STUDY OF RENAL FUNCTION IN CHRONIC LIVER DISEASE

By

DR. PANKAJ KUMAR SAKSENA

Dissertation submitted to

BLDE (DEEMED TO BE UNIVERSITY)

VIJAYAPURA, KARNATAKA

In partial fulfillment of the requirements for the degree of

MD

IN

GENERAL MEDICINE

Under the guidance of

Dr. R.C.BIDRI$_{\text{M.D.}}$

Professor and Unit Chief

Department of Medicine,

SHRI. B. M. PATIL MEDICAL COLLEGE,

VIJAYAPURA, KARNATAKA

2018

B.L.D.E (DEEMED TO BE UNIVERSITY)

SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL &

RESEARCH CENTRE, VIJAYAPUR.

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation/thesis entitled **" STUDY OF RENAL FUNCTION IN CHRONIC LIVER DISEASE''** is a bonafide and genuine research work carried out by me under the guidance of **Dr. R.C.BIDRI** M.D., Professor and Unit chief, Department of Medicine, Shri B. M. Patil Medical College, Vijayapura.

Date:

Place: Vijayapura

Dr.PANKAJ KUMAR SAKSENA
B.L.D.E. (deemed to be University)
Shri. B.M.Patil Medical College,
Hospital & Research Centre,
Vijayapur, Karnataka

B.L.D.E (DEEMED TO BE UNIVERSITY)

SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA.

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"STUDY RENAL FUNCTION IN CHRONIC LIVER DISEASE"** is a bonafide and genuine research work carried out by **Dr. Pankaj kumar Saksena** in partial fulfillment of the requirement for the degree of MD in General Medicine.

Place:

Date:

Dr. R.C.BIDRI M.D.
Professor and Unit chief,
Medicine Department,
B.L.D.E. (deemed to be University)
Shri. B.M.Patil Medical College,
Hospital & Research Centre,
Vijayapur, Karnataka

B.L.D.E (DEEMED TO BE UNIVERSITY)

SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL &

RESEARCH CENTRE, VIJAYAPURA.

ENDORSEMENT BY THE HOD, PRINCIPAL / HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"STUDY OF RENAL FUNCTION IN CHRONIC LIVER DISEASE"** is a bonafide research work done by **Dr. Pankaj kumar Saksena** under the guidance of **Dr. R.C.BIDRI M.D.,** Professor, Department of Medicine, BLDE (Deemed to be University) Shri. B. M. Patil Medical College Hospital and Research Centre, Vijayapur.

HOD of Medicine

Seal & Signature

Dr. M. S. MULIMANI
M.D. (Medicine)
B.L.D.E. (Deemed to be University)
Shri. B. M. Patil Medical College,
Hospital & Research Centre,
Vijayapur, Karnataka

Date:

Place: Vijayapur

Principal

Seal & Signature

Dr. S. P. GUGGARIGOUDAR
M.S. (ENT)
B.L.D.E. (Deemed to be University)
Shri. B. M. Patil Medical College,
Hospital & Research Centre,
Vijayapur, Karnataka

Date:

Place: Vijayapur

B.L.D.E (DEEEMED TO BE UNIVERSITY)
SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA.

COPYRIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that the BLDE (DEEEMED TO BE UNIVERSITY), Karnataka shall have the rights to preserve, use and disseminate this dissertation / thesis in print or electronic format for academic / research purpose.

Date: **DR. PANKAJ KUMAR SAKSENA**

Place: Vijayapur

ACKNOWLEDGEMENT

I have got no words to express my deep sense of gratitude and regards to my guide **Dr. R. C. BIDRIM.D.,** Professor and Unit chief of Medicine, under whose inspiring guidance & supervision, I am studying and continuing to learn & master the art of medicine. His deep knowledge, logical approach, devotion to work and zeal of scientific research makes him a source of inspiration not only for me but for others too. It is because of his generous help, expert and vigilant supervision, that has guided & helped me to bring out this work in the present form.

I would also like to express my sincere thanks to our vice chancellor **Dr. M. S. BIRADAR,** and our beloved principal **Dr. S. P. GUGGARIGOUDAR** for their useful advice and kind support.

I wish to acknowledge my Professors and take this opportunity to express my deep sense of gratitude and sincere thanks to **Dr. M. S. MULIMANI, Dr. SHARAN BADIGER, Dr. S. S. DEVARMANI, Dr. L. S. PATIL, Dr. R. M. HONNUTAGI, Dr. S. N. BENTOOR, Dr. A. P. AMBALI, Dr. S. M. BIRADAR, Dr. P. G. MANTUR** and **Dr. V. G. WARAD** for their supervision and timely advice.

I am also thankful for the support extended by **Dr. S. G. BALAGANUR, Dr. S. S. PATIL** and **Dr. SANTOSH PATIL.**

My sincere thanks to all the staff of the Department of Biochemistry, the Department of Pathology, microbiology & the Department of Radiology Shri. B. M. Patil Medical College Hospital & Research Centre, Vijayapur who helped me in the laboratory investigation work.

I would be failing in my duty, if I would not acknowledge my thanks to all the patients who were kind enough to help for this study.

Finally, I would like to thank the God who gave me the energy, skill and the enthusiasm to complete this as well as the other tasks in my life & also for continuing to shower blessings upon me.

DR. PANKAJ KUMAR SAKSENA

LIST OF ABBREVIATIONS

ACE	-	Angiotensin converting enzyme
ADQI	-	Acute Dialysis Quality Initiative
AKI	-	Acute Kidney injury
AKIN	-	Acute Kidney Injury Network
ATN	-	Acute tubular necrosis
AUC	-	Area under the curve
ARF	-	Acute renal failure
A	-	Absent
ALD	-	Alcoholic liver diseases
CKD	-	Chronic kidney diseases
CVVH	-	Continuous veno-venous hemofiltration
CLD	-	Chronic liver diseases
CRF	-	Chronic renal failure
GFR	-	Glomerular filtration rate
GI	-	Gastro intestinal
HBV	-	Hepatitis B Virus
HBC	-	Hepatitis C virus
HRS	-	Hepatorenal syndrome
ICU	-	Intensive care unit
IL	-	Interleukin
KIM -1	-	Urinary kidney injury molecule -1
KDOQI	-	Kidney diseases Outcome Quality Initiative
MDRD	-	Modification of diet in Renal Diseases
MELD	-	Model for end stage liver diseases
NGAL	-	Neutrophil gelatinase lipocalin

NASH	-	Nonalcoholic steatohepatitis
N	-	NO
NO	-	Nitric oxide
NRD	-	No Renal Diseases
OLT	-	Orthotopic liver transplantation
PHTN	-	Portal hypertention
P	-	Present
RAA	-	Renin-angiotensin-aldosterone
RIFLE	-	Risk, Failure, Loss, End Stage renal diseases
SBP	-	Spontaneous bacterial peritonitis
SGOT	-	Serum glutamic oxaloacetic transaminase
SGPT	-	Serum glutamic pyruvate transaminase
sNGAL	-	Serum neutrophil gelatinase lipocalin
UTI	-	Urinary tract infection

ABSTRACT

Background and objectives

Renal dysfunction is common in chronic liver diseases. The cause of renal dysfunction is either multi-organ involvement in acute conditions or secondary to advanced liver diseases. The present study was undertaken to assess the renal function test in chronic liver diseases and find out the association of alteration of renal function with gradation of liver diseases (assessed by child –pugh criteria) and find out the association of alteration of renal functions among the case of chronic liver disease of different aetiology.

Methodology

This prospective cross sectional study was conducted in the Department of Medicine, Shri. B. M. Patil Medical College, Hospital & Research Centre, Vijayapur during November 2016 to August 2018 with 65 case of chronic liver diseases after considering the exclusion criteria. The patient were interviewed with predesigned and pre tested schedule examined clinically followed by some laboratory investigation relevant to diagnose the aetiology of chronic liver diseases, and to assess the severity of renal dysfunction. Statistical analysis was done by appropriate statistical software including but not restricted to MS Excel, SPSS ver.20

Results

Majority of the patients were male(90.8%) and the mean age of the patients was 45.78 ±13.19 years. 72.2% patients suffered from Alcoholic liver diseases while 13.9% and 10.8% patients had chronic hepatitis B and chronic hepatitis C respectively. Two patients had Nonalcoholic steatohepatitis. It was observed that

36.9% patients had renal dysfunction and most common type of renal dysfunction was Acute kidney injury (58.3%) followed by hepatorenal syndrome(41.7%). Majority of the case of renal dysfunction (19 out of 24 ; 79.2%) were associated with chronic alcoholic liver diseases. The distribution of serum urea and creatinine across the categories of Child Pugh classification and there was increase in renal dysfunction with increases the severity of liver diseases as per Chi –Square test($p<0.05$)

Conclusion

This study has showed significant association between severity of liver dysfunction and certain parameters of renal dysfunction

Key Words: child pugh classification, Hepato renal syndrome.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

Chronic liver disease is common clinical problem in our country. Chronic liver disease involves a process of progressive destruction and regeneration of liver parenchyma leading to fibrosis and cirrhosis.[1] Acute kidney injury, chronic kidney disease and the evaluation of numerous exogenous and endogenous measures of kidney function continue to be the focus of much research different patient population.[2] The presence of renal impairment in both groups is a poor prognostic indicator. Hepato-renal syndrome is a unique form of renal failure associated with advanced liver disease or cirrhosis and is characterized by functional renal impairment without significant changes in renal histology.[3]

Renal failure is a common occurrence in patients with chronic liver disease. Based on etiology, renal failure is divided into prerenal, renal, and postrenal categories. "It is caused by a variety of factors, some specific to chronic liver disease (eg.Hepatorenal syndrome), and others affecting the general patient population. An episode of acute renal failure may be reversible, but renal function may remain diminished over the long term, and patients may develop chronic kidney disease. Patients with chronic liver disease who develop renal failure pose unique diagnostic and therapeutic challenges.

Chronic liver disease and cirrhosis are frequently complicated with renal dysfunction and this combination leads to significant morbidity and mortality.[4] There is considerable evidence that renal failure in patient with cirrhosis primarily related to disturbances in circulatory function-mainly, a reduction in system vascular resistance due to primary arterial vasodilatation in the splanchnic circulation, triggered by portal

hypertension.[5] Intrinsic renal diseases may occur in patient with hepatitis B or hepatitis C and alcoholic cirrhosis. Moreover, patients with cirrhosis may develop a specific acute renal failure called type-I hepatorenal syndrome. Independent of event that leads to acute renal failure, patient with cirrhosis may have diseases, such as diabetes mellitus or hypertension and atherosclerosis, which may cause chronic renal injury.[6,7]

In clinical practice plasma creatinine level and endogenous creatinine clearance are commonly used as more convenient but less accurate method for glomerular filtration rate" assessment.[8]

Non-alcoholic steato-hepatitis and "non-alcoholic fatty liver disease are increasing causes of chronic liver disease in the general population of Western countries with prevalence rates of 1–5% and 10–24%, respectively. Hepatitis C has long been associated with several glomerulopathies, most notably cryoglobulin and noncryoglobulin associated membranoproliferative glomerulonephritis. The prevalence of cryoglobulinemia is around 50%.Hepatitis C has also been associated with an increased risk of albuminuria, progression of diabetic nephropathy, and progression of chronic kidney disease to end stage renal disease".[9]

Renal failure in patient with cirrhosis primarily related to disturbances in circulatory function-mainly, a reduction in system vascular resistance due to primary arterial vasodilatation in the splanchnic circulation, triggered by portal hypertension.[5]

The pivotal prognostic role of renal function in cirrhosis is reflected by the inclusion of serum creatinine (sCr) in "the Model for End Stage Liver Disease (MELD) Score, which is currently used for assessment of severity of liver disease and prioritization of

patients with advanced liver disease for liver transplantation.[10-12] As a consequence of systemic and splanchnic arterial vasodilatation and consecutive reduction in effective circulating blood volume, renal perfusion may be critically impaired in patients with advanced cirrhosis and portal hypertension".[13] As a result, patients with cirrhosis are prone to developing renal dysfunction.

