follow up ( in hospital mortality)

# REVIEW OF LITERATURE

## HISTORY

- **Frerichs** and **Flint** made first description of disturbances in renal function in chronic liver disease from the late nineteenth century. They were the first to discuss about the development of oliguria in chronic liver disease patients in the absence of proteinuria and with a normal renal histology. They proposed the first pathophysiologic interpretation of hepatorenal syndrome by linking the abnormalities of renal function to the disturbances present in systemic circulation.

- Term " Hepato renal syndrome" was coined by **Helwig** and **Schutz** in 1932. However, studies by **Sherlock,Papper**and**Vessin** in 1950s gave detailed description of HRS.

## PATHOPHYSIOLOGY OF RENAL DYSFUNCTION IN LIVER DISEASE

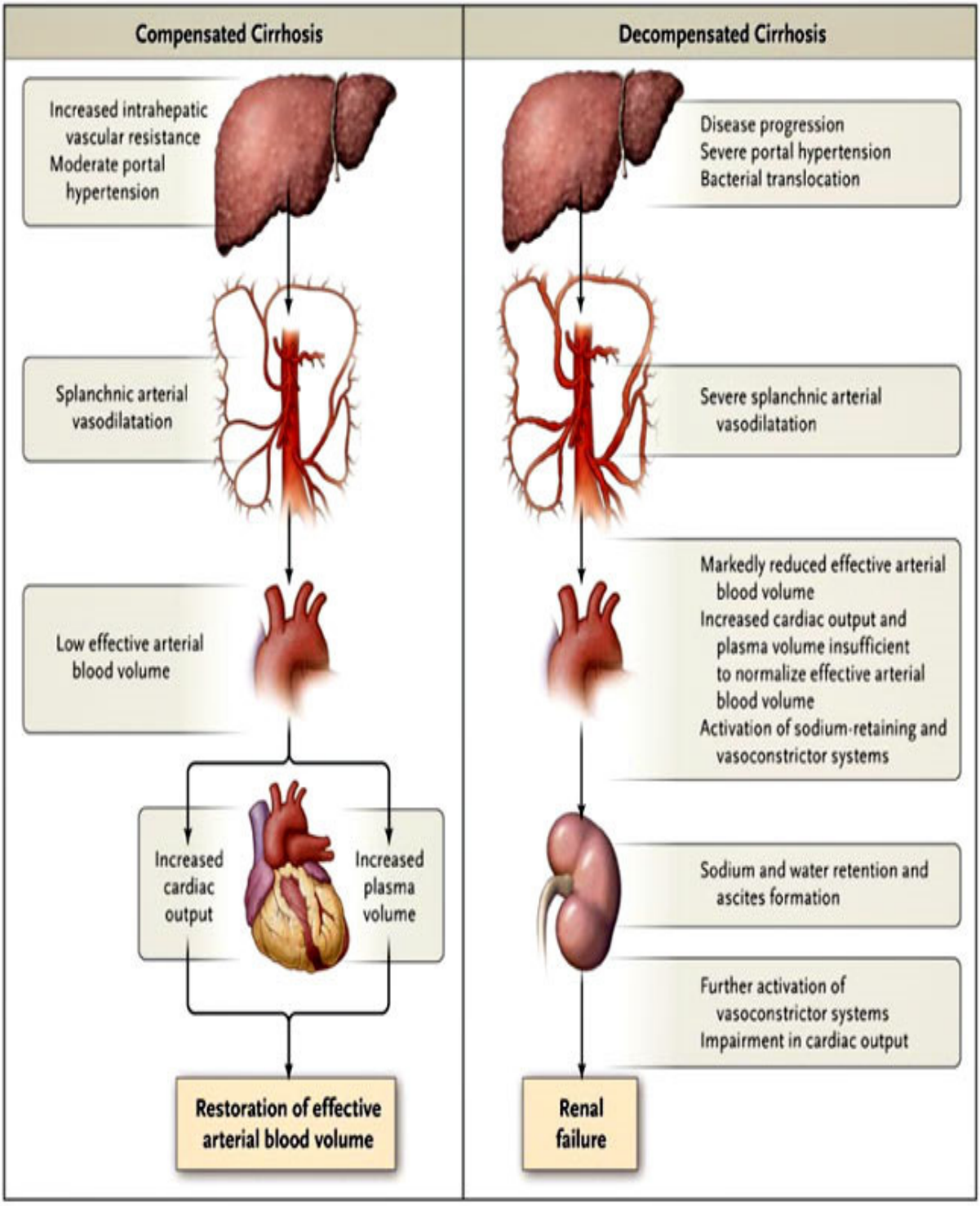
- Interaction between changes in the systemic arterial circulation, portal hypertension, activation of vasoconstrictors and suppression of vasodilatory factors acting on the renal circulation is the basis for the development of renal dysfunction in advanced liver disease.

- Pre-renal failure frequently occurs in patients with advanced liver disease due to disturbances in circulatory function-mainly portal hypertension induced primary arterial vasodilation in the splanchnic circulation leading to decreased systemic vascular resistance. Increased production of vasodilator factors like nitric oxide,carbon monoxide and cannabinoids leads to further arterial vasodilation.

- True hypovolemia induced by gastrointestinal tract hemorrhage from varices,peptic ulcers or gastropathy,excessive diuresis, GI loses in the form of vomiting and diarrhea ,large volume paracentesis without intravascular volume replacement further worsens renal dysfunction.

  NSAIDs and bacterial infections also worsens pre-renal failure in these patients.

**PATHOPHYSIOLOGY OF BOTH COMPENSATED AND DECOMPENSATED CIRRHOSIS**



## SODIUM RETENTION AND ASCITES

- This is considered as the first manifestation of renal dysfunction in cirrhosis. Amount of sodium retained depends on the balance between sodium intake and excretion. Ascites develops when sodium intake is increased or when treated with drugs which increase sodium reabsorption like NSAIDs or mineralocorticoids.

- Increased renal tubular reabsorption of sodium in the proximal and distal tubules is the basis for renal sodium retention. This can occur even with normal or only moderately reduced GFR.

- Renin-angiotensin-aldosterone system and sympathetic nervous system are the two main sodium retaining systems which are activated as a homeostatic response to circulatory dysfunction

## DILUTIONAL HYPONATREMIA

- Excessive retention of solute free water due to decreased excretion by kidneys results in hyponatremia in patients with cirrhosis and ascites.

- Solute free water retention in cirrhosis is due to decreased delivery of filtrate to the ascending limb of loop of Henle,reduced renal synthesis of prostaglandins and increased secretion of anti-diuretic hormone.

- Central nervous system disturbances are the cause for morbidity and mortality associated with hyponatremia. Steroid and peptide hormone changes in cirrhotic patients leads to hyponatremia induced encephalopathy which often overlaps with hepatic encephalopathy and uremia. Development of hyponatremia in cirrhotic patients can be considered as a marker of unrecognized underlying renal dysfunction.

## RENAL VASOCONSTRICTION

Decreased renal perfusion as a result of renal vasoconstriction develops last in patients with cirrhosis and ascites. Marked vasodilation of splanchnic circulation leads to extreme underfilling of the systemic arterial circulation which results in activation of homeostatic vasoconstrictor system.This cannot be counteracted by either renal or systemic vasodilators. Renal vasoconstriction leads to the development of hepatorenal syndrome

## TYPES OF RENAL FAILURE IN PATIENTS WITH CIRRHOSIS

### A. HYPOVOLEMIA INDUCED RENAL FAILURE

Gastrointestinal hemorrhage, excessive diuretic use,prolonged diarrhea due to excessive lactulose administration leads to hypovolemia which then leads to renal failure.

## B. PARENCHYMAL RENAL DISEASE

When proteinuria(more than 500 mg of protein/day), hematuria more than 50 red cells/hpf) or both are present, parenchymal renal disease should be considered as a cause of renal failure which can be confirmed by renal biopsy, if not contraindicated. Renal tubular epithelial cells in urine sediment supports the diagnosis of acute tubular necrosis.

## C. DRUG INDUCED RENAL FAILURE

Nonsteroidal anti-inflammatory drugs or aminoglycosides use suggests drug induced renal failure.

## D.HEPATORENAL SYNDROME

HRS is regarded as the ultimate stage of pathophysiologic condition characterized by decreased renal blood flow as a result of decompensated liver function in patients with cirrhosis and ascites. It is a type of functional renal failure which develops as a complication of advanced liver disease,liver failure or portal hypertension. It is a result of severe constriction of renal arterial vasculature with resulting oliguria and sodium retention. Hemodynamic changes associated with

endothelial shear stress occur before the onset of ascites which are sustained by an increase in pro angiogenic factors like VEGF, PDGF and vasodilators like carbon monoxide, endocannabinoids and nitric oxide which are able to promote the formation of hepatic, splanchnic and portosystemic collateral vessels. HRS can occur spontaneously or as a result of infection, gastrointestinal bleeding and post-paracentesis circulatory dysfunction.

The renal impairment is further worsened by progressive cardiac dysfunction (cirrhotic cardiomyopathy). Its characteristic features include diastolic impairment with septal ventricular hypertrophy, blunted ventricular response to stress, systolic and diastolic dysfunction and electrophysiological abnormalities (prolonged QT interval). Systolic dysfunction results from impaired β-adrenergic receptor and increased endogenous cannabinoids and cardiosuppressants like nitric oxide, inflammatory cytokines and myocyte apoptosis.

Diastolic dysfunction results from activation of renin-angiotensin system and salt retention. Myocardial dysfunction in cirrhosis is regarded as a precipitating factor for HRS.

There are two forms of hepatorenal syndrome

**TYPE I HRS**

It is a form of AKI. It is characterized by acute onset and rapidly progressing kidney failure with a doubling of serum creatinine to more than 2.5 mg/dl (corresponding to a 50% reduction in the creatinine clearance rate) in less than 2 weeks, usually associated with multi organ damage. The prognosis is poor with only 10% of patients surviving longer than 90 days.

This type of hepatorenal syndrome can either develop spontaneously or due to precipitating factors.The precipitating factors / events are mostly due to gastrointestinal bleeding, spontaneous bacterial peritonitis, infections like pneumonia, cellulitis, urinary tract infections. Other potiential risk events are viral, alcoholic or ischemic hepatitis like TIPS(transjugular intrahepatic portosystemic shunt) and include surgical procedures

## TYPE II HRS

It is a form of CKD. It represents the final kidney response to hemodynamic impairments in cirrhosis.This type of renal failure is more gradual in onset and associated with diuretic resistant refractory ascites.Most often patients will have gross ascites.It is less severe form compared to type1 HRS. The increase in creatinine is gradual with mean values of around 1.5-2.0 mg/dl.Type 2 HRS can precipitate Type 1 HRS either with or with out precipitating event. Patients after developing HRS type 2 can survive upto 6- 8 months duration depends on the various factors.

**CHARACTERISTICS OF TYPE I AND TYPE II HEPATORENAL SYNDROME**

| HRS I | HRS II |
|---|---|
| **Doubling of serum creatinine in<2 wk** | Renal impairment gradually progressive |
| **A precipitating event is present in most of the cases** | No precipitating event |
| **No history of diuretic resistant ascites** | Always diuretic resistant ascites |
| **10% survival in 90 days without treatment** | Median survival is 6 months |

The differential diagnosis between these two types of HRS is based on the rate of progression and extent of renal impairment. Spontaneous recovery is rare in both types.

The AKI network(AKIN) has proposed a newer definition of AKI for the diagnosis of HRS for prompt recognition of kidney damage. AKI is defined as the abrupt loss of kidney function resulting in a 0.3 mg/dl increase in serum creatinine in 48 h or a 50% increase over the basal value. Recent studies have shown that AKI with serum creatinine values <1.5 mg/dl is a relatively benign and potentially reversible condition, whereas the progression of renal deterioration to a significant decrease in GFR (values >1.5 mg/dl) carries a poor prognosis.

With the onset of AKI in patients with cirrhosis, we have to differentiate from other forms of kidney injury: Pre-renal (45%), Acute tubular necrosis and Glomerulonephritis(32%) and Obstructive nephropathy(<1%). The traditional parameters used to differentiate AKI from CKD (urinary sodium concentration, serum and urine osmolarity) cannot be used in patients with cirrhosis and ascites. Impaired hepatic synthesis leads to reduced synthesis of urea. Raised urinary levels of neutrophil gelatinase associated lipocalin (NGAL) helps to differentiate functional kidney damage from acute tubular necrosis or necrosis due to HRS.

## PATHOGENESIS OF HEPATORENAL SYNDROME

HRS can lead to gross reduction in GFR with less renal histologic abnormalities which is a consequence of functional renal vasoconstriction. Correction of portal hypertension by liver transplantation leads to restoration of renal function.

Primary abnormality in HRS is peripheral and splanchnic arterial vasodilation due to portal hypertension. Ensuing vasoconstriction and renal sodium and water retention are adaptive responses to vasodilation.

Mechanisms contributing to pathogenesis of HRS :

1. **Renin-Angiotensin-Aldosterone system (RAAS)**

   Most cirrhotic patients with ascites and marked sodium retention have elevated plasma aldosterone levels which is caused by stimulation of aldosterone secretion and not due to impaired degradation.

Increased tubular sensitivity to aldosterone is seen in patients with cirrhosis which explains the renal sodium retention even with normal levels of aldosterone. Hence, aldosterone antagonistic drugs like spironolactone helps to reverse sodium retention and causes natriuresis in cirrhotic patients.

Patients with decompensated cirrhosis have elevated plasma renin activity. Administration of vasopressin analogues like terlipressin improves renal function in patients with HRS by causing marked suppression of RAAS activity.

**2. Sympathetic nervous system**

Higher plasma norepinephrine levels are seen in patients with hepatorenal syndrome than those without renal failure. This has inverse correlation with renal blood flow which suggests the role of sympathetic nervous system in causing renal vasoconstriction seen in patients with HRS.

Patients with HRS are also found to have elevated circulating levels of Neuropeptide Y, a neurotransmitter with potent vasoconstrictor action in the renal circulation released when there is activation of sympathetic nervous system. Its levels are not elevated in those with ascites without renal failure.

**3. Prostaglandins:**

Lower urinary excretion of PGE2 and PGI2 is seen in patients with hepatorenal syndrome than do patients with ascites and without renal failure. This hints at the fact that decreased renal synthesis of vasodilator prostaglandins might play a role in the pathogenesis of HRS. Arterial vasodilation in cirrhosis can be attributed to increased systemic prostaglandin synthesis, which are potent vasodilators in the systemic circulation.

Non steroidal anti-inflammatory drugs decrease GFR and renal plasma flow which shows prostaglandins have a role in maintaining normal renal perfusion.

Irreversible vasoconstriction seen in HRS can be attributed to an imbalance between vasodilator and vasoconstrictor metabolites of arachidonic acid, with the latter dominating.

4. **Adenosine**:

Intrahepatic adenosine triggers hepatorenal reflex by causing an increase in portal venous blood flow which increases sympathetic activity in the kidney leading to a decrease in renal blood flow and GFR, leading on to hepatorenal syndrome. Advanced liver dysfunction induced tissue hypoxia leads to increased synthesis of adenosine.

**5. Nitric oxide(NO) :**

Nitric oxide released from vascular smooth muscle is a powerful vasodilator agent. It causes splanchnic vasodilation in cirrhosis. It modulates arteriolar tone and the contractility of mesangial cells thereby regulating glomerular microcirculation. It is involved in the regulation of renin release and facilitates natriuresis.

With the progression of liver disease, level of nitric oxide increases significantly which indicates that NO is essential for the progression of cirrhosis.

6. **Endothelin**:

Endothelin-1 is an endothelial derived peptide with potent vasoconstrictor effect whose levels are increased in cirrhosis as a result of increased release of the peptide from the hepatic and splanchnic circulation. Excessive intrarenal production and increased circulating levels of endothelin may lead to renal vasoconstriction and cause hepatorenal syndrome.

7. **Natriureticpeptides**:

In patients with cirrhosis and ascites, plasma concentration of atrial natriuretic peptide and brain natriuretic peptide are elevated. Increased cardiac release is responsible for it and it is not a result of decreased hepatic or systemic clearance.

They have strong effect on renal function( vasodilator and natriuretic effects) and inhibits renin release. Thereby, they counteract the effects of anti-natriuretic and vasoconstrictor systems in renal circulation. Coexistence of elevated plasma levels of ANP in cirrhosis in the presence of renal sodium retention signals renal resistance to the effects of ANP.

8. **Endotoxins**:

Because of patient's immunosuppressed status in cirrhosis, entire gastrointestinal tract becomes densely colonized with bacteria. Jaundice in cirrhosis promotes reabsorption of endotoxin into the bloodstream. Absorbed endotoxin would appear in the arterial circulation due to incomplete destruction by hepatic Kupffer cells which in turn is due to compromised function of reticuloendothelial cells of the liver in advanced cirrhosis. Vasoconstriction of renal microcirculation is the end result of continuous reabsorption of endotoxin from gastrointestinal tract into the circulation of cirrhotic patients.

To conclude, the fluid retention and hepatorenal syndrome is attributed to the peripheral vasodilation which is the early event in the pathogenesis. The maintenance of normal renal perfusion depends on the balance between vasodilatory and vasoconstricting factors following initial vasodilation. There is a preponderance of vasoconstriction over vasodilation in hepatorenal syndrome which leads to increased renal vascular resistance, decrease in GFR and avid sodium and water retention.

| **NEWER DIAGNOSTIC CRITERIA FOR HEPATORENAL SYNDROME** |
|---|
| Cirrhosis and ascites |
| Serum Creatinine more than 1.5 mg/dl |
| No shock |
| No improvement in serum creatinine(decrease to a level of 1.5mg/dl or less) after at least 2 days of diuretic withdrawl and volume expansion with albumin(The recommended dose of albumin is 1g/kg of body weight per day up to a maximum of 100g/day) |
| No current or recent exposure to nephrotoxic drugs |
| Absence of parenchymal disease as indicated by proteinuria more than 500 mg/d, microscopic hematuria(i.e, 50 red blood cells in high power field) and abnormal renal ultrasonography |

## PREVENTION AND SUPPORTIVE CARE

The cirrhotic patient with ascites must be closely monitored to avoid precipitating factors and treat them. The aim of treatment must be to stabilize patients until liver transplantation and optimize their clinical condition for a successful transplant.

| PREVENTION OF HEPATORENAL SYNDROME AND GENERAL PATIENT MANAGEMENT STRATEGIES |
|---|
| Avoid drugs that reduce renal perfusion or nephrotoxic substances |
| Minimize exposure to organ-iodated contrast agents |
| Intravenous albumin is recommended for volemic filling after large volume paracentesis(8 g of albumin for each litre of ascites removed) |
| Diuretic therapy should be suspended |
| Pentoxifylline as drug's anti-TNF alpha activity |
| Antibiotic prophylaxis to prevent infections reducing intestinal bacterial translocation(norfloxacin 400mg/d) |
| Intravenous albumin administered in association with ceftrixone in SBP |
| Adrenal insufficiency should be identified and treated |
| Drug dosages must be adjusted according to renal function |

## TREATMENT OF HEPATORENAL SYNDROME

Currently available treatments enhance patient's short term survival but offer little benefit in the longer term. Liver transplant remains the only truly effective treatment but is limited by the high mortality rate in HRS patients and the shortage of available organs. Pre-transplant kidney function is the most important predictor for patient survival after liver transplant. Pharmacological treatment and medical care serve as a "bridge" to transplant to improve the patient's prognosis.

### Medical management

- Ideal treatment is to exert splanchnic vasoconstriction and renal vasodilation to reduce portal hypertension and raise systemic arterial pressure.
- Vasoconstrictor agents (terlipressin,norepinephrine,midodrine) are used to correct circulatory changes.
- Intravenous administration of terlipressin and albumin is currently the treatment of choice for patients with type I and type II HRS, resulting in an overall reduction in short term mortality rates.

- The vasocontrictive effect of terlipressin corrects the circulatory dysfunction typical of end stage liver disease, indirectly rebalancing intrarenal vasoconstriction and lowering levels of renin, noradrenaline and ultimately serum creatinine. Also,terlipressin increases hepatic arterial blood flow and improves hepatocellular oxygenation.

- Terlipressin can be administered as an intravenous bolus starting from a dose of 0.5mg every 4-6 h or as a continuous infusion (2mg/d). Total daily dose should not exceed 2mg IV bolus every 4-6 h or 12 mg/d in continuous infusion.

- Terlipressin should be combined with albumin (at a dose of 1g/d on the first day, without exceeding 100g/d, followed by 20-40g/d). It raises oncotic pressure and expands circulating volume. In addition, it has metabolic, immune and vasoconstrictor effects by binding to endotoxins, nitric oxide, bilirubin and fatty acids. The terlipressin-albumin association improves renal function by 40-60%. Treatment is completed when serum creatinine values reach <1.5 mg/dl.

- The alpha-adrenergic receptor agonist norepinephrine is effective in the treatment of HRS. Continuous norepinephrine infusion (at a dose of 0.5-3 mg/h) must be associated with albumin administered as an IV bolus at least twice daily (1g/kg up to a maximum of 100g/d). Aim is to raise mean arterial pressure by 10 mmHg and urinary output >200 mL every four hours. The maximum period of treatment must not exceed 2 weeks

- Midodrine is an alternative to terlipressin. It is a prodrug which is metabolized by the liver and then excreted through urine.

- If the midodrine is given along with octreotide , it has favourable effect on renal failure. Possibility of even 50% improvement is there. It is administered orally 7.5 mg every 8 hrly maximum upto 12.5 mg thrice a day. Albumin must be used as routine dosage.

**TIPS -** It can be used as short term procedure to gain benefits from awaiting liver transplant patients. High incidence of hepatic encephalopathy is major side effect of this procedure.

**Renal replacement therapy**

It is indicated in patients with severe renal failure with complications like metabolic acidosis, hyperkalemia etc.. It is used as bridging therapy in liver transplant patients. No evidence proved that dialysis will improve the long term survival rate. Continous renal replacement is better than intermittent dialysis in view of hemodynamic fluctuations. Peritoneal dialysis is option to resolve the ascites and correct other complications with exposing the patient to hemodialysis

The **molecular adsorbent recirculating system (MARS)** has been used in the treatment of acute decompensation of chronic liver disease, acute liver failure and hepatorenal syndrome.This liver support system utilizes either intermittent (6-8 h daily) or continuous hemodialysis with dialysate enriched with 20% human serum albumin as a means to remove albumin-bound toxins (bilirubin, bile acids, fatty acids, tryptophan, aromatic amino acids, and copper)

**Liver transplantation**- It is the definitive treatment of hepatorenal syndrome for both types. Recovery of renal function is not universal. MELD score is used for organ transplantation.RRT prior to liver transplant has poor prognosis. This patients may require **combined liver-kidney transplant**.

**Causes of Renal Failure in Patients With Cirrhosis**

- Infections
- UGI Bleeding (with / without shock)
- Spontaneous bacterial peritonitis
- Spontaneous bacteremia
- Urinary tract infection
- Pneumonia
- skin infection ( celluluitis), other bacterial infections
- Hypovolemia-induced renal dysfunction
- Diuretic-induced
- Acute gastro enteritis
- Hepatorenal syndrome

**Intrinsic renal diseases**

**Glomerulopathy**:

Membranous nephropathy, membranoproliferative glomerulonephritis, polyarteritis nodosa, or cryoglobulinemia due to viral hepatitis, Chronic kidney disease due to diabetes, hypertension, or other causes

**Drug-induced renal failure**

Hemodynamically induced: non steroidal anti-inflammatory agents or angiotensin receptor blockers

**Acute tubular necrosis**: aminoglycosides, amphotericin B, or tenofovir

**Acute interstitial nephritis**: penicillin, rifampacin, or sulfonamides

## EVALUATION OF PATIENTS WITH CIRRHOSIS AND RENAL FAILURE

- Renal function should be routinely monitored in all patients with advanced cirrhosis, especially in patients those with ascites. Patients who have ascites, particularly those with hyponatremia, bacterial infections, gastrointestinal bleeding, or severe sodium retention, are at high risk for renal failure, as are all patients hospitalized for acute decompensation of cirrhosis

- Other than renal function tests, serum sodium, urine analysis(urine routine and 24 hr urinary protein) , renal ultrasonography, renal biopsy has to be done.

- Renal biopsy is useful only in patients with protenuria/hematuria or both. It is contraindicated in severe coagulation abnormalities

- Patient should be evaluated for bacterial infections, iatrogenic causes. Patient medications should be checked for diuretics , NSAIDS. These drugs should be discontinued.