Acute kidney injury (AKI), defined by a significant reduction in glomerular filtration rate (GFR) over a short time period, "is a common and severe complication in patients with cirrhosis and is often triggered by a precipitating event (i.e. overdose of diuretics, large-volume paracentesis without albumin replacement, gastrointestinal bleeding, bacterial infections, etc.).[14] AKI has an estimated prevalence of approximately 20–50% among hospitalized patients with cirrhosis[15-18] and patients with cirrhosis are more likely to develop renal failure compared to individuals without liver" disease.[19] AKI is associated with poor prognosis and represents an important predictor for short-term mortality in patients with cirrhosis.[15,16,20-22]

The spectrum of causes for AKI in cirrhosis includes (i) "prerenal AKI (i.e. hypovolemia due to gastrointestinal bleeding, aggressive diuretic treatment, lactulose-induced diarrhea or infections), (ii) the hepatorenal syndrome-type AKI (HRS-AKI), which is defined as a potentially reversible deterioration of renal function unresponsive to volume resuscitation, caused by renal vasoconstriction in the absence of alternative identifiable causes",[23,24] (iii) intrinsic causes such as acute tubular necrosis and, although very rare, (iv) postrenal causes.[18]

With a yearly incidence of 8–12%, HRS-AKI is quite common in decompensated cirrhosis with ascites.[25-27]The correct "classification of AKI is essential since HRS-

AKI, representing one of the most lethal complications of portal hypertension, requires a specific treatment approach. However, despite adequate treatment mortality is still about 60% and higher".[22,28,29] HRS-AKI is a diagnosis by exclusion and thus, often difficult to establish.[30,31]

Treatment includes general measures such as withdrawal of diuretics and intravascular volume expansion with albumin to rule out prerenal component and discontinuation of nephrotoxic medications. Other modalities of treatment include use of vasopressor drugs (eg.terlipressin), "Renal Replacement Therapy & Orthoptic Liver Transplant. In general renal failure in chronic liver disease indicates a worse prognosis. Increased creatinine to be one of the factors (along with bilirubin and international normalized ratio) independently associated with higher mortality. Mortality is especially high with hepatorenal syndrome (HRS). The greatest chance to recover renal function and improve overall survival in patients with HRS is successful liver transplantation.

The accurate assessment of kidney function and injury is currently affected by the reliance on the measured concentration of serum creatinine, which is significantly affected by the degree of cirrhosis, hyperbilirubinemia and the nutritional state of the patient. Improved understanding of the pathophysiology of kidney injury and development of more accurate measures of kidney function and injury are necessary to evoke a positive shift in kidney injury diagnosis, treatment, and outcomes. Furthermore, the number of patients with chronic liver disease and chronic kidney disease continues to rise, due to the large numbers of individuals worldwide affected by viral hepatitis, obesity, hypertension, and diabetes. Consequently, preventative

health care messages must be louder and further reaching in order to reverse" this trend.

Hence the present study was done at our tertiary care centre to evaluate the assessment of renal function in chronic liver disease.

AIMS AND OBJECTIVES

- Assessment of renal function in chronic liver disease.

REVIEW OF LITERATURE

Chronic Liver Disease is a clinical terminology used for Cirrhosis of Liver, which is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, that leads to portal hypertension and end stage liver disease.

HISTORICAL ASPECTS

Association between the liver and the kidney

The association of fulminant renal failure with diseases of the liver and the biliary tract is known for more than a century and has already been reported, in 1863 by Austin Flint, in a case series of patients with "cirrhosis and ascites.[32] From the 1920s up to the 1950s, the abdominal surgeon James Gordon Heyd described this clinical phenomenon thoroughly, which has thus also been referred to as Flint's syndrome or Heyd's syndrome, respectively.[33,34] During the past century, the term 'hepatorenal syndrome' has undergone several and often drastic redefinitions and reclassifications while the understanding of the underlying pathophysiology was improving.

Heyd's syndrome was initially described as a fulminant clinical deterioration following bilio-hepatic surgery (i.e. cholecystectomy) or appendectomy that was associated with progressive reduction in vigilance and often resulted in death.[35] Heyd defined a syndrome that was characterized by anuria and a rise in blood urea nitrogen despite after 24-36 hours apparently normal renal function prior to surgery which was later referred to as 'hepatorenal failure'.[35,36] In 1927, Furtwangler was the first to report a case series on fulminant cortical necrosis in both kidneys following hepatic trauma.[37] He suspected endotoxin-induced vasospasm and ischemia as the

pathophysiologic mechanism.[38] During the following decades, the 'hepatorenal syndrome' became increasingly recognized as its own entity as an own entity of renal failure in patients with cirrhosis characterized by fulminant progression and high mortality.[33,34,39-42]

The first consensus conference on a uniform definition for the hepatorenal syndrome (HRS) took place in 1978 in Sassary, Italy.[43,44] HRS was then considered an acute renal dysfunction associated with extensive renal sodium retention associated with acute or chronic liver disease.[44] However, the evolving understanding of the pathophysiology of HRS has led to several reclassifications and redefinitions.[23,30,44]

In the past two decades, two different types of HRS have been distinguished. While type 1HRS describes a fulminant decline in renal function in patients with advanced liver disease that is associated with a detrimental prognosis, type 2HRS is defined as slowly progressive functional renal failure that typically occurs in patients with refractory ascites. The traditional diagnostic criteria for acute renal failure in cirrhosis—a relative increase in serum creatinine (sCr) by≥50% from baseline to a final value ≥1.5mg/dL[30] —were replaced by the Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcome (KDIGO) diagnostic criteria for AKI and specifically adapted for patients with cirrhosis in order to improve applicability into clinical practice (ICA criteria).[45]

The most recent definition criteria were published in 2015 by both a community of hepatologists (ICA) together with the Acute Dialysis Quality Initiative (ADQI), a

community of nephrologists, and reclassified the former type 1HRS as a special entity of acute kidney injury: the 'HRS type of AKI" (HRS-AKI).[46]

Recent advances in the understanding of the natural history and "pathophysiology of Chronic Liver Disease, and in treatment of its complications, resulting in improved management, quality of life and life expectancy of cirrhotic patients. At present, liver transplantation remains the only curative option for a selected group of patients, but pharmacological therapies that can halt progression to decompensated Chronic Liver Disease or even reverse it are currently" being developed.

Pathogenesis and pathophysiology of Chronic Liver Disease

(Cirrhosis of Liver)

Fibrosis describes encapsulation or replacement of injured tissue by a collagenous scar. Liver "fibrosis results from the perpetuation of the normal wound healing response resulting in an abnormal continuation of fibrogenesis (connective tissue production and deposition). Fibrosis progresses at variable rates depending on the cause of liver disease, environmental and host factors.[46] Cirrhosis is an advanced stage of liver fibrosis that is accompanied by distortion of the hepatic vasculature. It leads to shunting of the portal and arterial blood supply directly into the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma, i.e., hepatocytes. The hepatic sinusoids are lined by fenestrated endothelia which rest on a sheet of permeable connective tissue (the space of Disse) which contains hepatic stellate cells (HSC) and some mononuclear cells. The other side of the space of Disse is lined by hepatocytes which execute most of the known liver functions. In cirrhosis the space of Disse is filled with scar tissue and

endothelial fenestrations are lost, a process termed sinusoidal capillarization.[47]Histologically, cirrhosis is characterized by vascularized fibrotic septa that link portal tracts with each other and with central veins, leading to hepatocyte islands that are surrounded by fibrotic septa and which are devoid of a central vein. The major clinical consequences of cirrhosis are impaired hepatocyte (liver) function, an increased intrahepatic resistance (portal hypertension) and the development of hepatocellular carcinoma (HCC). The general circulatory abnormalities in cirrhosis (splanchnic vasodilation, vasoconstriction and hypoperfusion of kidneys, water and salt retention, increased cardiac output) are intimately linked to the hepatic vascular alterations and the resulting portal hypertension. Cirrhosis and its associated vascular distortion are traditionally considered to be irreversible but recent data suggest that cirrhosis regression or even reversal is possible".[48]

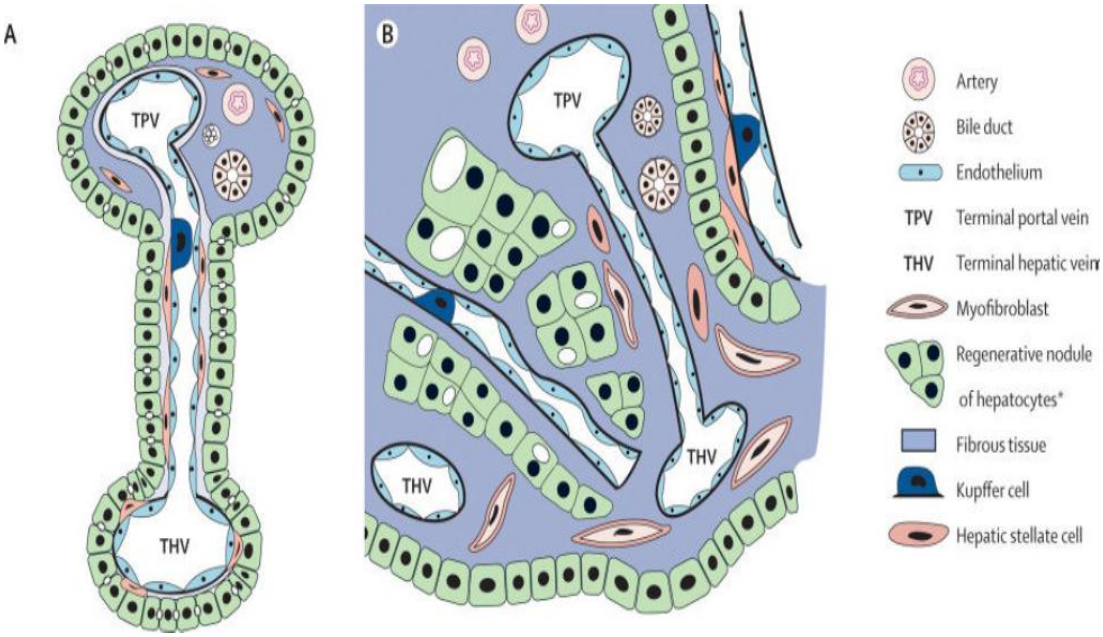


FIGURE 1:VASCULAR AND ARCHITECTURAL ALTERATIONS IN CIRRHOSIS

Mesenteric blood flows via the portal vein and the hepatic artery that extend branches into terminal portal tracts. A) normal liver: "Terminal portal tract blood runs through the hepatic sinusoids where fenestrated sinusoidal endothelium which rest on loose connective tissue (space of Disse') allow for extensive metabolic exchange with the lobular hepatocytes; sinusoidal blood is collected by terminal hepatic venules which disembogue into one of the 3 hepatic veins and finally the caval vein. B) cirrhosis: Activated myofibroblasts that derive from perisinusoidal hepatic stellate cells and portal or central vein fibroblasts proliferate and produce excess extracellular matrix (ECM). This leads to fibrous portal tract expansion, central vein fibrosis and capillarization of the sinusoids, characterized by loss of endothelial fenestrations, congestion of the space of Disse' with ECM, and separation/encasement of perisinusoidal hepatocyte islands from sinusoidal blood flow by collagenous septa. Blood is directly shunted from terminal portal veins and arteries to central veins, with consequent (intrahepatic) portal hypertension and compromised liver synthetic function".

Etiology of cirrhosis

The etiology of cirrhosis can usually be identified by the patient's history combined with serologic and "histologic evaluation. Alcoholic liver disease and hepatitis C are the most common causes in the Western world, while hepatitis B prevails in most parts of Asia and sub Saharan Africa.[49] After the identification of the hepatitis C virus in 1989 and of nonalcoholic steatohepatitis (NASH) in obese and diabetic subjects, the diagnosis of cirrhosis without an apparent cause (cryptogenic cirrhosis) is rarely made. It is important to know the etiology of cirrhosis, since it can predict complications and direct treatment decisions. It also allows the discussion of

preventive measures, e.g., with family members of patients with alcoholic cirrhosis or chronic viral hepatitis, and consideration of (genetic) testing and preventive advice for relatives of patients with genetic diseases, such as hemochromatosis or Wilson's disease. Frequently multiple etiological factors contribute to the development of cirrhosis, as exemplified in epidemiological studies that identified regular (moderate) alcohol consumption, age above 50 years, and male gender as risk factors in chronic hepatitis C9-11, or older age obesity, insulin resistance/type 2 diabetes, hypertension and hyperlipidemia (all features of the metabolic syndrome) in NASH".[50]

TABLE 1: ETIOLOGY OF CIRRHOSIS

Alcoholism	Chronic viral hepatitis
Cardiac cirrhosis	Inherited metabolic liver disease
Hepatitis B	Hemochromatosis
Hepatitis C	Wilson's disease
Autoimmune hepatitis	$Alfa_1$ Antitrypsin deficiency
Nonalcoholic steatohepatitis	Cystic fibrosis
Biliary cirrhosis	Cryptogenic cirrhosis
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Autoimmune cholangiopathy	

Clinical Presentations

Patients can present with nonspecific symptoms such as vague right upper quadrant pain, fever, nausea and vomiting, diarrhea, anorexia, and malaise. "Alternatively, they may present with more specific complications of chronic liver disease, including

ascites, edema, or upper gastrointestinal (GI) hemorrhage. Many cases present incidentally at the time of autopsy or elective surgery. Other clinical manifestations include the development of jaundice or encephalopathy.

On physical examination, the liver and spleen may be enlarged, with the liver edge being firm and nodular. Other frequent findings include scleral icterus, palmar erythema, spider angiomas (Photo 1), parotid gland enlargement, digital clubbing, muscle wasting, or the development of edema and ascites. Men may have decreased body hair and gynecomastia as well as testicular atrophy, which may be a consequence of hormonal abnormalities or a direct toxic effect of alcohol on the testes. In women with advanced alcoholic cirrhosis, menstrual irregularities" usually occur, and some women may be amenorrheic.

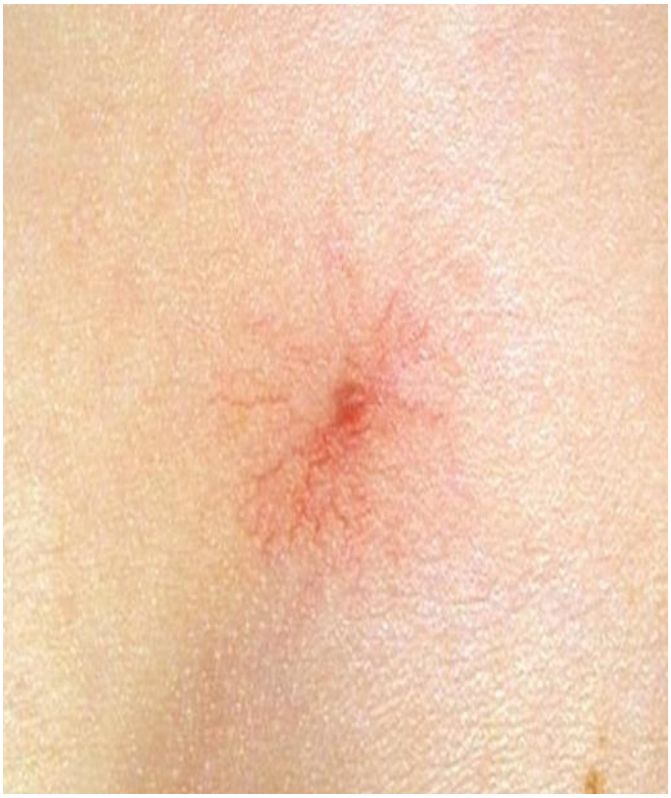


FIGURE 2: SPIDER NEVUS

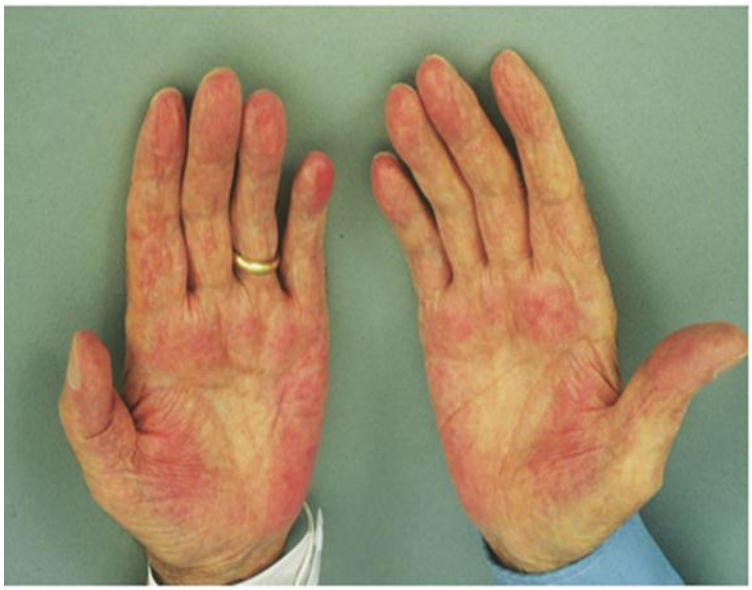


FIGURE 3 : PALMAR ERYTHEMA

TABLE 2 : COMPLICATIONS OF CIRRHOSIS

Portal hypertension	Coagulopathy
Gastroesophageal varices	Factor deficiency
Portal hypertensive gastropathy	Fibrinolysis
Splenomegaly, hypersplenism	Thrombocytopenia
Ascites	Bone disease
Spontaneous bacterial peritonitis	Osteopenia
Renal failure	Osteoporosis
Hepatic encephalopathy	Osteomalacia
Hepatopulmonary syndrome	Hematologic abnormalities
Portopulmonary hypertension	Anemia
Malnutrition	Hemolysis
	Thrombocytopenia
	Neutropenia

ACUTE RENAL FAILURE

William Heberden in his "Commentaries on the History and Cure of Diseases' was the first to describe the clinical course of AKI (then termed 'ischuria renalis') in 1802. Bowman, Charcot, and William Osler all made important contributions. However, the syndrome was largely overlooked until Bywaters and Beal classically described anuric AKI after crush syndrome during the German bombing of London during WWII. Also during WWII, Andre Cournand (later winner of the 1956 Nobel Prize in Physiology or Medicine) and co-workers were the first to study extensively changes in kidney function associated with circulatory failure or shock in man during an investigation carried out at Bellevue Hospital.

Perhaps, the modern era in the study of AKI truly began in 1951, when Homer W Smith introduced the term acute renal failure in his seminal text 'The Kidney – Structure and Function in Health and Disease.'[51] Smith comprehensively reviewed data from animal models, as well as physiologic, pathologic, and clinical data from human cases of acute renal failure". Homer Smith's term acute renal failure stood the test of time until the twenty-first century.

Although the term "acute renal failure" was introduced since 1951, there has never been a standard biochemical definition and there has not been consensus as to the diagnosis criterion, clinical definition, or disease stages for it. This has resulted in the appearance of multiple definitions used for research. Kellum et al[24] have described more than 35 different definitions. Such variation limits the ability to compare studies, to standardize study protocols, or even to communicate effectively across research groups.

As a consequence of the confusion surrounding the definition of acute renal failure, demands for a consensus definition and a classification system for acute renal failure have emerged. Following long advocacy and persistent work, such a system, the RIFLE system, was ultimately developed, involving a broad consensus of experts.The acronym RIFLE represents the increasing severity classes Risk, Injury, and Failure and the two outcome classes Loss and End-Stage Kidney Disease. The severity grades R–F are defined on the basis of changes in serum creatinine or urine output, wherein the worst of each criterion is used. The two outcome criteria, L and E, are defined by the duration of loss of kidney function. Moreover, the term Acute Kidney Injury (AKI) was introduced to encompass the entire spectrum of the syndrome, from minor impairment in renal function to the need for renal replacement therapy.

AKI Definition

AKI is "defined by an abrupt decrease in kidney function that includes, but is not limited to, ARF. It is a broad clinical syndrome encompassing various etiologies, including specific kidney diseases (e.g. acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g. ischemia, toxic injury); as well as extra renal pathology (e.g., prerenal azotemia, and acute postrenal obstructive nephropathy). More than one of these conditions may coexist in the same patient and, more importantly, epidemiological evidence supports" the notion that even mild reversible.