## DIFFERENTIAL DIAGNOSIS OF RENAL FAILURE IN CIRRHOSIS

- It includes pre- renal failure , intrinsic renal failure and hepatorenal failure.
- The patients should be evaluated both clinically and laboratory investigations to arrive at a specific diagnosis. Renal biopsy is not mandatory in patients with acute renal failure in cirrhotic patients.
- Since the cirrhotic patients have sustained vasodilation, more prone for renal dysfunction which may be reversible if identified at early stage of the disease.
- Presence of glomerulonephritis in the form of hypertension.purpura , arthralgia, Reynauds phenomenon would favour cryoglobulinemia associated with hepatitis C infection.

Rapid improvement with fluid challenge suggest pre-renal failure. If no improvement in renal parameters represents acute tubular necrosis or hepatorenal syndrome. Hepatorenal syndrome can improve with terlipressin or noradrenaline.

Duplex ultrasonography is sensitive method for assessing the intrarenal hemodynamics with patients with cirrhosis and ascites

## PROGNOSIS OF RENAL FAILURE IN CIRRHOSIS PATIENTS

According to the literature, the prognosis in patients with cirrhosis and associated renal failure is poor. The survival rateis only 50% at 1 month and at the end of 6 months is 20%. The bad prognosis is probably due to combination of liver cell failure and renal dysfunction , also associated with complications (hyponatremia, thrombocytopenia, coagulopathy, infections)

Survival rate depends on the type of renal failure and duration. With modern treatment modalities and early diagnosis can prevent the poor prognosis associated with renal failure.

Hepatorenalsyndrome is associated with bad prognosis. Survival rate is poor with most of them has to undergo liver transplant for permanent treatment.

HRS type 2 ( 6 months) has good prognosis compared to HRS type 1 ( 1 month).

## PREVENTION OF RENAL FAILURE IN CIRRHOSIS

Early identification of reversible risk factors can reduce the high mortalilty. Two strategies are used to prevent hepatorenal syndrome.

First strategy is to perform liver transplantation in patients with cirrhosis and ascites with high risk of developing HRS based on MELD score before hepatorenal syndrome develops.

Secondy strategy is to prevent development of renal failure by avoiding the precipitating factors( adequate management of bleeding and infection)

Spontaneous bacterial peritonitis is an important precipitating factor for hepatorenal / renal dysfunction in cirrhotic patients. SBP stimulates the production of tumour nerosis factor, pro inflammatory mediators leading activation of vasodilatory mechanism which further precipitates renal failure.

Use of proper antibiotics(cefotaxime ) and albumin intravenously 1.5g/kg followed by 1gm/kg after 48 hrs) can reduce the in hospital mortality.

The beneficial effect of albumin is probably by preventinng circulatory failure and subsequent activation of vasoconstriction mechanism during active infection

**OTHER RENAL ABNORMALITIES IN CIRRHOSIS**

- **GLOMERULAR DISEASES**

In association with hepatitis B and C viruses and alcoholic liver disease

- **RENAL TUBULAR ACIDOSIS**

May occur in cirrhosis of different etiologies: primary biliary cirrhosis, autoimmune hepatitis and alcoholic cirrhosis

- **DRUG INDUCED RENAL DYSFUNCTION**

Especially with drugs like NSAIDs, aminoglycosides, diuretics or vasodilators

- **ACUTE TUBULAR NECROSIS**

Due to volume depletion as seen in sepsis or hypovolemic shock( UGI Bleed) or due to nephrotoxic drugs

**SEVERITY OF CIRRHOSIS CAN ASSESSED BY EITHER WITH MELD SCORE OR CHILD PUGH CLASSIFICATION**

## CHILD PUGH CLASSIFICATION

| Child-Turcotte-Pugh Classification for Severity of Cirrhosis | | | |
|---|---|---|---|
| Clinical and Lab Criterias | Points* | | |
| | 1 | 2 | 3 |
| Encephalopathy | None | Mild to moderate (grade 1 or 2) | Severe (grade 3 or 4) |
| Ascites | None | Mild to moderate (diuretic responsive) | Severe (diuretic refractory) |
| Bilirubin (mg/dL) | < 2 | 2-3 | >3 |
| Albumin (g/dL) | > 3.5 | 2.8-3.5 | <2.8 |
| Prothrombin time<br>Seconds prolonged<br>International normalized ratio | <br><4<br><1.7 | <br>4-6<br>1.7-2.3 | <br>>6<br>>2.3 |

***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

# MELD SCORING

## Model for End Stage Liver Disease (MELD) Score

$$\text{MELD} = 3.78 \times \log_e \text{serum bilirubin (mg/dL)} + 11.20 \times \log_e \text{INR} + 9.57 \times \log_e \text{serum creatinine (mg/dL)} + 6.43 \text{ (constant for liver disease etiology)}$$

NOTES:

- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)

## PROGNOSIS OF LIVER DISEASE

Prognosis of liver disease depends on multiple factors

Poor prognostic indicators

- Marked ascites
- Upper GI bleed
- Advanced age
- High daily alcohol consumption
- High serum bilirubin
- High alkaline phosphatase
- Low serum albumin
- Poor nutrition
- Coagulopathy
- Low serum sodium
- Hepatic encephalopathy
- Low platelet count

Scoring system to assess the prognosis

1. Child pugh classification
2. MELD Scoring system

Child pugh scoring depends on – serum bilirubin, serum albumin, hepatic encephalopathy,ascites,prothrombin time. Previously used poor nutrition factor is replaced by prothrombin time.

MELD score was developed initially for the prognosis in patients undergoing TIPS surgery. It has been used for over all prognosis of liver disease and considered superior to child pugh score.

It includes three variables- serum bilirubin, prothrombin time with INR , serum creatinine also includes the etiology of the liver disease. It is calculated based on the formula.

MELD can be used a prognostic marker in patients with cirrhosis who developed renal failure. Predicts 3 month mortality.

# MATERIALS AND METHODS

All the inpatients admitted with chronic liver disease in thanjavur medical college were followed up prospectively from January 2016 to June 2016 in Thanjavur medical college and hospital.

Among those patients, irrespective of etiology of the cirrhosis( chronic liver disease) were followed up for a period of 2 weeks duration

These patients were monitored for the elevated renal parameters in 2 weeks period. So, the patients with increased renal parameters (serum creatinine) were included in the study

All the patients were prospectively studied irrespective of age, sex and cause of chronic liver disease

Data regarding demographic variables ( age, weight, height , BMI) were included for all the patients.

Clinical history including presenting complaints (hematemesis, malena, jaundice, abdominal distension, abdominal pain, fever, altered sensorium)were noted accurately.

Past history of alcoholism, alcoholic liver disease( duration, illness, course, previous similar complaints).Other major diseases ( SHT/DM/ CAD/CKD/PTB/EPILEPSY) were noted. History of native treatment and chronic drug intake were noted

All the patients with known case of CKD were excluded from the study.

Complete general examination and gastrointestinal system examination done for all the patients including other system examination like cardiovascular, respiratory and central nervous system examination

Clinical examination regarding the signs of liver cell failure were noted for all the patients

Laboratory investigations included complete blood count, liver functions, renal function tests, prothrombin time, serum electrolytes were done.

Ultrasound abdomen for diagnosis( echotexture of liver), complications like portal hypertension, ascites , splenomegaly ,to rule out chronic kidney disease( size of the kidneys) and to detect the structural pathology of kidneys and obstructive pathology of urinary tract.

Renal function tests were sequentially followed for 2 weeks duration( depends on individuals).Urine analysis in the form of urine routine and 24 hr urinary protein excretion to detect significant proteinuria.Viral markers were done for the cause of cirrhosis in all the patients

Ascitic fluid culture, chest x ray, urine culture and sensitivity, blood culture and sensitivity were done to find out the foci of infection. Cause of liver failure were identified by the history and laboratory investigations

Precipitating factors were identified for the renal failure, factors affecting renal failure were analysed. Finally mortality of the patients with in 2 weeks duration of inpatient hospitalisation has been assessed.

MELD score and child Pugh score were calculated for the prognostic signifance in all patients. Patients were followed up only for 2 weeks since many patinents either discharge/die with in this period.

Finally the outcome of the patient whether discharged/improved, worsened and died has been accounted.

# MANAGEMENT STRATEGY

1. All patients are treated adequately with antibiotics
2. Avoided both nephrotoxic drugs and hepatotoxic drugs
3. Blood transfusion for massive UGI bleed
4. Fresh frozen plasma if there is documented/clinical coagulopathy
5. Platelet transfused as per need
6. Serum electrolytes were moniotored and corrected
7. Diuretics are stopped if patient develops renal failure
8. Adequate iv fluids were given
9. Hepatoprotective drugs were given
10. Albumin if necessary is given with proper dosage
11. Due to non- availability, terlipressin, midodrine were not given to the patients in the study group

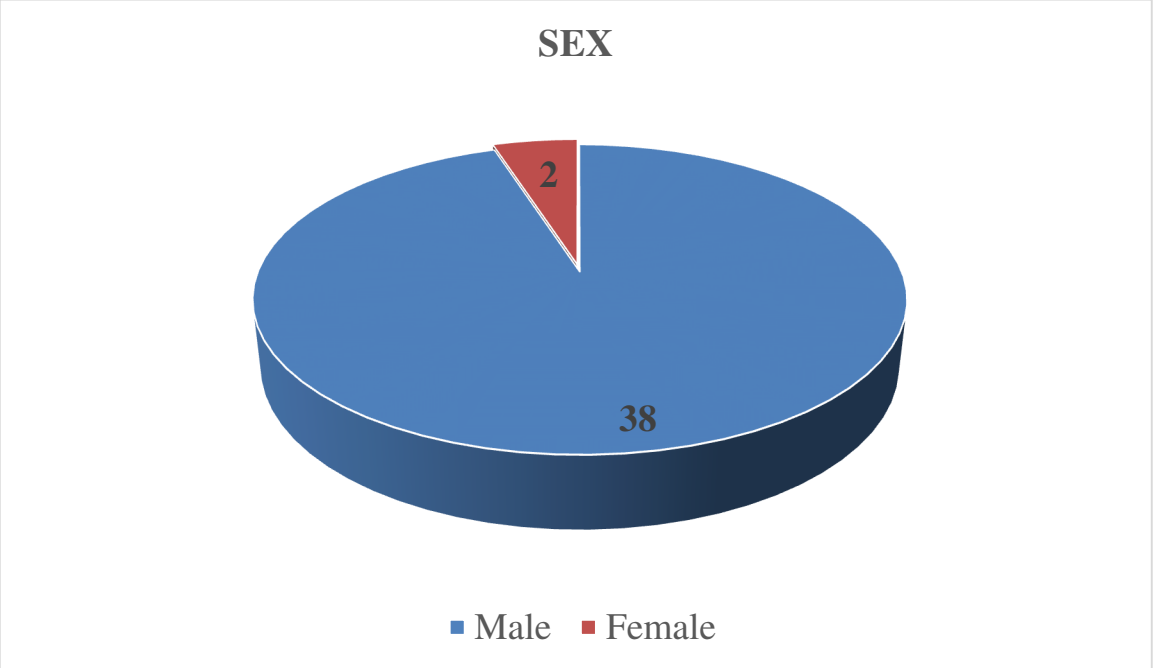
# OBSERVATION AND ANALYSIS

Totally 40 patients with chronic liver disease along with renal dysfunction were enrolled in the study group from thanjavur medical college during the period of January 2016 to june 2016.