TALE 3: ESTIMATED BASELINE SERUM CREATININE

Age (years)	Black males (mg/dl)	Black males (mg/dl)	Black females (mg/dl)	Other females (mg/dl)
20-24	1.5	1.3	1.2	1.0
25-29	1.5	1.2	1.1	1.0
30-39	1.4	1.2	1.1	0.9
40-54	1.3	1.1	1.0	0.9
55-65	1.3	1.1	1.0	0.8
>65	1.2	1.0	0.9	0.8

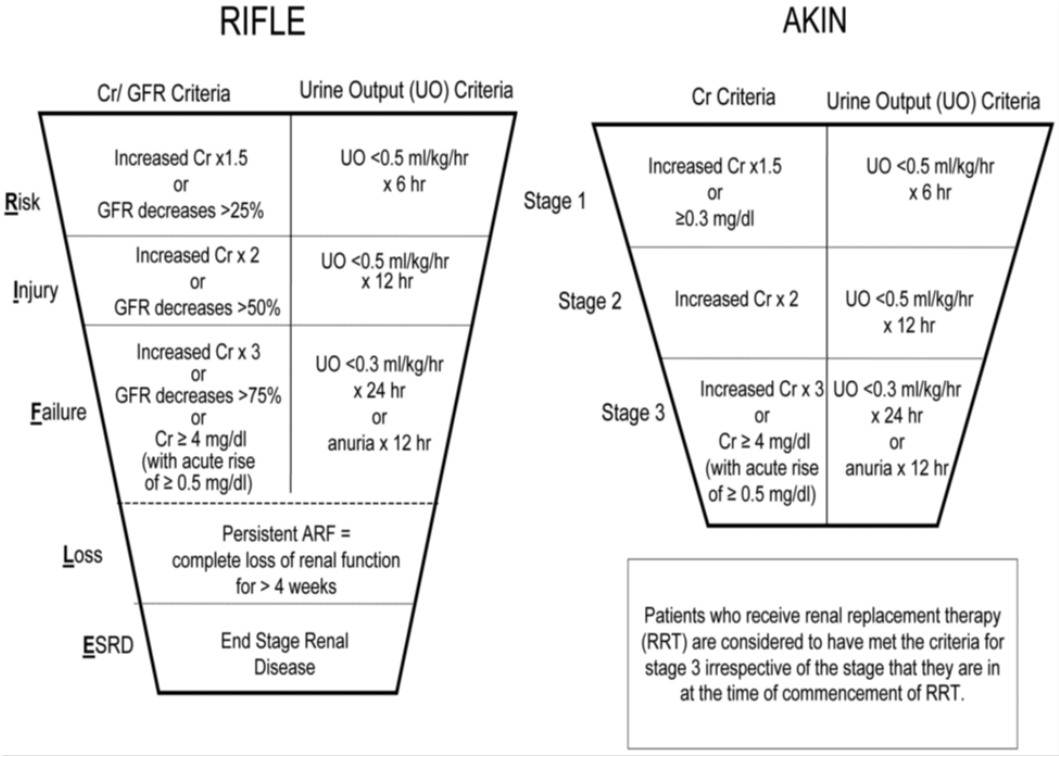


FIGURE 4 : CRITERIA FOR ARF/AKI

RIFLE and AKIN classifications for acute kidney injury. Risk–Injury–Failure–Loss–Endstage renal disease (RIFLE) and Acute Kidney Injury Network (AKIN) classifications for acute kidney injury (adapted from 20,21. ARF, acute renal failure; Cr, creatinine; GFR, glomerular filtration rate.

TABLE 4 : Etiology of ARF/AKI

Causes of renal failure in chronic liver disease

Acute	Chronic
• Hypovolemia (diuretics, hemorrhage, diarrhoea)	• Hepatorenal syndrome - type 2
• Hepatorenal syndrome - type 1	• Glomerulonephritis (HCV infection)
• Acute tubular necrosis	• Glomerulonephritis (HBV infection)
• Nephrotoxic agents (NSAIDs, aminoglycosides, radiological contrasts)	• Immunoglobulin A nephropaty
• Sepsis	

Causes of Acute Renal Failure Not associated with Chronic Liver Disease

Prerenal causes

- Intravascular volume depletion and hypotension
- Gastrointestinal fluid loss (nasogastric suction) or pooling of fluid (pancreatitis, bowel disease)
- Trauma, surgery, burns
- Decreased effective intravascular volume
- Congestive heart failure or other causes of myocardial failure
- Nephrotic syndrome
- Anaphylaxis
- Anesthetic agents
- Renal artery or renal vein occlusion by thrombosis; atheroembolism

Intrinsic causes

- Tubular necrosis
- Ischemic (as a consequence of above-mentioned prerenal events)
- Toxic due to cyclosporin, tacrolimus, amphotericin B, methotrexate, foscarnet, pentamidine, organic solvents (carbon tetrachloride, ethylene glycol), heavy metals (mercury, cisplatin), heme pigments (rhabdomyolysis), myeloma light-chain
- Interstitial nephritis related to drugs (penicillins, cephalosporins, sulfonamides, rifampicin, ciprofloxacin, selective and nonselective NSAIDs, thiazide diuretics, furosemide, cimetidine, phenytoin, allopurinol),
- infection, cancer, or sarcoidosis
- Small-vessel vasculitis or acute glomerulonephritis due to connective-tissue disorders, scleroderma, microscopic polyarteritis, rapidly progressive glomerulonephritis, or other disorders

Postrenal causes

- Upper urinary tract obstruction: ureteral obstruction of one or both kidneys
- Lower urinary tract obstruction: bladder-outlet obstruction

Pathophysiology of ARF in Chronic Liver Disease

Traditionally, “three types of ARF/AKI are identified:

(1) Prerenal azotemia, which results from renal hypoperfusion without a glomerular or tubular lesion;

(2) Intrinsic renal failure, which results from tubular cell necrosis (ischemic or toxic), glomerulonephritis, or interstitial nephritis; and

(3) Post-renal failure, which results from urinary tract obstruction causing hydronephrosis.

Patients with cirrhosis can develop all types of AKI but they can additionally develop HRS, a type of prerenal AKI that is not responsive to volume expansion and is seen exclusively in patients with severe liver dysfunction HRS is a unique potentially reversible form of ARF secondary to renal vasoconstriction that results from extreme vasodilatation. It is therefore a functional disorder, not associated with structural kidney damage. The 1-year and 5-year probabilities of developing HRS in patients with ascites are approximately 20% and 40%, respectively and are highest in patients with more marked sodium and water retention and marked activation of vasoconstrictive systems.[52]

HRS is divided into two types (1 and 2) based on prognosis and clinical characteristics. Survival of patients with HRS-1 is shorter than that of patients with HRS-2 (median survival 1.0 versus 6.7 months). HRS-1 is characterized by an abrupt deterioration in renal function that occurs mostly in an inpatient setting and often develops after a precipitating event, particularly spontaneous bacterial peritonitis (SBP). HRS-2 is characterized by a steady or slowly progressive course that occurs mostly in an outpatient setting in patients with refractory ascites. Because this more "chronic" form of HRS does not meet criteria for AKI, it is not considered in this review. The term HRS will refer to HRS-1, unless otherwise specified".

Acute tubular necrosis "(ATN) is more common than HRS as a cause of AKI, accounting for about a third of the cases (Fig. 1). It is mainly caused by an ischemic insult to the renal tubules as a result of a hypotensive event after bleeding or severe sepsis. However, the use of aminoglycosides, which are directly toxic to renal tubules, was found to be the most important predictor of ARF in cirrhosis in a study performed

in U.S. veterans. Postrenal causes of AKI in cirrhosis are rare and represent less than 1% of the cases. Similarly, chronic kidney injury also appears to be a rare diagnosis in hospitalized patients, although a small study has recently shown that immune-complex glomerulonephritis is quite common in patients with end-stage hepatitis C–induced cirrhosis. A recent review has suggested that an additional subtype of HRS should include patients with chronic kidney injury who develop" superimposed AKI.[53]

Mechanisms:

ARF/AKI is common in cirrhosis for several reasons. Patients with cirrhosis are prone to intravascular volume depletion secondary to gastrointestinal bleeding, diuretic use, and lactulose-induced diarrhea & Infections. Patients with cirrhosis have a particular predisposition to bacterial infections that is mostly a result of impaired reactivity of reticuloendothelial cells and neutrophils. Bacterial infections develop in 30%-60% of patients with cirrhosis, being responsible for about 25% of overall mortality in this disease. The most common site of infection is the ascitic fluid, and less frequent are the respiratory system, urinary tract or subcutaneous tissue. Gastrointestinal bleeding, irrespective of its source, is associated with increased translocation of intestinal bacteria through ischemic mucosa and very high risk of SBP. "Moreover, these patients are often exposed to nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, contrast agents, and aminoglycosides, to which they are particularly susceptible. Perhaps most importantly, because of the hyperdynamic circulatory state of cirrhosis, renal blood flow in patients with cirrhosis (particularly in those with more severe liver disease) is very susceptible to events associated with a further decrease in effective arterial blood volume. As recently reviewed, the hyperdynamic circulation in cirrhosis is a progressive vasodilatory syndrome that was

first recognized clinically in patients with cirrhosis by observing that they frequently had "warm extremities, cutaneous vascular spiders, wide pulse pressure, and capillary pulsations in the nail beds." Progressive vasodilatation (both splanchnic and systemic) is a key factor in the pathogenesis of many of the complications of cirrhosis, prominently in the kidney. Splanchnic and systemic vasodilatation in cirrhosis is a consequence of portal hypertension and is attributable mostly to nitric oxide overproduction, although other molecules also participate in this complex process.[54] As shown in Fig. 2, vasodilatation leads to a decreased effective arterial blood volume (relative hypovolemia) and activation of neurohumoral systems such as the renin-angiotensin-aldosterone system; sympathetic nervous system; and non-osmotic release of antidiuretic hormone). Relative hypovolemia initially leads to sodium and water retention (with ascites formation), increased intravascular volume, and increased cardiac output. With progression of cirrhosis, vasodilatation worsens and activated vasoconstrictive systems lead to renal vasoconstriction and decreased renal blood flow. (Fig. 2). Additionally, as in other forms of high cardiac output syndrome, the heart response becomes insufficient to maintain perfusion pressure (high-output heart failure) and further contributes to a decrease in renal blood flow and renal failure (Fig. 2). It has been proposed that the sympathetic nervous system causes a rightward shift in the renal autoregulatory curve that makes renal blood flow critically dependent on renal perfusion pressure and that this further contributes to the development of renal failure". Although the "spontaneous" development of renal failure in a patient with cirrhosis and hyperdynamic circulation indicates the presence of HRS, this syndrome often presents after a precipitating event. In the setting of hyperdynamic circulation, rapid fluid loss (from gastrointestinal bleeding or diarrhea) or sepsis/systemic inflammatory response syndrome-related vasodilation leads to a

further decrease in effective arterial blood volume, renal vasoconstriction, and prerenal AKI (Fig. 3).This is further complicated by the fact that these same events, through the development of circulatory shock, can lead to intrinsic renal failure from renal tubular necrosis. Intense renal vasoconstriction, as seen in HRS, can in turn lead to tubular ischemia and necrosis as demonstrated by electron microscopy or by urine markers of acute tubular necrosis.