The following observations were made

**AGE DISTRIBUTION**

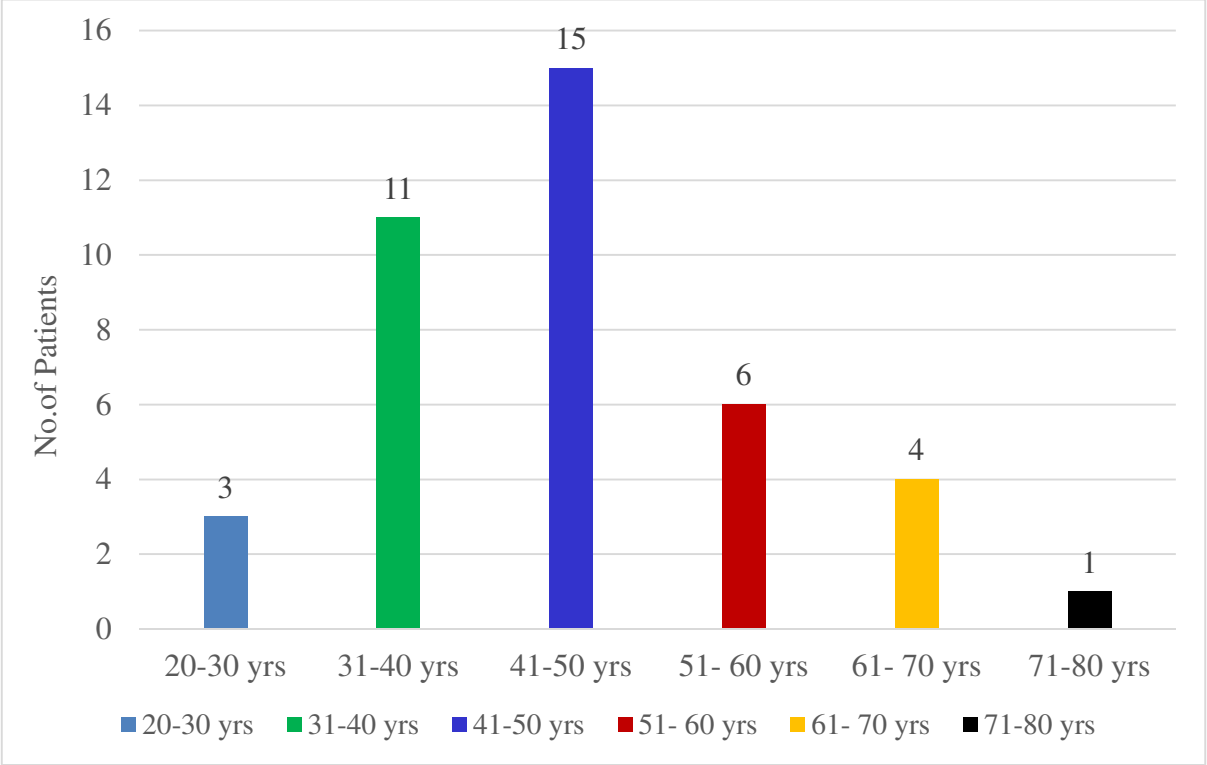
Males- 38
Females- 02



## AGE GROUP

Patients were selected in all age groups.(above 13 yrs).

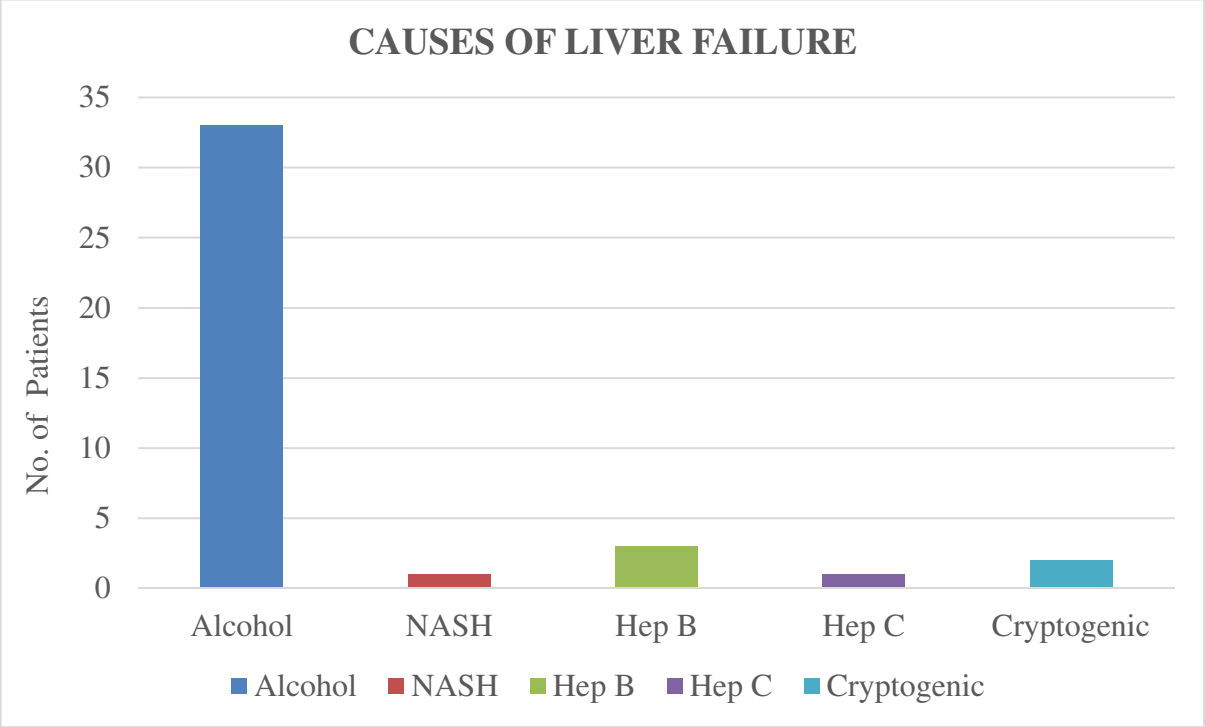
Age distribution is as follows in the study group.



## ETIOLOGY OF LIVER FAILURE

Liver failure caused by different etiologies were noted. All the patients irrespective of etiology were selected.

Most of the patients in the study group are alcoholics




Out of 40 patients

Alcoholic related- 33

NASH - 01

Hepatitis B- 03

Hepatitis C- 01

Cryptogenic- 02

## CAUSES/ PRECIPITATING FACTORS FOR RENAL FAILURE

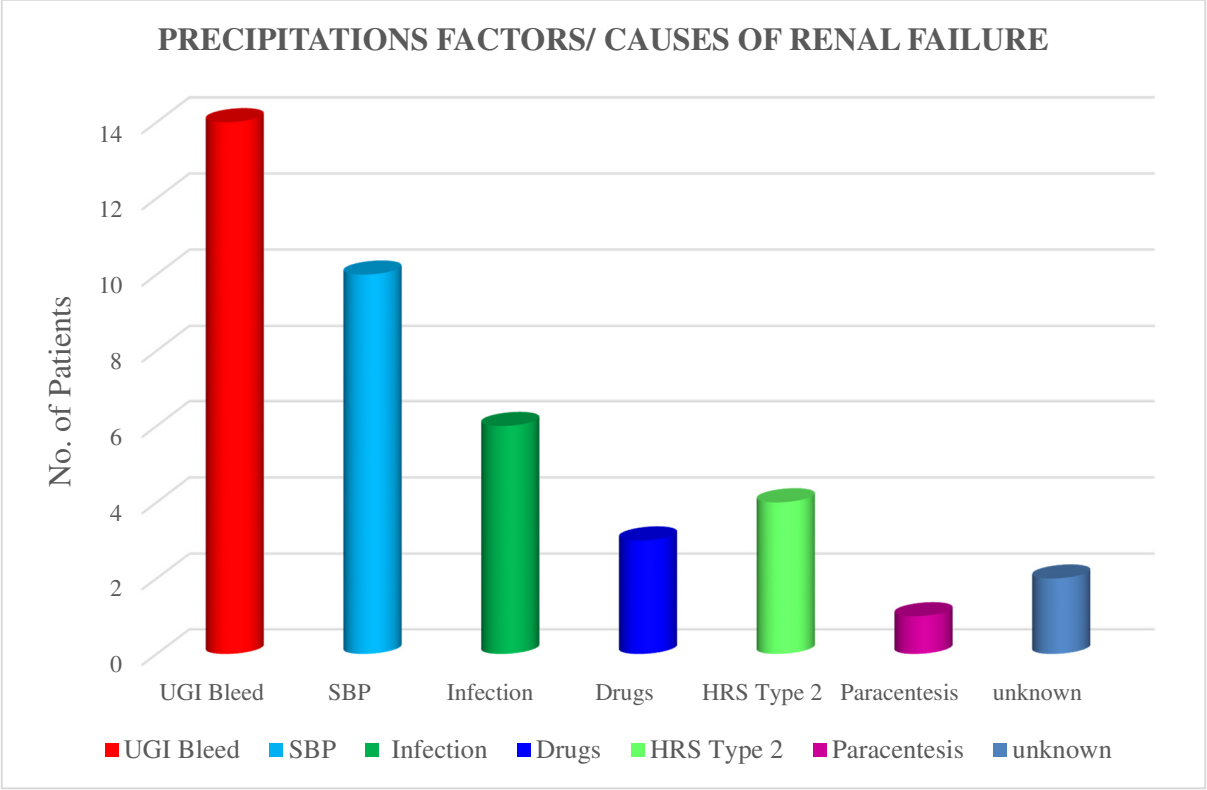
The most important precipitating factor for renal dysfunction is UGI Bleed in the study.

3 patients with drug induced renal failure namely- diuretics,NSAIDS,entecavir.

Other Infection related renal failure – UTI, Pneumonia, cellulitis

| **Cause/precipitating factor** | **No of patients** | **Percentage (%)** |
|---|---|---|
| UGI BLEED | 14 | 35% |
| SBP | 10 | 25% |
| OTHER INFECTIONS | 06 | 15% |
| DRUGS | 03 | 7.5% |
| HRS TYPE 2 | 04 | 10% |
| PARACENTESIS | 01 | 2.5% |
| UNKNOWN | 02 | 5.0% |

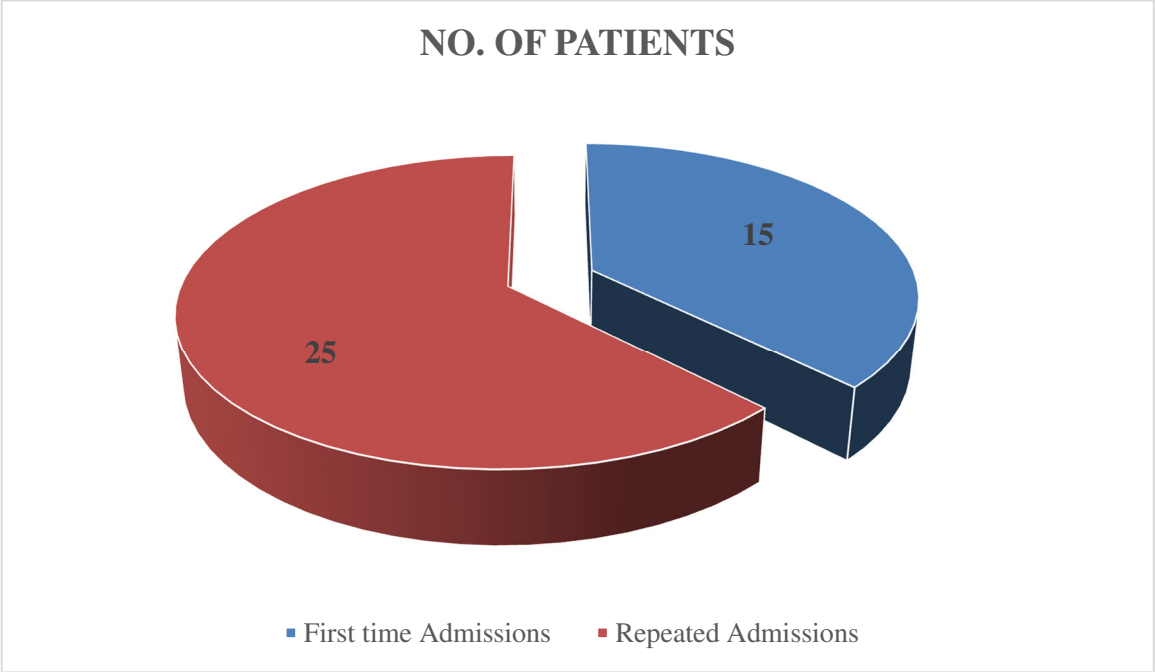
**Various precipitating factors for renal failure in the study group**