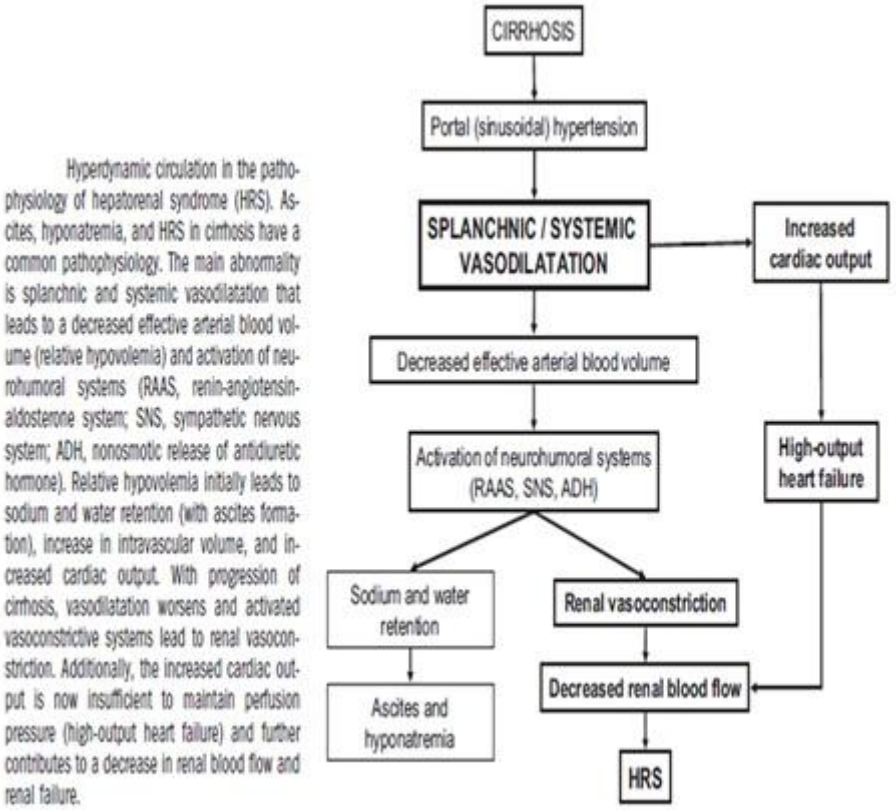


FIGURE 5 : PATHO PHYSIOLOGY OF HEPATORENALSYNDROME

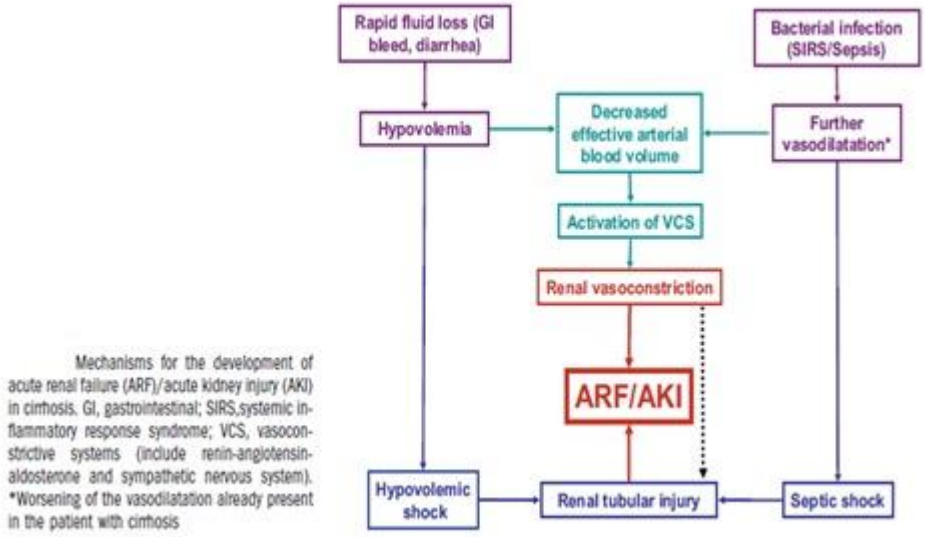


FIGURE 6 : MECHANISM OF DEVELOPMENT OF ARF

Diagnosis

Serum Creatinine is the most established, simple, and inexpensive parameter of glomerular filtration rate (GFR) and is the primary method of detection of all forms of renal failure. However, "it has several limitations. First, Serum Creatinine is not helpful in distinguishing among various causes of renal injury. Second, Serum Creatinine lags behind renal injury and is therefore a delayed marker of decreased renal function. Third, significant renal disease can exist with minimal or no changes in Serum Creatinine because of renal reserve, enhanced tubular creatinine secretion, or other factors. Lastly, Serum Creatinine is greatly influenced by numerous nonrenal factors such as body weight, race, age, sex, total body volume, drugs, muscle metabolism, and protein intake. Although the simplified "modification of diet in renal disease" formula provides a robust estimate of GFR relative to Serum Creatinine corrected by age, race, and sex in chronic kidney disease when Serum Creatinine is at a steady state, it is not useful in AKI when Serum Creatinine is not in equilibrium. In cirrhosis, Serum Creatinine may be an even poorer reflection of kidney function

because of a reduced muscle mass, particularly in patients with severe liver disease. In this setting, the release of creatinine is considerably reduced, and therefore, patients may have a normal Serum Creatinine in the setting of a very low GFR. Additionally, severe hyperbilirubinema gives a falsely low value of Serum Creatinine if the chemical rather than enzymatic method is used for measurement.[55] As recently reviewed, other methods of renal function assessment also have limitations and do not correlate well with GFR. Newer serum markers such as cystatin C

are promising; however, they require further validation using "gold standard" measures of GFR such as iodothalamate or inulin clearance". Therefore, and despite its limitations; SCr remains the key biomarker in the diagnosis of ARF in cirrhosis.

Diagnosis of HRS

HRS type 1 has been defined by consensus as a doubling of "Serum Creatinine to a level greater than 2.5 mg/dL (226mol/L) in less than 2 weeks. As Per the AKI consensus criteria, this level of renal failure would correspond to a stage 2 (that is, a greater than twofold to threefold increase in Serum Creatinine from baseline).The diagnosis of HRS has been defined in two International Ascites Club consensus conferences in 1996 and in 2005 (Table 6). The new definition of HRS:

(1) Excludes creatinine clearance because it is more complicated to perform and does not increase the accuracy of renal function estimation;

(2) Includes renal failure in the setting of ongoing bacterial infection (but in the absence of septic shock), indicating that the diagnosis can be established before completing antibiotic therapy;

(3) Determines that plasma volume expansion should be performed with intravenous albumin rather than saline solution; and

(4) Excludes minor diagnostic criteria (urinary indices) because these criteria have poor sensitivity and specificity.

Although HRS is a diagnosis of exclusion, certain patient characteristics are more or less typical of HRS. The presence of ascites is a prerequisite for the diagnosis of HRS because the same mechanisms that lead to ascites formation lead to HRS"[56]

HRS New Diagnostic Criteria[30]

- Cirrhosis with ascites
- Serum creatinine 1.5 mg/dL (133 mol/L) HRS-1 doubling of the initial serum creatinine concentrations to a level greater than 2.5 mg/dL (226 mol/L) in less than 2 weeks
- No improvement in serum creatinine (decrease to 1.5 mg/dL or less) after at least 2 days of diuretic withdrawal and expansion of plasma volume with albumin (1 g/kg body weight/day up to a maximum of 100 g/day)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs or vasodilators
- Absence of parenchymal kidney disease as indicated by proteinuria 500mg/day, microhematuria (50 red blood cells per high power field), or abnormal renal ultrasonography

Differential Diagnosis

Differentiation "among the three main causes of AKI may be difficult in patients with cirrhosis because the clinical presentations do not match classical paradigms and, as factors that lead to prerenal azotemia can precipitate HRS and can also precipitate ATN (Fig. 3).Tubular ability to reabsorb sodium and to concentrate urine is preserved in prerenal azotemia and HRS but is impaired in ATN. Prerenal azotemia and HRS are therefore classically described as sodium avid states with low (20 mEq/L) urinary

sodium (UNa), low (1%) fractional excretion of sodium(FENa), and elevated (500 mOsm/kg) urine osmolality. Conversely, patients with ATN have high UNa (40 mEq/L), high FENa (2%), and urine osmolality under 350 mOsm/kg. However, in patients with HRS, particularly in those on a high dose of diuretics, UNa is consistently greater than 10 mEq/L.[57] Conversely, ATN that occurs in patients with sodium avid states, such as cirrhosis, has been described as having a FENa 1%. UNa and FENa are thus less useful in patients with cirrhosis and have been eliminated as diagnostic criteria in HRS. Classic descriptions of prerenal azotemia and HRS describe a "bland" urine sediment, and bile-stained granular and epithelial casts are described in ATN. However, these casts may be seen as nonspecific findings in patients with advanced liver disease and jaundice. Conversely, ATN has been described morphologically and by urine biomarkers such as β-2 microglobulin in HRS. Thus, urine sediment may not be helpful either in the differential" of ARF in cirrhosis.

Differentiation between prerenal azotemia and "HRS also may be difficult. By definition, prerenal azotemia improves with volume expansion. However, assessment of exact intravascular volume deficit in a patient who is already total body sodium overloaded is difficult; the rate of fluid administration is unspecified, and thus the rate of response in Serum Creatinine is highly variable and often incomplete. The difficulty in establishing an early diagnosis of HRS leads to a significant delay in the initiation of specific therapy and is one of the barriers in the development of new agents. In noncirrhotic patients, urinary biomarkers such as interleukin-18 have an accuracy of 95% in differentiating ATN from other causes of renal dysfunction such as prerenal azotemia, urinary tract infection", and chronic kidney disease and are being investigated in patients with cirrhosis.

Treatment

Treatment of AKI in cirrhosis depends on its cause. “Prerenal azotemia should be managed by treating/discontinuing the precipitant and through volume repletion. ATN should be treated using renal replacement therapy, particularly in the presence of volume overload, hyperkalemia, or metabolic acidosis not responding to medical therapy. Because of a lack of clinical studies, there are no special recommendations for dose, intensity, and duration of dialysis in patients with cirrhosis who develop ATN. Interestingly, a recent study has demonstrated benefit of terlipressin in a consecutive series of patients with cirrhosis with ATN.[58]It is likely that mesenteric/ systemic vasoconstriction induced by terlipressin will lead to renal vasodilatation with improvement of renal blood flow to the damaged renal” tubules.

Treatment of HRS.

Orthotopic Liver Transplantation (OLT)

OLT is the only definitive therapy for “HRS, because it is the only therapy associated with improvement in survival. However, it is important to reverse HRS because improving renal function pretransplantation is associated with improved posttransplantation outcomes. It has been shown that renal insufficiency, including HRS, has a negative impact on OLT outcomes, with a higher mortality and higher posttransplantation end-stage renal disease. Patients who are transplanted with HRS have more complications and a higher in-hospital mortality rate than those undergoing transplantation without HRS. Conversely, the outcome of OLT in patients with HRS treated with vasopressin analogs before transplantation is similar to that of patients undergoing transplantation without HRS. Simultaneous liver and kidney transplant (SLKT) is increasingly considered in patients with renal dysfunction undergoing

OLT. There is specific concern that some patients who undergo SLKT may have reversible renal failure. HRS alone should not be a reason for SLKT; however, this is now being considered in patients with HRS who become dialysis dependent and in whom there is no recovery after 6 to 8 weeks of dialysis (the usual recovery time for ATN).[59] The need for dialysis should theoretically be prevented by early treatment of HRS with the "bridging" therapies outlined below, particularly the use of vasoconstrictive therapy.