**Frequency of Admissions**

Number of patients with first time of admission- 15

Number of patients with repeated admission - 02



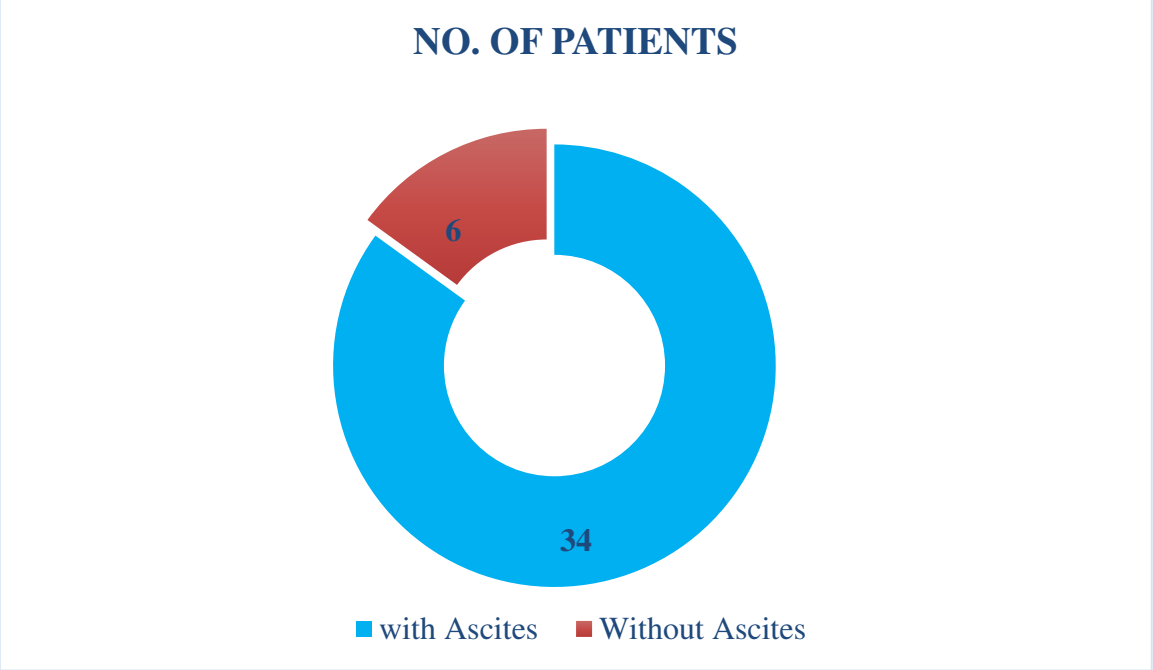
## LIVER FAILURE AND ASCITES

As we know,Most of the decompensated liver disease present with ascites as their presenting complaint. Some patients may present with other forms like jaundice, UGI bleed, asymptomatic etc..

It may depends on the stages of liver disease.

Patients presenting with Ascites- 34

Patients without Ascites - 06



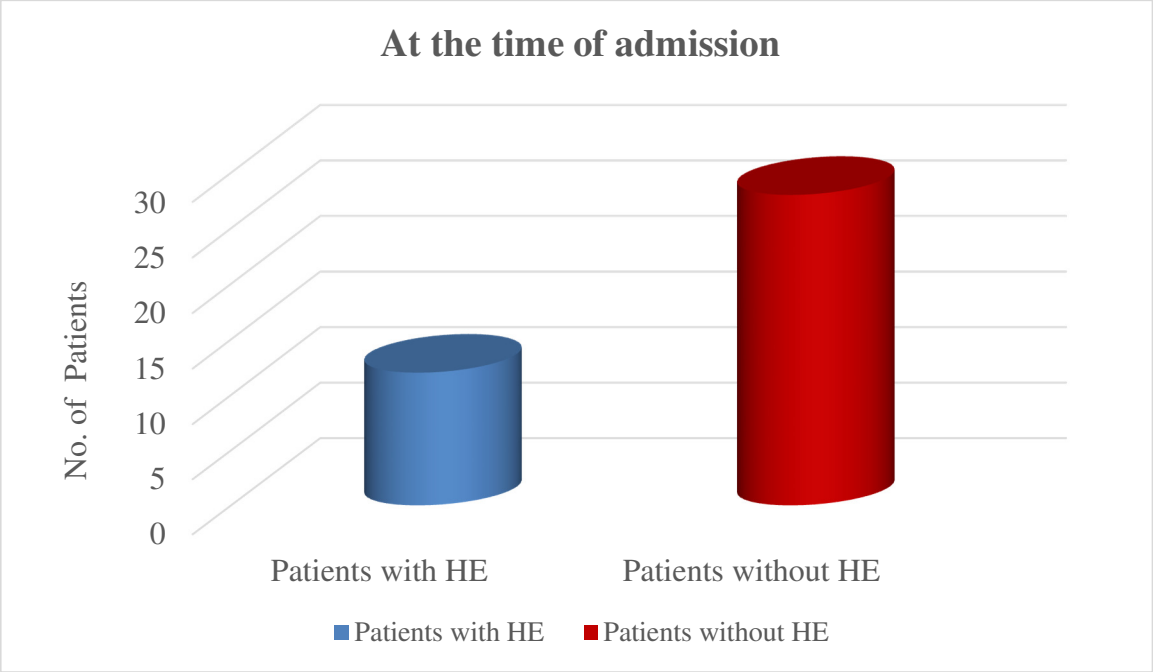
## HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is important cause for mortality in patients with advanced liver disease. Early intervention is needed for the patients presenting with hepatic encephalopathy.

### Grades of hepatic encephalopathy

| Grade | Detailed description |
|---|---|
| I | Mild confusion, euphoria, anxiety or depression, reversed sleep rhythm,slurred speech |
| II | Drowsiness , lethargy, gross deficits in the ability to perform mental tasks, relatively moderate confusion |
| III | Somnolent but arousable, severe confusion, inability to perform mental tasks |
| IV | Coma with or with out response to painful stimulus |

Patients at the time of admission with hepatic encephalopathy were totally 12 out of 40 patients



## SERAL MONITORING OF RENAL PARAMETERS IN STUDY GROUP

| S.NO | NAME OF THE PATIENT | DAY 1 (mg/dl) | | DAY 3(mg/dl) | | DAY 7(mg/dl) | | DAY 10(mg/dl) | | DAY 14(mg/dl) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | U | C | U | C | U | C | U | C | U | C |
| 1 | RAMU | 84 | 3 | 65 | 2.8 | 60 | 1.2 | 45 | 1 | - | - |
| 2 | PUNNIAMOORTHY | 32 | 1.3 | 140 | 1.8 | 156 | 2 | 180 | 3.6 | - | - |
| 3 | ARUL PRAKASH | 43 | 2.1 | 48 | 1.5 | 2.8 | 1.1 | - | - | | |
| 4 | YESURAJ | 76 | 1.3 | 100 | 2 | 102 | 2.1 | 136 | 4.2 | 92 | 1.9 |
| 5 | SAUVIRAJ | 43 | 1.5 | 42 | 1.9 | 36 | 1.2 | 28 | 1 | - | - |
| 6 | SIVAKUMAR | 64 | 2.8 | 96 | 3.8 | 36 | 1.6 | 30 | 1.2 | - | - |
| 7 | NATARAJAN | 112 | 5.8 | 135 | 4 | 140 | 4.2 | 120 | 3.8 | - | - |
| 8 | MURUGESAN | 102 | 2.1 | 120 | 1.8 | 42 | 0.9 | - | - | - | - |
| 9 | SHEIKH ALI | 45 | 1.2 | 68 | 1.8 | 60 | 1.6 | 76 | 3 | 110 | 4.6 |
| 10 | MEGANATHAN | 115 | 3.5 | 134 | 4.2 | 130 | 4.8 | 140 | 4.2 | 80 | 3.6 |

| S.NO | NAME OF THE PATIENT | DAY 1 (mg/dl) | | DAY 3(mg/dl) | | DAY 7(mg/dl) | | DAY 10(mg/dl) | | DAY 14(mg/dl) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | U | C | U | C | U | C | U | C | U | C |
| 12 | KALAISELVAN | 60 | 2 | 70 | 1.9 | 40 | 0.6 | 30 | 0.8 | 30 | 0.5 |
| 13 | MURUGANANDHAM | 87 | 2 | 110 | 2.5 | 100 | 2.2 | 89 | 2.1 | 42 | 1.2 |
| 14 | VENKATESH | 42 | 1.4 | 69 | 2.3 | 42 | 1.1 | 40 | 1 | - | - |
| 15 | DATCHANA MOORTHY | 80 | 2.7 | 100 | 2.5 | 92 | 2.1 | 80 | 1.5 | 40 | 1.2 |
| 16 | NAINA MOHAMMED | 70 | 1.5 | 72 | 1.4 | 60 | 1.2 | 30 | 0.8 | - | - |
| 17 | MURUGIYAN | 50 | 1.9 | 58 | 2.2 | 28 | 3.3 | | | - | - |
| 18 | AROKIASAMY | 46 | 1.7 | 70 | 1.6 | 60 | 1.4 | 30 | 0.8 | - | - |
| 19 | SHEK ALI | 28 | 0.9 | 45 | 1.2 | 60 | 1.5 | 102 | 4.6 | 180 | 6.3 |
| 20 | THIRUVIYA SAYARAJ | 80 | 1.5 | 48 | 1.2 | 22 | 0.7 | 28 | 0.7 | - | |

| S.NO | NAME OF THE PATIENT | DAY 1 (mg/dl) | | DAY 3(mg/dl) | | DAY 7(mg/dl) | | DAY 10(mg/dl) | | DAY 14(mg/dl) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | U | C | U | C | U | C | U | C | U | C |
| 21 | PALANI | 108 | 2 | 115 | 1.5 | 100 | 1.2 | 64 | 1.4 | 43 | 1.1 |
| 22 | CHELLAPAN | 105 | 2.3 | 85 | 1.5 | 90 | 1.6 | 85 | 1.2 | 36 | 1 |
| 23 | THIAYAGARAJAN | 85 | 1.9 | 86 | 1.5 | 52 | 1.7 | 90 | 1.6 | 38 | 1.2 |
| 24 | SUSILA | 55 | 1.9 | 95 | 2.6 | 86 | 1.9 | 50 | 1.8 | 40 | 1.2 |
| 25 | MURUGAN | 28 | 1.1 | 50 | 1.5 | 85 | 2 | 100 | 3.4 | 115 | 4.1 |
| 26 | VIJAYA BHASKAR | 70 | 1.4 | 50 | 1.3 | 88 | 2.5 | 65 | 1.9 | 42 | 0.8 |
| 27 | KALIYAPERUMAL | 88 | 1.9 | 46 | 1.4 | 28 | 0.8 | 20 | 0.6 | - | - |
| 28 | DHENADOSS | 32 | 1.2 | 78 | 1.9 | 60 | 1.3 | 46 | 1 | 30 | 0.9 |
| 29 | VENKATESAN | 78 | 2.6 | 96 | 3.2 | 86 | 3 | 78 | 2.6 | 46 | 1.4 |
| 30 | RAVICHADRAN | 118 | 2.3 | 135 | 3 | 140 | 4 | 110 | 3.2 | 112 | 3.6 |
| 31 | RAJENDRAN | 43 | 1.2 | 67 | 1.4 | 110 | 1.9 | 112 | 2.2 | 76 | 1.3 |

| S.NO | NAME OF THE PATIENT | DAY 1 (mg/dl) | | DAY 3(mg/dl) | | DAY 7(mg/dl) | | DAY 10(mg/dl) | | DAY 14(mg/dl) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | U | C | U | C | U | C | U | C | U | C |
| 32 | SAMPATH | 40 | 1.5 | 58 | 2.5 | 60 | 2.1 | 42 | 1.9 | 48 | 1.8 |
| 33 | MANIMAVAN | 30 | 0.9 | 76 | 2 | 94 | 2.9 | 152 | 4.1 | 146 | 3.6 |
| 34 | SAVITHRI | 34 | 1.2 | 42 | 1.7 | 38 | 1.2 | 28 | 0.9 | - | - |
| 35 | BHASKAR | 76 | 1.6 | 72 | 1.8 | 56 | 1.6 | 30 | 0.8 | - | - |
| 36 | RAMADOSS | 72 | 1.9 | 76 | 2.1 | 116 | 3.2 | - | - | - | - |
| 37 | RAVI | 76 | 1.3 | 86 | 1.9 | 92 | 2.1 | 56 | 1.1 | 40 | 0.8 |
| 38 | MUNIYANDI | 50 | 2 | 56 | 1.5 | 38 | 2.1 | 42 | 1.9 | 46 | 2 |
| 39 | SUNDARAJ | 63 | 2.1 | 67 | 1.6 | 62 | 1.5 | 42 | 1.4 | 30 | 0.8 |
| 40 | SAKTHIVEL | 76 | 1.8 | 99 | 2.8 | 96 | 2.1 | 56 | 1.9 | 44 | 1.2 |

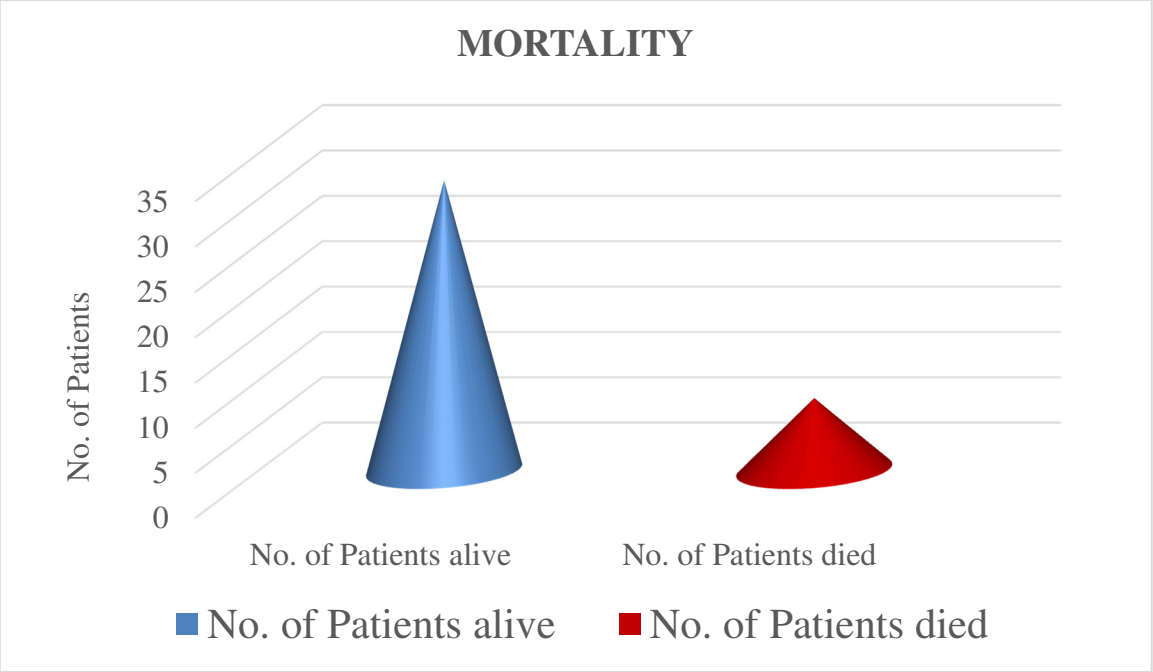
U- Blood Urea

C- Serum Creatinine

## MORTALITY

Mortality at the end of 2 weeks is 20 % i.e 8 out of 40 patients died

There are various factors associated with death of the patients.



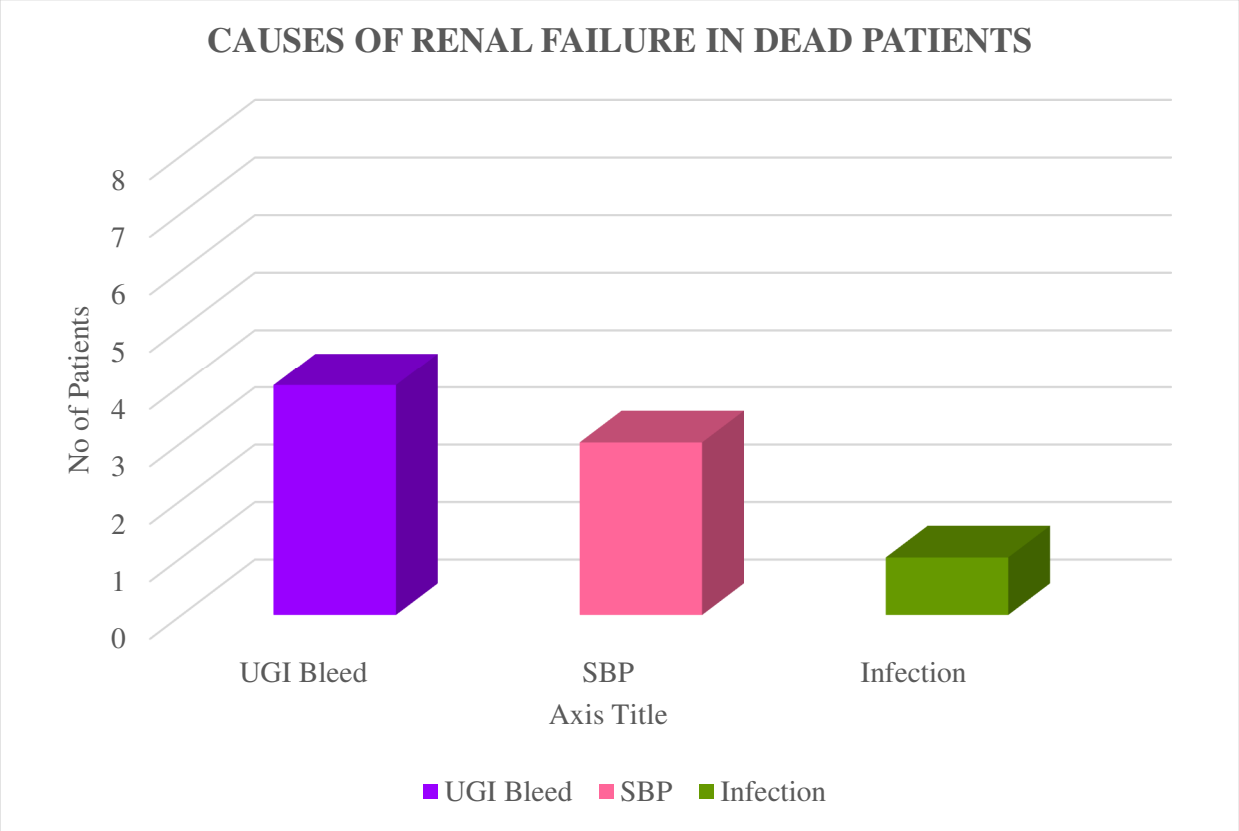

Number of patients Alive – 32

Number of died – 02

Some of the patients were discharged after improvement. Some of them survived after the end of 2 weeks with or with out improvement in renal parameters. Finally 8 patients died with in two weeks due to various factors.

Analysis of clinical profile in dead patients is as follows

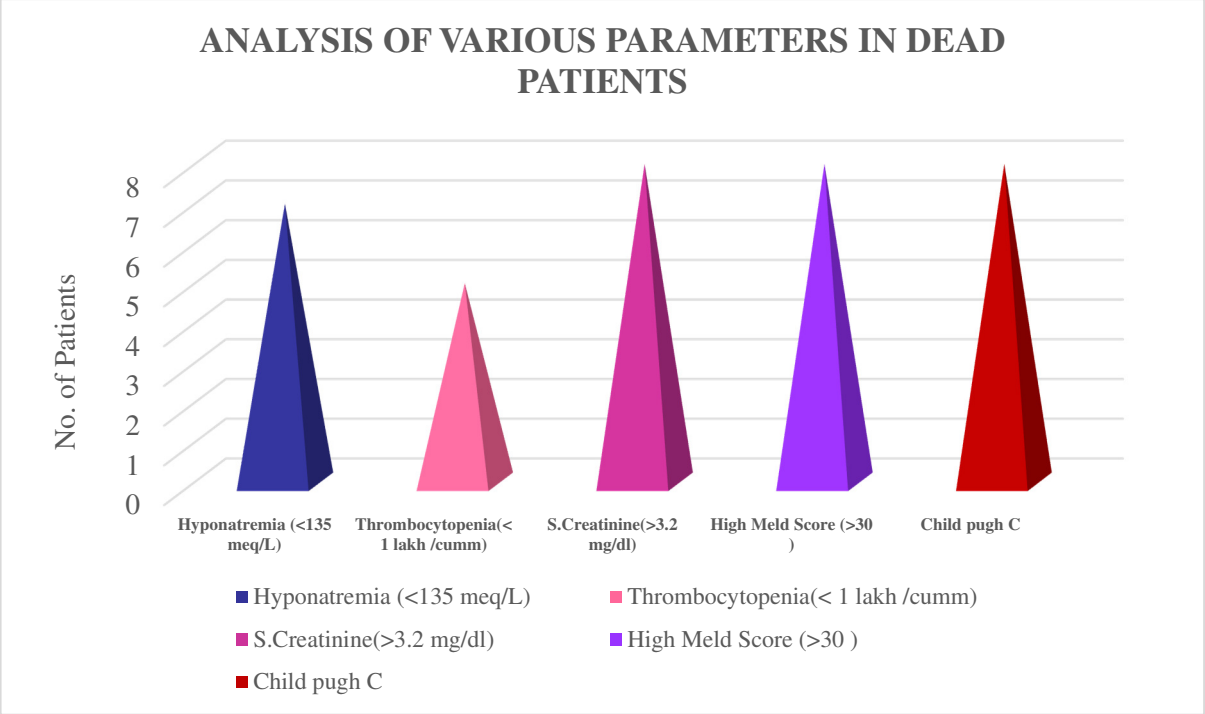
We analysed the possible causes of renal failure in died patients as postulated Below



## Causes of renal failure in dead patients

| Cause of renal dysfunction | No of patients |
|---|---|
| UGI bleed | 04 |
| SBP | 03 |
| Infection (cellulitis) | 01 |

## ANALYSIS OF VARIOUS FACTORS IN DEAD PATIENTS



| Parameters | No of patients |
|---|---|
| **Hyponatremia ( <135 meq/l)** | 07 |
| **Thrombocytopenia(<1 lakh/cumm)** | 06 |
| **Serum creatinine(>3.2mg/dl)** | 08 |
| **MELD Score(>30)** | 08 |
| **Child C score** | 08 |

**Descriptive Statistics**

| | N | Min | Max | Mean | S.D |
|---|---|---|---|---|---|
| S.CR | 40 | 1.50 | 6.30 | 2.7275 | 1.08675 |
| MELD | 40 | 11 | 43 | 25.75 | 8.605 |

N- N.o of patients

S.CR- serum creatinine

S.D- Standard deviation

## Percentage analysis

| Particulars | No.of respondents (n=40) | Percentage (100%) |
|---|---|---|
| **S.CR** | | |
| <3.2 | 30 | 75.0 |
| >3.2 | 10 | 25.0 |
| **MELD** | | |
| <32 | 30 | 75.0 |
| >32 | 10 | 25.0 |
| **Child** | | |
| A | 4 | 10.0 |
| B | 20 | 50.0 |
| C | 16 | 40.0 |
| **Outcome** | | |
| Improved | 32 | 80.0 |
| Died | 8 | 20.0 |

## Chi –sqaure test

| | Outcome | | | | | | Statistical inference |
|---|---|---|---|---|---|---|---|
| | Improved | | Died | | Total | | |
| | (n=32) | (100%) | (n=8) | (100%) | (n=40) | (100%) | |
| **S.CR** | | | | | | | |
| <3.2 | 29 | 90.6% | 1 | 12.5% | 30 | 75.0% | $X^2$=20.833 Df=1 .000<0.05 Significant |
| >3.2 | 3 | 9.4% | 7 | 87.5% | 10 | 25.0% | |
| **MELD** | | | | | | | |
| <32 | 30 | 93.8% | 0 | .0% | 30 | 75.0% | $X^2$=30.000 Df=1 .000<0.05 Significant |
| >32 | 2 | 6.3% | 8 | 100.0% | 10 | 25.0% | |
| **Child** | | | | | | | |
| A | 4 | 12.5% | 0 | .0% | 4 | 10.0% | $X^2$=15.000 Df=2 .001<0.05 Significant |
| B | 20 | 62.5% | 0 | .0% | 20 | 50.0% | |
| C | 8 | 25.0% | 8 | 100.0% | 16 | 40.0% | |

## T- test

| | n | Mean | S.D | t | df | Statistical inference |
|---|---|---|---|---|---|---|
| **MELD** | | | | | | |
| Improved | 32 | 22.63 | 6.328 | -6.694 | 38 | .000<0.01 Significant |
| Died | 8 | 38.25 | 3.454 | | | |
| **S.CR** | | | | | | |
| Improved | 32 | 2.3719 | .78380 | -5.457 | 38 | .000<0.01 Significant |
| Died | 8 | 4.1500 | .98416 | | | |

Df- degree of freedom

# DISCUSSION

In this prospective study, totally 40 patients of cirrhosis with renal failure developed either initially at the time of admission or during the hospitalisation of 2 weeks duration are studied.