Vasoconstrictors Plus Albumin

Because the main pathogenic mechanism in HRS is splanchnic and systemic vasodilatation, vasoconstrictors should ameliorate vasodilatation and improve effective arterial blood volume, renal vasoconstriction, and renal flow. Vasoconstrictors have been used in conjunction with intravenous albumin with the intention of increasing effective blood volume. Because albumin dialysis is associated with an increase in MAP attributable to the ability of albumin to bind vasodilators, it is conceivable that an improvement of renal function in patients with HRS treated with vasoconstrictors and albumin is attributable to the additive effects of both compounds in producing vasoconstriction. The need for albumin has only been examined in a nonrandomized small study that showed that treatment with terlipressin and albumin was associated with a significant decrease in Serum Creatinine and an increase in MAP, changes that were not observed in a non concurrent group of patients treated with terlipressin alone. Terlipressin is the preferred vasopressin analog because of a lower incidence of side effects and because its administration does not require continuous intravenous infusion. Noradrenaline, in continuous infusion, has also been shown to ameliorate the hemodynamic/renal abnormalities in HRS, as has the combination of midodrine plus octreotide, which has the advantage of

oral/subcutaneous administration. However, octreotide alone is no more effective than placebo and did not improve SCr. It is therefore uncertain whether the effectiveness of the combination octreotide/midodrine is attributable to midodrine alone or to the combination. Experimental studies showing that octreotide potentiates the effect of vasoconstrictors[60] would suggest the latter. Specifics such as the optimal time for initiation of vasoconstrictive therapy, dose and duration, failure criteria, and the influence and dose of albumin remain to be determined. Vasoconstrictor therapy has been used at different doses and with different side effects; patients that receive higher doses appear to have a higher rate of adverse events.[61]

Transjugular Intrahepatic Portosystemic Shunt

TIPS decreases SCr in most patients, even in a few with organic renal failure, but slower than that obtained using terlipressin plus albumin. Recurrence of HRS is rare as long as the shunt remains patent, but hepatic encephalopathy is a frequent complication. Post-TIPS resolution of HRS appears to improve survival".

Approach to the Patient with Cirrhosis and ARF

A diagnosis of HRS (type 1) be considered whenever there is an increase in Serum Creatinine of 0.3 mg/dL or more (26.4 mol/L) or an increase of 150% or more (1.5-fold) from baseline. Delaying therapy until higher Serum Creatinine levels are reached would not seem warranted because baseline Serum Creatinine is a predictor of HRS reversal and the probability of HRS reversal decreases by 39% for each 1-mg/dL increase in baseline creatinine. Treatment for HRS should therefore be initiated earlier, with only 1.5- fold increases in creatinine. "The setting in which AKI occurs is essential. In patients in whom there is a clear history of septic or hypovolumic shock, or in whom there is a recent history of nephrotoxin

administration , the most likely cause is ATN. In all other patients, the first step is to discontinue diuretics, lactulose (because it is a frequent cause of diarrhea), vasodilators, and any potential nephrotoxins. Secondly, intravascular volume should be expanded with intravenous albumin at a dose of 1 g/kg body weight up to a maximum of 100g. This dose can be repeated in 12 hours if the SCr has not normalized. A reduction in Serum Creatinine indicates that AKI is attributable to prerenal azotemia. Intravenous albumin is preferred over saline solution as a volume expander because sodium load is significantly lower with albumin, and it will not worsen fluid retention, and because it will not be associated with a dilutional decrease in Serum Creatinine. Third, and concurrently, investigations to rule out precipitants of AKI should be undertaken, specifically diagnostic paracentesis (to rule out SBP), blood and urine bacteriological cultures, and chest x-ray (to rule out bacterial infections other than SBP) and patients treated accordingly. If SCr does not improve or continues to worsen despite these measures, the differential diagnosis is between intrinsic renal failure (ATN), HRS, and postrenal failure. Treatment of HRS can be initiated before completion of antibiotic therapy in patients with bacterial infection whose Serum Creatinine does not improve despite a clear amelioration in the signs of infection. Because assessment of volume status may be uncertain, and to ensure that volume has been adequately expanded, intravascular volume should be assessed by measuring central venous pressure. A normal or increased central venous pressure indicates that the cause of renal failure is not volume-related. To rule out postrenal failure, a renal ultrasound should be obtained, although this is a rare cause of AKI in cirrhosis. To rule out intrinsic renal failure, urinary sediment should be analyzed. Finding granular or epithelial casts suggests ATN but is not definitive. The differentiation between ATN and HRS is the most difficult, and studies using urine

biomarkers of ATN are awaited. It has been suggested that the response to vasoconstrictors plus albumin may be used to establish" this differential.[62]

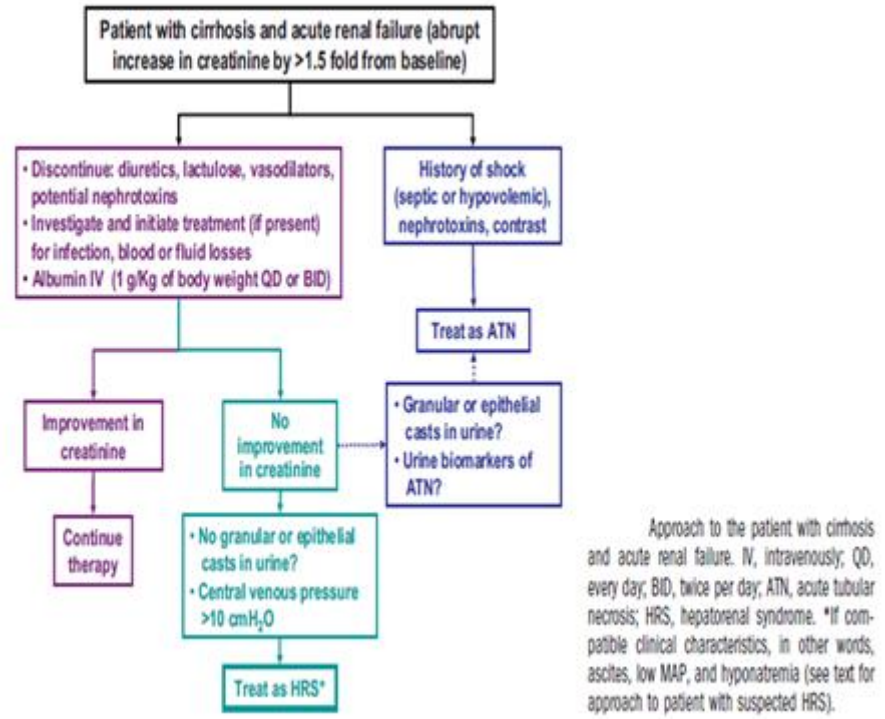


FIGURE 7 : APPROACH TO PATIENT WITH CIRRHOSIS AND ARF

Co-existing liver and kidney disease

Chronic liver disease and primary "liver cancer account for 1 in 40 (2.5%) deaths worldwide, with hepatitis B the commonest cause in the developing world, followed by alcoholic liver disease and hepatitis C in the Western world.[63] Non-alcoholic steato-hepatitis and non-alcoholic fatty liver disease are increasing causes of chronic liver disease in the general population of Western countries with prevalence rates of 1-5% and 10-24%, respectively. This observation is related to the increasing incidence of obesity in the Western population and the associated metabolic syndrome, consisting of atherosclerotic coronary vascular disease, hypertension, hyperlipidemia, diabetes, and chronic kidney disease. Metabolic syndrome and non-alcoholic steato-hepatitis/non-alcoholic fatty liver disease are linked by the key

feature of insulin resistance. Although initially considered to be a benign disease, non-alcoholic fatty liver disease seems to represent a spectrum of disease with benign hepatic steatosis at one end and steatotic hepatitis at the other. Approximately 30-50% of individuals with steatohepatitis will develop fibrosis, 15% cirrhosis, and 3% liver failure. Importantly, non-alcoholic fatty liver disease probably accounts for a large proportion of patients diagnosed with cryptogenic cirrhosis and at least 13% of cases of hepatocellular carcinoma.

Obesity and metabolic syndrome are also strongly associated with the development of hypertension and diabetes, which affect 70% of the patient population with endstage renal disease in the USA.[64]There is increasing evidence that obesity itself is an independent risk factor, albeit small, for the progression of chronic kidney disease. Some work has highlighted the association of low-birth weight and reduced nephron mass with an increased risk of obesity and the phenomenon of chronic kidney disease later in life. A small proportion of obese patients will develop obesity-related glomerulosclerosis, a focal segmental glomerulonephropathy associated with proteinuria and progression to end-stage renal disease. Despite numerous obesity-related factors, the overall individual risk for the development of chronic kidney disease in the absence of diabetes and hypertension is low; nevertheless, obesity is likely to contribute increasingly to the burden of chronic disease and end-stage renal disease in the future.

Hepatitis C has long been associated with several glomerulopathies, most notably cryoglobulin and non-cryoglobulin-associated membranoproliferative glomerulonephritis. The prevalence of cryoglobulinemia is around 50%, although

extrarenal manifestations are often absent in the majority of these patients. Viral RNA, proteins and particles have been inconsistently isolated from kidney biopsy specimens, making it difficult to establish whether hepatitis C is causative in other forms of glomerulopathy. In seropositive hepatitis C populations, hepatitis C infection has been reported to be associated with focal segmental glomerulosclerosis, membranous nephropathy with or without nephrotic range proteinuria, IgA nephropathy, and proliferative glomerulonephritidies.

Hepatitis C has also been associated with an increased risk of albuminuria, progression of diabetic nephropathy, and progression of chronic kidney disease to end-stage renal disease. The worldwide prevalence of hepatitis C among patients on hemodialysis is high, ranging from 4-60%. This rate is on the decline, due to stricter adherence to universal infection control measures, with or without isolation, which have been implemented to a greater extent in the USA and in European countries. Risk factors for infection include the length of time of hemodialysis, the number of blood transfusions for renal anemia, and nosocomial transmission. These patients often develop significant chronic liver disease, which adds an additional mortality burden while on hemodialysis. The presence of hepatitis C infection also has a negative effect on patient and renal survival following kidney transplantation.[65]

Hepatitis B virus (HBV) is also associated with renal disease, but it is mostly encountered in children from endemic areas. The incidence of HBV-associated renal disease in Europe is low due to the lower prevalence of chronic HBV infection. HBV is associated with a number of renal diseases, including polyarteritis nodosa, membranous and membranoproliferative glomerulonephritis. Most patients have a history of active HBV but are asymptomatic with positive surface antigen and core

antibody; in those with membranous nephropathy, e antigen is positive. The pathogenic role of HBV has been demonstrated by the presence of antigen-antibody complexes in kidney biopsy specimens and in particular deposition of HBV e antigen in membranous glomerulonephritis.