Association of various factors, etiology/precipitating factors for renal failure and the final outcome of the patients during early hospitalisation was followed up.

The mortality rate in our study is **20%** with early diagnosis and adequate treatment in 2 weeks of follow up.

As we know that patients with cirrhosis associated with renal failure have poor prognosis

As stated by **Chrysoulapippilli&evangeloscholongites** , patients with advanced cirrhosis and renal failure are the high risk people who can be hardly be grouped to form precise instructions for diagnosis and treatment.

Acute kidney injury is portentous manifestation of circulatory failure on the patients with cirrhosis which has detriemental effect.Major etiology for development of liver disease is alcohol related. Etiology of liver disease has no relation with development of renal dysfunction.Ofcourse , development of renal dysfunction depends on various precipitating factors.

According to the prospective study done by **Andres cardenas & Pere Gines,** renal failure is a frequent complication in patients with cirrhosis.In the study done by them, renal failure has occurred in about 11% of bleeding episodes in patients with cirrhosis. Out of those, 60% has irreversible renal failure.

Independent risk factors for the development of renal failure in patients with UGI bleed are amount and intensity of bleed, hypovolemia/shock, late transfusion of blood and their products.

Prognosis of patient depends on severity of cirrhosis, ascites at the admission, platelet count, hepatic encephalopathy at the time of admission, child pugh score, serum creatinine ( >2.1mg/dl), serum sodium value (< 128meq/l) , MELD score.

High mortality in UGI Bleed is due to the combination effect of liver failure and renal failure along with persistent circulatory dysfunction as a consequence of cirrhosis with often precipitated by the bleeding.

In our study , major cause/ precipitating factor for developing renal failure is UGI bleed. **14 ( 35%) of out 40 patients** developed renal dysfunction due to UGI bleed which is significant number.Cirrhotic patients are more prone to develop various infections due to multiple pathological factors.

**Marilynn G Foreman, David M Mannino** observed that cirrhotic patients are more likely to develop both gram negative and gram positive sepsis with high mortaliy rate.

It is due to

- Acquired hypocomplementemia(decreased C3 levels)
- Abnormal lymphocyte function
- Reduction in reticuloendothelial system

All these factors leads to reduced clearance of bacteria from the portal circulation which consequently leads to both Gram Negative and Gram Positive sepsis.

**In OUR study**, we detected both Gram Negative ( E.coli, klebsiella, psudeomonas) and Gram Positive( streptocococi, enterococcus) from the ascitic fluid.

**SBP( spontaneous bacterial peritonitis**) is an important precipitating factor for renal dysfunction in cirrhotic patients.It is due to arteriolar vasodilation,high cardiac output, hypotension, increased RAAS( renin angiotensin activating system), elevated AVP , increased endothelin and vasoactive cytokines leads to circulatory dysfunction.

**Hae Suk Cheong** observed that SBP occurs about 10%–25% of patients with liver cirrhosis and ascites, with a mortality rate ranging from 20% to 40% in his study.

Passage of bacteria from intestine to systemic circulation and then finally ascitic fluid is possible mechanism.Increased levels of IL- 6, TNF- alpha indicates severe infection.

Renal impairment occurs in patients with increased levels of cytokines and deterioration of renal function is most important predictor for in hospital mortality.

**In our study**, SBP is the second most important risk factor after UGI bleed. 25% of patients developed the renal failure due to spontaneous bacterial peritonitis in our study.

According to the studies done by **Richard & Didier lebree,** acute renal failure in cirrhosis mainly due to pre- renal ( GI bleed, renal and GI loses), sepsis, type 1 HRS.

True hypovolemia is important reversible factor.So, treatment directed against towards the cause of hypoperfusion/hypotension. Adequate fluid replacement is given to most of the pre- renal failure which is reversible.

We managed all the patients with adequate fluid replacement, blood and their products(platelets) at the appropriate time.

The study done by **Silvanofasolato,** investigated the prevalence and clinical course of renal dysfunction which is induced by the bacterial infection in patients with cirrhosis and ascites.

He found that prevalence of renal failure is higher in patients who develop complications like gastrointestinal infections, SBP, urinary tract infection. In his study, about 1/3 rd of cirrhotic patients with ascites will develop bacterial induced renal failure.

**In our study**, 16 patients developed renal failure due to infection related( SBP, UTI, Pneumonia,cellulutis).so, 40% of the cirrhotic patients developed renal failure due to infection in various forms.

Progressive form of renal failure with feature of HRS type 1 can be precipitated not only by SBP, but also by the GI tract infections( Acute gastroenteritis,biliary infections), UTI. The probability of infection related renal failure is related to MELD score, severity of infection, lack of resolution of infection.

According to hepatologist named **L-Ruiz-del- arbo**, large volume paracentesis can cause paracentesis induced circulatory dysfunction( PICD). Initially paracentesis ( >4L) can cause asymptomatic hypovolemia which further leads to renin system activation.PICD develops in 80% of patients who are not receiving plasma volume expanders ( like Albumin).There may be impaired renal function and rapid recurrence of development of ascites occurs.

**In our study** , only 1 patient (2.5%) developed paracentesis induced renal dysfunction and reversed by albumin infusion and diuretic withdrawl. Incidence of paracentesis induced renal failure has been drastically reduced to modern treatment modalities.

There are many nephrotoxic drugs that can cause renal failure in cirrhosis patients. Aminoglycosides will increase the risk of occurrence of renal dysfunction in hospitalised patients which is supported by **Fransceso savelenero.**

Drugs like diuretics,NSAIDS will cause renal failure by hemodynamically mediated. Close monitoring of renal function is essential in patients with ascites and SBP. With drawl of offending drug will reverse the damage.

In our study , three patients developed renal failure due to drugs (NSAIDS, Diuretics,tenofivir) in cirrhotic patients. All the patients survived at the end of 2 weeks.

A prospective study done by **Fede G & D' aminco –G,** provides the evidence of increased risk of death in cirrhosis with renal failure. Finally , they have concluded renal failure increases the mortality with 7 fold rise with 50% patients dying with in 1 month of duration. **In our study, we assessed the outcome for 2 weeks( early hospitalisation).**

Child pugh scoring has been widely used for severity of cirrhotic patients. According to modern literature, MELD score is used to assess the prognosis and is better prognostic indicator which is more specific( liver specific) as it includes multiorgan ( liver and renal failure)

Most of the patients with severe liver disease with MELD(Score>30) and child pugh C are associated with development of renal failure and also significant mortality ( 68%) as evidenced by the retrospective study of **Dominique thalabut and Julien massard**. Functional renal failure is major mechanism in cirrhosis patients. Outcome in those patients was poor.

**In our study**, we found that total MELD score (>32 score) is associated with significant mortality in all died patients with **significant P value <0.02**
Use of **pentoxylline** can increase the renal blood flow. It can not reduce the short term prognosis, but can prevent long term complications in cirrhosis.

**MELD** scoring is used for good prognostic indicator /marker especially in patients with cirrhosis who developed renal failure.It predicts the mortality in 3 months period.MELD scoring depends on serum bilirubin value,serum creatinine, International normalised ratio and etiology of the liver disease.

As supported by **Teh-la huo, Jaw chingwv** report which states that Ascites and Hepatic encephalopathy were significantly associated with increased MELD score at 3 months duration .MELD score has better prognostic significance than child pugh score.

The occurrence of renal failure is a indicator of bad prognosis in cirrhosis irrespective of child's classification.According to the retrospective study done by **Yaghicsayegh R,** increased serum creatinine is a bad prognostic factor with significant decreased survival rate.So ,we made a correlation between the serum creatinine value in died and survived patients.

In our study, Maximum serum creatinine value in all died patients were **more than 3.2mg/dl** with bad prognostic index of **significant P <0.02** compared with survived patients

As evidenced by systemic analysis of **PuneetaTandoon Guadalupe Garie – Tsao**, renal dysfunction is the main prognostic indicator for cirrhotic patients with SBP followed by MELD score

# CONCLUSION

- Alcohol is the main etiological factor for chronic liver disease in the group
- Patients should be watched for the development of renal failure in advanced liver disease
- Identification of precipitating factors for renal failure is important
- UGI bleed followed by SBP are the important precipitating factors/ events for the cause of renal failure
- With adequate hydration, avoiding use of diuretics, prompt reversal of hypovolemia,early reversal of bleeding, use of adequate antibiotics, use of albumin , we encountered only 20% mortality rate during the early hospitalisation ( 2 weeks).
- All the 8 patients who died present with high serum creatinine ( > 3.2mg/dL), with child C score, high MELD score

- MELD score and Serum creatinine values are co- related with the mortality in cirrhotic patients with renal failure
- We found high MELD score(> 32) has significant association ($p<0.02$) even with the short term mortality in cirrhotic patients complicated with renal dysfunction
- In dead patients with cirrhosis and renal failure, Serum creatinine(> 3.2 mg/dl) has significant mortality co- relation ( $P<0.02$)
- Child pugh score also plays major role in mortality which significant ($P<0.05$) in died patients compared to survived patients
- Even with out using terlipressin and midodrine, we encountered only 20% mortality rate.
- We conclude that early identification, intervention and treating the risk factors for renal failure will prevent / reduce the mortality in early hospitalisation( 2 weeks).
- As many patients got either discharged/died during the study period, we could follow up patients only for 2 weeks duration.

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# PROFORMA

NAME : I P NO-

AGE /SEX: WARD/UNIT:

ADDRESS: HEIGHT/WEIGHT:

BMI

HISTORY OF PRESENTING ILLNESS

jaundice

fever

abdominal pain

abdominal distension

decreased urine output

hematemesis

malena

vomiting

diarrhoea

altered sensorium

other symptoms

**PAST HISTORY**

DM / SHT/ CKD/ EPILEPSY/ HEPATITIS/CAD/TB/OTHERS

Detailed history of Chronic Liver Disease -

**PERSONAL HISTORY**

alcoholic ( duration)-

Smoker-

native medicine-

h/o drug intake ( nephrotoxic)-

**VITAL SIGNS**

BP- SPO2-

PULSE- TEMP-

**GENERAL EXAMINATION**

consciousness -

orientation -

icterus -

edema of legs -

**SYSTEMIC EXAMINATION**

CVS -

RS -

ABDOMEN -

CNS-

**INVESTIGATIONS**

Complete blood count -

RBS -

**RENAL FUNCTION TEST**

| DAY | 0 | 2 | 5 | 10 | 15 |
|---|---|---|---|---|---|
| | | | | | |

LFT( liver function test)

urine routine ( casts)-

**Serum Electrolytes -**

PT and INR -

24 hr urinary protein excretion-

Ultrasound Abdomen -

Upper GI SCOPY -

Ascitic fluid analysis

sugar -

protein -

cytology-

cell count -

culture and sensitivity -

chest x ray-

urine culture & sensitivity-

blood culture & sensitivity-

viral markers- HEPA / HEP B/ HEP C/ HEP D

CHILD SCORE - MELD SCORE-

OUTCOME -DISCHARGED/ DIED/ RECOVERED/WORSEN

# CONSENT FORM

Name of the participant:

Documentation of the informed consent:

I have read the information in this form (or it has been read to me ). I was free to ask any questions and they have been answered. I am over 18 years of age and I am exercising my free power of choice, hereby give my consent to be included as a participant in the study of "**A STUDY ON RENAL FAILURE PATIENTS IN CHRONIC LIVER DISEASE PATIENTS**". The nature and purpose of data is for research work. The procedure has been explained to me in detail in the language understandable to me by the investigator. It has been made clear to me that all personal details like name, place, religion, past history etc., will be kept strictly confidential. I permit the result obtained to be also used for academic purpose.

Thanjavur

Date:

Signature of the patient:

Investigator Certificate:

I certify that all the elements including the nature, purpose and possible risks of the above study as described in this consent document have been fully explained to the subject.

Signature of the investigator:

Date:

Name of the Investigator:

## PATIENT INFORMATION SHEET:

You are being asked to take part in a research study entitled "**A STUDY ON RENAL FAILURE PATIENTS IN CHRONIC LIVER DISEASE PATIENTS** ".

You will not get any financial benefits from this study, but your participation may help future generations as it might help to reduce the mortality of renal failure in cirrhotic patients.