Autosomal-dominant polycystic kidney disease is associated with polycystic liver disease in up to 75-90% of cases. There are a number of risk factors for liver involvement, including female gender, age, and degree of renal dysfunction. A distinct form of autosomal dominant isolated liver cystic disease was recognized in the mid-1980s. Most patients are asymptomatic, but when symptoms do occur, they are often related to cyst size and number. Symptoms include abdominal pain, nausea, early satiety, breathlessness, ascites, and biliary obstruction; all can precipitate to result in a significantly malnourished state related to gastric compression. The medical complications seen with autosomal-dominant polycystic kidney disease including intracranial aneurysms, and valvular heart lesion are also encountered in those with cystic liver disease. Therapies involve cyst rupture or sclerosis and liver transplantation if symptoms persist.[66]

Familial amyloidosis polyneuropathy is an autosomal dominant disease caused by a point mutation in the gene coding for transthyretin, also called pre-albumin. The amino acid, valine, is replaced by methionine. The mutated protein produced by the liver forms a beta-pleated sheet structure, which accumulates in tissues, particularly nerves and the kidney, resulting in amyloid deposition. Familial amyloidosis polyneuropathy appears in the second decade of life leading to death within 8-13 years. Orthotopic liver transplantation (OLT) represents the best form of treatment, when performed early in the course of the disease, by halting the progression of the

peripheral neuropathy and chronic kidney disease. The kidneys are frequently affected and this is recognized by proteinuria and declining kidney function. OLT reduces serum pre-albumin levels but the amount deposited in the kidney remains the same post transplantation. OLT should not be contemplated for patients with severe proteinuria or advanced chronic kidney disease".[67]

Serum creatinine concentration for the assessment of kidney function in chronic liver disease

Kidney function is evaluated by assessing the "glomerular filtration rate (GFR), which can be determined by measuring the volume of plasma that can be completely cleared of a given substance over a defined unit of time. The ideal marker for GFR determination is often quoted as having the following characteristics: Appears constantly in the plasma, can be freely filtered at the glomerulus, and does not undergo tubular reabsorption, secretion or extra renal elimination.[68] For many years now, the assessment of GFR has relied on the measurement of the concentration of serum creatinine, which is associated with many problems. Creatinine is a product of the metabolism of creatine, which is produced in the liver from three amino acids, methionine, arginine, and glycine, and stored in muscle to be used as a source of energy once phosporylated. Creatinine does not appear in the plasma at a constant rate; it is secreted in the tubule and can undergo extrarenal elimination, thought to involve creatinase in the gut. Serum creatinine concentration displays an exponential relationship with GFR, rendering it specific, but not a sensitive measure of GFR. The creatinine pool is affected by gender, age, ethnicity, nutritional state, protein intake and importantly liver disease.[69]

In chronic liver disease, the reduction in the serum creatinine pool is due to a 50% decrease in hepatic production of creatine; increases in the volume of distribution due to the accumulation of extracellular fluid, edema, and ascites; malnutrition and loss of muscle mass, which is related to repeated episodes of sepsis and large volume ascites affecting satiety.[70] Ultimately, patients with chronic liver disease have a significantly lower baseline serum creatinine concentration than the general population (35-75 μmol/l).

Analytical methods for measuring the serum creatinine concentration have been associated with problems, particularly related to interference from chromatogens, like unconjugated and conjugated bilirubin. The degree of error can be up to 57%, but modern auto-analyzers using the endpoint Jaffe method have overcome such interference. Nevertheless, interpreting serum creatinine results in the context of hyperbilirubinemia still requires a degree of caution despite these adjustments. In particular, patients with chronic liver disease display smaller and delayed (up to 48-72 hours) changes in serum creatinine for a given change in GFR, thus impairing the recognition and underestimating the degree of change in GFR".[71]

Patients with "chronic liver disease are more susceptible to acute kidney injury Advanced chronic liver disease is responsible for a significant number of physiological changes that affect the circulation and kidney perfusion. Cirrhosis results in the accumulation of vasodilatory mediators, in particular nitric oxide (NO), which specifically vasodilates the splanchnic circulation reducing the effective circulating blood volume and mean arterial pressure. Hypoperfusion of the kidneys leads to a reduction in the sodium concentration of tubular fluid reaching the distal tubule stimulating the macular densa, to release renin, thus activating the

reninangiotensin-aldosterone (RAA) axis. Glomerular filtration pressure is dependent on afferent and efferent vascular tone. Chronic disease states often seen in association with chronic liver disease, such as atherosclerotic vascular disease, hypertension and chronic kidney disease, affect the responsiveness of the afferent arteriole, thus shifting the auto regulation curve to the right. Consequently, adjustments in vascular tone of the afferent arteriole are smaller, reducing the ability to increase glomerular perfusion during episodes of hypotension. This, coupled with increased levels of angiotensin II, a product of RAA activation, causes vasoconstriction of blood vessels, in particular the afferent and efferent arteriolar renal vessels. Aldosterone acts on the distal tubule increasing the retention of salt and water. Consequently, there is decreased renal perfusion coupled with avid retention of fluid which increases abdominal ascites accumulation causing abdominal distension and elevation of the intra-abdominal pressure, which further compromises renal perfusion and propagates the vicious cycle.

Furthermore, in advanced chronic liver disease, an intrinsic defect in cardiac performance during exercise has been demonstrated and termed cirrhotic cardiomyopathy.[72]This syndrome encompasses a number of myocardial and electrophysiological changes that occur in cirrhosis and lead to attenuated cardiac function, particularly when exposed to stressful events like sepsis. The features of this condition include: A hyperdynamic myocardium with an increase in baseline cardiac output; attenuated systolic contraction and diastolic relaxation; electrophysiological abnormalities; and unresponsiveness to beta-adrenergic stimulation. Portal hypertension leads to shunting of blood away from the liver, thus reducing portal venous blood flow in the liver. This is thought to affect sodium and water excretion by the kidney via the postulated hepatorenal reflex mechanism whereby the release of

adenosine is believed to act as a neuro-transmitter stimulating sympathetic nerves supplying the renal vasculature causing vasoconstriction and oliguria. These mechanisms, attempting to maintain the effective circulating blood volume coupled with cirrhotic cardiomyopathy and reduced venous return from raised intra-abdominal pressure, render the circulation helpless in the pursuit of renal perfusion preservation.

Stress events like sepsis, gastrointestinal bleeding, and the use of diuretics, vasodilators or nephrotoxic drugs, which cause renal vasoconstriction, like non-steroidal anti-inflammatory drugs and radiographic contrast agents, can tip this fine balance between circulatory performance and adequacy of renal perfusion resulting in renal ischemia and its associated multi-faceted sequelae". Subsequently, AKI ensues, unless timely interventions targeted at reversing these physiological changes are initiated.

Assessment of chronic kidney disease in patients with chronic liver disease

The reliance on serum creatinine concentration is pivotal to the problems with estimated GFR and the gulf between the original "MDRD study population and patients with chronic liver disease. This has been highlighted by a meta-analysis that reviewed creatinine clearance and estimated GFR and demonstrated a mean overestimation of 18.7 ml/min/1.73 m2.[73] Timed urine creatinine clearance also performs poorly, significantly overestimating GFR in patients with chronic liver disease, particularly at the lower range of GFR measurements.[74] So why use estimated GFR if it performs so poorly? Despite its drawbacks, it is the most cost-effective method of assessing kidney function in the chronic setting and provides greater clarity on the extent of disease if one considers the overestimation and uses the extended

version, which incorporates albumin and urea. Serial measures tend to provide greater information than measures in isolation.

Patients with chronic liver disease and chronic kidney disease warrant better evaluation of residual kidney function than is currently offered. Cystatin C has been shown to be a better marker of GFR in patients with chronic liver disease both before and in the immediate period after transplantation. Equations have been developed to give better accuracy to the estimation of GFR using measured cystatin C concentration. However, these equations have been evaluated in small study populations using different gold standard measures of GFR compared to the creatinine based equations. Cystatin C equations have, though, been shown to perform better, with greater accuracy in predicting GFR, in cirrhotic and post-transplant patients using either the Hoek or Larsson equations.[75,76]

uNGAL has also been shown to be significantly elevated in proteinuric patients with membranous nephropathy or membranoproliferative glomerulonephritis with chronic kidney disease when compared to a control group with normal kidney function and no proteinuria. sNGAL has been shown to be significantly elevated in patients with chronic kidney disease or kidney transplant compared to controls. It also appears to increase with chronic kidney disease stage and severity suggesting a role in tracking progression of chronic kidney disease.[77] However, increased sNGAL in the setting of chronic kidney disease is poorly understood; the suggested hypothesis links proteinuria and the apoptotic effect this has on proximal tubular cells. Further evaluation is required, but these biomarkers have shown promise as markers of chronic kidney disease progression.

Ultimately, patients with chronic liver disease and chronic kidney disease need residual kidney function to be evaluated using gold standard measures of GFR, probably at 3-6 monthly intervals. The evaluation of cystatin C and serum NGAL in the interim period to monitor progression and perhaps detect acute changes could lead to improved outcomes" for this group of patients.

Alternatives to creatinine and creatinine-based equation for the assessment of renal function

Clearance of exogenous markers

Direct measurement of GFR using exogenous markers remains the reference to assess renal function in cirrhotic patients. Direct measurement of GFR is mandatory to precisely assess renal functionand adequately classify patients into the different categories of impaired renal function.[78]Inulin clearance has been considered the ''gold standard". "Inulinis freely filtered by the glomerulus and not secreted, reabsorbed, synthesized or metabolized by the kidney.Consequently, for a stable concentration of inulin in the plasma,the amount of filtered inulin by the glomerulus is equal to the amount excreted in the urine. However, this technique requires a continuous intravenous infusion and timed urine collections over a period of several hours. This technique is time consuming, costly and potentially invasive if bladder catheterization has to be done for urine collection. Other techniques using markers such as synthetic inulin-like polyfructosans, radiolabeled compounds (51Cr-EDTA, 99mTc-DPTA and 125I-iothalamate)or non-radioactive agents (iohexol or iothalamate) have been proposed. The main advantage of these markers is a single-injection with measurement of GFR based on the total area under the curve of the plasma concentration of the marker. Time collection of urine samples is not needed. The use of radiolabeled compounds is limited by exposure to radiation and costs. Contrast

agents seem to be safer even though rare allergic events have been reported. None of these alternative techniques have been specifically validated in cirrhosis. However, since markers are exogenous and only eliminated by the kidney, it can be assumed that their accuracy is similar to that of inulin clearance.

Measurements using iohexol or iothalamate can be recommended. However, these techniques which are technically demanding and costly can hardly be repeated at close intervals.

Cystatin C and other markers

Recently, it has been shown that serum cystatin C, another endogenous marker, could represent an interesting alternative to serum creatinine. Cystatin C is a low molecular weight protein produced at a constant rate by all nucleated cells and eliminated almost exclusively by glomerular filtration.After filtration, cystatin C is reabsorbed and catabolized by the tubular epithelial cells. Consequently, urinary clearance cannot be measured. In contrast to creatinine, serum cystatin C is independent of gender, age and muscle mass. The dosage is not influenced by serum bilirubin, inflammation or malignancy. A recent meta-analysis has shown that, in non-cirrhotic patients, cystatin C is better correlated with GFR than creatinine.[79]Interestingly, it has been shown that the sensitivity of cystatin C for the diagnosis of impaired renal function, with a cut-off value of 1.25 mg/dl, is similar in cirrhotic patients and in non-cirrhotic patients. Several small studies have suggested that, after kidney or liver transplantation, serum cystatin C could be useful to monitor renal function. Finally, several equations using serum cystatinC have been proposed to estimate GFR. Although serum cystatin C is easy to obtain routinely, it has several limitations. Firstly, the cost of the assay is significantly higher compared to serum creatinine.