Confidentiality is guaranteed. Your identity will not be revealed. You will have to sign a informed consent form.

Your participation is completely voluntary. You may refuse to participate in the study or end your participation in the study at any time without penalty or loss of benefits to which you are otherwise entitled. You are free to ask any question during anytime of the study. We will try to answer any query that you may have.

| S.NO | NAME | AGE | SEX | ETIOLOGY | S.B | S.A | PT | INR | HE | S.Cr | U.P (mg) | PLT (lakh) | CAUSE OF RF | USG ABDOMEN | | | MELD | CHILD | UGI SCOPY | S.Na+ | OUTCOME |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | L | A | K | | | | | |
| 1 | RAMU | 30 | M | Alcoholic | 10.4 | 2.2 | 30 sec | 2.2 | + | 3 | 400 | 1.1 | UGI BLEED | S | + | N | 35 | C(12) | SV | 132 | IMPROVED |
| 2 | PUNNIAMOORTHY | 42 | M | Alcoholic | 7.2 | 2 | 51 sec | 4.63 | + | 3.6 | 210 | 0.21 | UGI BLEED | S | + | N | 43 | C (14) | N V | 111 | DIED |
| 3 | ARUL PRAKASH | 80 | M | NASH | 3.6 | 2.2 | 16 sec | 1.1 | - | 2.1 | 450 | 1.2 | SBP | S | + | N | 19 | B(9) | S.V | 125 | IMPROVED |
| 4 | YESURAJ | 34 | M | Alcoholic | 9.6 | 3 | 11 sec | 1.2 | - | 4.6 | 418 | 1.7 | SBP | N | + | N | 30 | B(9) | S.V | 142 | IMPROVED |
| 5 | SAUVIRAJ | 60 | M | Hep B | 1.2 | 3.6 | 14 sec | 1 | - | 1.9 | 312 | 2.9 | DRUG | N | - | N | 13 | A(5) | N V | 140 | IMPROVED |
| 6 | SIVAKUMAR | 45 | M | Alcoholic | 12 | 4 | 15 sec | 1.5 | - | 2.8 | 243 | 1.2 | UTI | S | + | N | 30 | B(8) | S.V | 139 | IMPROVED |
| 7 | NATARAJAN | 61 | M | Alcoholic | 1.8 | 3.2 | 16 sec | 1.2 | - | 4.8 | 418 | 1.7 | HRS TYPE 2 | S | + | N | 24 | B(7) | S.V | 135 | IMPROVED |
| 8 | MURUGESAN | 37 | M | Alcoholic | 2.2 | 2.8 | 30 sec | 2.8 | + | 2.1 | 200 | 0.07 | UGI BLEED | S | + | N | 28 | C(11) | L.V | 125 | IMPROVED |
| 9 | SHEK ALI | 44 | M | Alcoholic | 11.8 | 2.5 | 36 sec | 2.8 | - | 4.6 | 500 | 0.79 | CELLULITIS | S | + | N | 41 | C(12) | L.V | 130 | DIED |
| 10 | MEGANATHAN | 36 | M | Alcoholic | 1.6 | 3.6 | 15 sec | 1.2 | - | 3.5 | 260 | 2.4 | HRS TYPE 2 | N | + | N | 22 | A(6) | NV | 138 | IMPROVED |
| 11 | SIVA | 40 | M | Alcoholic | 1 | 3.2 | 13.3 sec | 1.1 | - | 1.5 | 410 | 1.2 | UGI BLEED | I | - | N | 11 | A(6) | L.V | 124 | IMPROVED |
| 12 | KALAISELVAN | 18 | M | Cryptogenetic | 12.6 | 3.5 | 25 sec | 2.3 | + | 2 | 900 | 1 | UTI | S | + | N | 32 | C(11) | S.V | 129 | IMPROVED |
| 13 | MURUGANANDHAM | 39 | M | Alcoholic | 5.8 | 2.8 | 35 sec | 2.8 | + | 2.5 | 600 | 0.08 | UGI BLEED | I | - | N | 33 | C(11) | L.V | 142 | IMPROVED |
| 14 | VENKATESH | 40 | M | Alcoholic | 2.6 | 4 | 25 sec | 2.18 | - | 2.3 | 512 | 2.6 | UGI BLEED | S | - | N | 26 | B(7) | L.V | 138 | IMPROVED |
| 15 | DATCHANA MOORTHY | 43 | M | Alcoholic | 1.2 | 2.5 | 25 sec | 1.8 | - | 2.7 | 400 | 0.78 | SBP | S | + | N | 23 | B(9) | S.V | 138 | IMPROVED |
| 16 | NAINA MOHAMMED | 42 | M | Alcoholic | 1.8 | 3 | 50 Sec | 2 | - | 1.5 | 480 | 1 | UGI BLEED | S | + | N | 20 | B(8) | L.V | 110 | IMPROVED |
| 17 | MURUGIYAN | 51 | M | Alcoholic | 6.8 | 2.7 | 27 Sec | 2.2 | + | 3.3 | 180 | 0.39 | UGI BLEED | N | + | N | 34 | C(13) | NV | 128 | DIED |
| 18 | AROKIASAMY | 36 | M | Alcoholic | 1.2 | 3.6 | 13.5Sec | 1.1 | - | 1.7 | 90 | 0.8 | DRUG(Diuetic) | S | + | N | 13 | A(6) | L.V | 142 | IMPROVED |
| 19 | SHEK ALI | 44 | M | Alcoholic | 11.8 | 2 | 50 Sec | 3.2 | - | 6.3 | 220 | 0.79 | SBP | N | + | N | 42 | C(12) | S.V | 133 | DIED |
| 20 | THIRUVIYA SAGARAJ | 37 | M | Alcoholic | 2.6 | 3 | 14 Sec | 1 | - | 1.5 | 300 | 1 | SBP | S | + | N | 14 | B(5) | S.V | 139 | IMPROVED |
| 21 | PALANI | 45 | M | Alcoholic | 2.8 | 2.4 | 20Sec | 1.6 | - | 2 | 338 | 0.51 | UGI BLEED | S | + | N | 22 | B(9) | L.V | 129 | IMPROVED |

| S.NO | NAME | AGE | SEX | ETIOLOGY | S.B | S.A | PT | INR | HE | S.Cr | U.P (mg) | PLT (lakh) | CAUSE OF RF | USG ABDOMEN | | | MELD | CHILD | UGI SCOPY | S.Na+ | OUTCOME |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | L | A | K | | | | | |
| 22 | CHELLAPAN | 50 | M | Alcoholic | 2 | 3 | 15Sec | 1.2 | - | 2.3 | 608 | 0.84 | PNEUMONIA | S | + | N | 19 | B(8) | L.V | 132 | IMPROVED |
| 23 | THIAYAGARAJAN | 68 | M | HCV | 1.2 | 3.3 | 19 Sec | 1.5 | - | 1.9 | 70 | 2 | ADD/AGE | S | + | N | 18 | B(7) | L.V | 149 | IMPROVED |
| 24 | SUSILA | 36 | F | Alcoholic | 3.8 | 3.2 | 25 Sec | 1.9 | - | 2.6 | 110 | 1.6 | UTI | S | + | N | 28 | C(10) | NV | 142 | IMPROVED |
| 25 | MURUGAN | 27 | M | Alcoholic | 4.2 | 2.2 | 48 Sec | 3.2 | - | 4.1 | 240 | 0.76 | SBP | S | + | N | 38 | C(12) | NV | 130 | DIED |
| 26 | VIJAYA BHASKAR | 31 | M | Alcoholic | 2.8 | 2.5 | 30 Sec | 2.7 | + | 2.5 | 320 | 0.5 | UGI BLEED | S | + | N | 30 | C(12) | L.V | 120 | IMPROVED |
| 27 | KALIYAPERUMAL | 44 | M | Alcoholic | 2.9 | 4.2 | 12 Sec | 1 | - | 1.9 | 100 | 1.7 | DRUG(NSAID) | S | + | N | 17 | B(7) | NV | 133 | IMPROVED |
| 28 | DHENADOSS | 55 | M | HBSAS (HepB) | 4.6 | 4 | 20Sec | 1.6 | - | 1.8 | 80 | 1.2 | UGI BLEED | S | - | N | 23 | B(7) | S.V | 136 | IMPROVED |
| 29 | VENKATESAN | 42 | M | Alcoholic | 4.2 | 3 | 23Sec | 1.6 | - | 3.2 | 300 | 1.1 | SBP(E-COLI) | S | + | N | 28 | B(9) | S.V | 140 | IMPROVED |
| 30 | RAVICHADRAN | 50 | M | Alcoholic | 2.2 | 2.6 | 40 Sec | 2.8 | + | 4 | 144 | 1 | UGI BLEED | S | - | N | 34 | C(12) | S.V | 130 | DIED |
| 31 | RAJENDRAN | 50 | M | Alcoholic | 10 | 2.4 | 19 Sec | 1.5 | + | 2.2 | 200 | 1.2 | SBP | S | + | N | 27 | C(11) | S.V | 142 | IMPROVED |
| 32 | SAMPATH | 55 | M | Alcoholic | 1 | 2 | 18 Sec | 1.6 | - | 2.5 | 502 | 2 | TYPE 2 HRS | S | + | N | 20 | B(8) | NV | 140 | IMPROVED |
| 33 | MANIMAVAN | 48 | M | Alcoholic | 5.8 | 1.7 | 30 Sec | 2.6 | + | 4.1 | 320 | 1 | SBP (NILGROWTH) | S | + | N | 37 | C(13) | NV | 120 | DIED |
| 34 | SAVITHRI | 55 | F | Cryptogenetic | 1.1 | 3.4 | 15 Sec | 1.1 | - | 1.7 | 142 | 1.8 | PARACENTESIS (>3L) | S | + | N | 13 | B(7) | NV | 144 | IMPROVED |
| 35 | BHASKAR | 38 | M | HCPB | 4 | 3.2 | 20 Sec | 1.9 | - | 1.8 | 159 | 1.2 | UGI BLEED | S | + | N | 24 | C(10) | L.V | 132 | IMPROVED |
| 36 | RAMADOSS | 42 | M | Alcoholic | 7.2 | 3 | 48Sec | 3 | + | 3.3 | 400 | 0.4 | UGI BLEED | S | + | N | 37 | C(13) | L.V | 128 | DIED |
| 37 | RAVI | 56 | M | Alcoholic | 5.6 | 3.2 | 16 Sec | 1.2 | + | 2.1 | 80 | 1.4 | IDIOPATHIC (UNKNOWN) | S | + | N | 22 | B(9) | S.V | 137 | IMPROVED |
| 38 | MUNIYANDI | 50 | M | Alcoholic | 1.8 | 2 | 20 Sec | 1.6 | - | 2 | 142 | 1.2 | HRS TYPE 2 | S | + | N | 21 | B(8) | NV | 140 | IMPROVED |
| 39 | SUNDARAJ | 55 | M | Alcoholic | 0.9 | 3.5 | 23 Sec | 1.5 | - | 2.1 | 400 | 0.9 | SBP | S | + | N | 18 | B(7) | S.V | 128 | IMPROVED |
| 40 | SAKTHIVEL | 48 | M | Alcoholic | 2.1 | 3.6 | 18 Sec | 1.2 | - | 2.8 | 366 | 1.4 | UNKNOWN | S | + | N | 21 | B(7) | S.V | 136 | IMPROVED |

## KEY TO MASTER CHART

M- MALES

F - FEMALES

S.B- SERUM BILIRUBIN

ETIOLOGY- CAUSE OF LIVER FAILURE

S.A – SERUM ASCITES

PT- PROTHROMBIN TIME

INR – INTERNATIONALISED NORMALISED RATIO

HE- HEPATIC ENCEPHALOPATHY

S.Cr- SERUMCREATININE ( mg/dl)

UP- 24 HR URINARY PROTEIN EXCRECTION (mg/day)

PLT- PLATELETS (Lakhs/cumm)

L-LIVER SIZE

A-ASCITES

K- KIDNEY SIZE

S- SHRUNKEN

I- INCREASED

N- NORMAL SIZE OF KIDNEYS/LIVER

CHILD- CHILD PUGH SCORE ( A,B,C)

MELD- MODEL FOR END STAGE DISEASE

S.V- SMALL VARICES

L.V – LARGE VARICES

N V – NO VARICES

S.NA – SERUM SODIUM (meq/l)