Secondly, the assays need further standardization. Thirdly, serum cystatin C is influenced by infection and by some drugs such as corticosteroids, angiotensin-converting enzyme inhibitors or calcineurin inhibitors (CNI). It has been suggested that cystatin C could be a marker of progression of liver fibrosis. This could represent a potential bias for the assessment of renal function in cirrhotic patients. However, there is no evidence that the increase in cystatin C in patients with fibrosis is not correlated to changes in renal function.[80]

Apart from cystatin C, other biomarkers, such as b2 microglobulin or b–trace protein have been proposed. They do not seem to be accurate enough for estimating renal function.[71]

Renal Doppler ultrasonography

Hepatorenal syndrome (HRS) is characterized by renal vasoconstriction. Renal vasoconstriction has been documented in several series of cirrhotic patients by Doppler ultrasound (US) analysis of renal arteries, showing increased resistive index (RI). RI is determined from the spectral waveforms and corresponds to the following formula: (peak systolic frequency shift – lowest diastolic frequency shift)/peak systolic frequency shift.

On average, renal RI is higher in cirrhotic patients compared to healthy individuals and high RI (over 0.7) can be observed in cirrhotic patients with serum creatinine within the normal range.[81] In patients without refractory ascites, RI decreases from the hilum towards the outer parenchyma, suggesting that the flow to the cortex is relatively preserved. In contrast, in patients with refractory ascites, RI is also increased in the cortical vessels suggesting cortical vasoconstriction. Paracentesis and albumin infusion are followed by a significant decrease in renal RI. Liver

transplantation is also followed by a decrease in RI.[82]In patients with normal serum creatinine, increased RI seems to be correlated with a higher risk of subsequent deterioration in renal function.[45] Therefore, Doppler ultrasound may be an early marker of renal dysfunction. In candidates for transplantation, high renal RI is associated with a greater risk of renal dysfunction and dialysis post-transplantation. However, in cirrhotic patients with impaired renal function, whether high RI predicts complete recovery is unclear.

Overall, Doppler US may be useful for identifying patients at high risk for developing impaired renal function at an early stage. It may be useful for clarifying the mechanisms involved in renal insufficiency. It may help clarify the role of therapeutic intervention on renal hemodynamics. However, RI is not correlated to GFR. In addition, there is no evidence that Doppler US helps differentiate cirrhotic patients with impaired renal function only related to vasoconstriction from patients who have both vasoconstriction and intrinsic" kidney damage.

Current diagnostic criteria of AKI and HRS-AKI in patients with cirrhosis

AKI in cirrhosis is "defined as an acute increase in serum creatinine of ≥ 0.3 mg/dL within 48 hours or by ≥ 50% from a stable baseline serum creatinine (sCr) within 3 months (presumed to have developed within the past 7 days when no prior readings are available).[45] The main modifications over the former, rather stringent criteria that were based on absolute serum creatinine level, was abandoning the arbitrary threshold of sCr ≥1.5 mg/dL to diagnose AKI, since milder degrees of renal failure in patients with cirrhosis had often remained under diagnosed. In addition, the use of urine output as part of the diagnostic criteria was eliminated, since many patients with cirrhosis and ascites maintain a preserved renal function despite being oliguric due to sodium and water retention.

AKI can be classified into three stages according to severity. Stage 1 AKI is defined by rather small changes in sCr, while stages 2 and 3 AKI are defined" by a two-fold and three-fold increase in sCr, respectively.

TABLE 5:ACUTE KIDNEY INJURY (AKI) STAGES ACCORDING TO THE INTERNATIONAL CLUB OF ASCITES (ICA) CRITERIA

ICA-AKI Stage 1	Increase in serum creatinine ≥0.3 mg/dl or
	Increase in serum creatinine by ≥ 50–100% from baseline
ICA-AKI Stage 2	Increase in serum creatinine by ≥ 100–200% from baseline
ICA-AKI Stage 3	Increase in serum creatinine by ≥ 200% from baseline or
	Increase in serum creatinine to ≥ 4 mg/dL with an acute increase by ≥ 0.3 mg/dL or
	Need for renal replacement therapy

Several clinical studies have evaluated the prognostic value of the "AKIN/KDIGO criteria that constitute the basis for the International Club of Ascites (ICA)-AKI criteria in patients with cirrhosis.[83] Similarly to the ICA-AKI criteria, most of these studies diagnosed AKI solely on sCr. In 2013, one study group developed a modified, AKIN-derived score for cirrhosis, by splitting AKI stage 1 into two groups depending on whether or not sCr surpassed the (former) threshold of 1.5 mg/dL (stages "B' and "A", respectively), and by merging AKI stages 2 and 3 into stage "C'; however, this re-classification did not gain wide acceptance [46,48,49]. Since their publication in 2015, the newer and cirrhosis-specific ICA criteria have been assessed within one

retrospective study in hospitalized patients with cirrhosis. Within this study, approximately 40% of patients experienced AKI during their hospitalization with the majority of cases having been diagnosed at stage 1. Also, in patients with AKI stage 1 and a sCr of < 1.5 mg/dL already a 3.5-fold increase in 30-day mortality as compared to patients without AKI was reported",[84] again underlining the prognostic importance of even small increases in sCr levels.

HRS type of AKI (HRS-AKI, formerly known as type 1 HRS)

The "hepatorenal syndrome type of AKI (HRS-AKI) is defined as ≥ stage 2 ICA-AKI that is diagnosed after other causes of renal failure have been ruled out.[45]The proper diagnosis of HRS-AKI further requires the fulfillment of several specific diagnostic criteria".

TABLE 6: Diagnostic criteria for hepatorenal syndrome

Presence of cirrhosis and ascites
No improvement in serum creatinine after 2 consecutive days of withdrawal of diuretics and plasma volume expansion with albumin (1 g per kg of body weight, maximum 100 g/day)
Absence of shock
Exclusion of recurrent or recent use of nephrotoxic agents (e.g. NSAIDs, aminoglycosides, contrast media)
Exclusion of parenchymal kidney disease: absence of proteinuria (>500 mg/day) absence of microhematuria (>50 RBCs per high-power field) normal renal ultrasonography

Based on reference. NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.

"Recent guidelines, in particular the Guidelines of the American Association for the Study of the Liver (AASLD) and the European Association for the Study of Liver Diseases (EASL) Clinical Practice Guidelines for ascites and hepatorenal syndrome, still proclaim the threshold of 2.5 mg/dL for diagnosing HRS-AKI. However, using this threshold in clinical practice would mean that proper diagnosis and treatment of HRS would be withheld as long as sCr does not reach this threshold. In order to prevent misclassification or even treatment delay, the newer ICA criteria focus on the relative increase in creatinine rather than absolute values, since also smaller rises in SCr (e.g. in case of stage 1 AKI) have been shown to have a negative prognostic impact in patients with cirrhosis".

From a clinical perspective, "HRS-AKI is characterized by a rapid increase in sCR and progressive oliguria in the absence of other identifiable causes of AKI such as hypovolemia, shock, parenchymal renal diseases, urinary tract obstruction and presence of nephrotoxins. In contrast to other forms of prerenal AKI, renal function in HRS-AKI does not improve by withdrawal of diuretics and plasma expansion using i.v. albumin. It can develop spontaneously or be triggered by a precipitating event that causes deterioration of the systemic circulation, most prominently bacterial infections such as spontaneous bacterial peritonitis or variceal bleeding. Concordantly, it has been shown that non-selective beta-blockers might also trigger HRS-AKI due to their impact on the systemic circulation".[85]

Hepatorenal syndrome type 2 (hepatorenal syndrome type of chronic kidney disease)

Type 2 HRS is "characterized by a stable or slowly progressive impairment in renal function in patients with decompensated liver disease who suffer from refractory ascites. Patients usually develop oliguria over a course of several weeks or months, marked by excessive salt and water retention and a slow but steady incline in renal retention parameters. Apart from the time of development, the same specific diagnostic criteria for HRS-AKI also apply for HRS type 2.

Type 2 HRS has been classified as a form of chronic kidney disease (CKD) in patients with cirrhosis, and (hepatorenal syndrome-type of chronic kidney disease, HRS-CKD). However, type 2 HRS or HRS-CKD is challenging to diagnose in clinical practice, as it is a diagnosis by exclusion, yet patients with liver cirrhosis often present with one or several other potential causes for kidney disease. However, according to the ADQI group, CKD due to other causes may develop on top of HRS type 2.[23] As a result, only a few studies have been published on type 2 HRS and data vary substantially. For instance, the reported prevalence among patients with HRS ranges from 16% to 61%. In general, prognosis in HRS type 2 is poor, but more favorable when compared to AKI-HRS.

Pitfalls in the diagnosis of AKI and HRS

Although sCr is an easily measurable and widely available marker of excretory renal function, it has limitations in assessing glomerular filtration rate (GFR) in patients with cirrhosis. Creatinine is non-enzymatically converted from creatinine, which is produced by the liver and stored in muscle cells, and eliminated via glomerular

filtration.[86] Due to impairment in liver function, muscle wasting, decreased creatinine synthesis and increased tubular secretion of creatinine at advanced stages of cirrhosis, baseline creatinine production is lower in patients with cirrhosis compared to the non-cirrhotic population, thus sCr-based equations (i.e. Modification of Diet in Renal Disease, MDRD; Chronic Kidney Disease Epidemiology Collaboration formula, CKD-EPI) tend to overestimate GFR in cirrhosis.

Nonetheless, due to its wide applicability, the MDRD-6 formula has been recommended to estimate GFR in patients with cirrhosis until better alternatives become available in clinical routines.

GFR estimates using CysC, a non-glycosylated low-molecular-weight protein of the cystatin superfamiliy of cysteine protease inhibitors, have been proposed to be superior predictors of renal function than sCr-based equations. Unlike sCr, CysC is not influenced by age, muscle mass, the presence of high bilirubin or malignancy. Measurement of CysC has, however, been reported to be influenced by factors such as low serum albumin levels, elevated white blood cell count and elevated C-reactive protein levels. These abnormalities are frequently present and are thus likely to impair the reliability of cystatin C-based equations in cirrhosis.[87] Several studies have shown that equations combining sCr and CysC predict glomerular filtration more accurately than those using sCr or CysC alone" (i.e. the CKD-EPI equation combining sCr and CysC).

Pathophysiology of the hepatorenal syndrome

The understanding of the various "pathophysiological pathomechanissm of renal dysfunction in cirrhosis has drastically evolved over the past few years and decades. Impairment of renal function in cirrhosis may occur within a wide spectrum of

diseases, some related to abnormalities in renal function, others related to renal damage. Although being widely accepted for many years in clinical practice, the term HRS certainly does not reflect the whole spectrum of renal dysfunction in cirrhosis, but rather refers to a specific form with a unique pathophysiology.

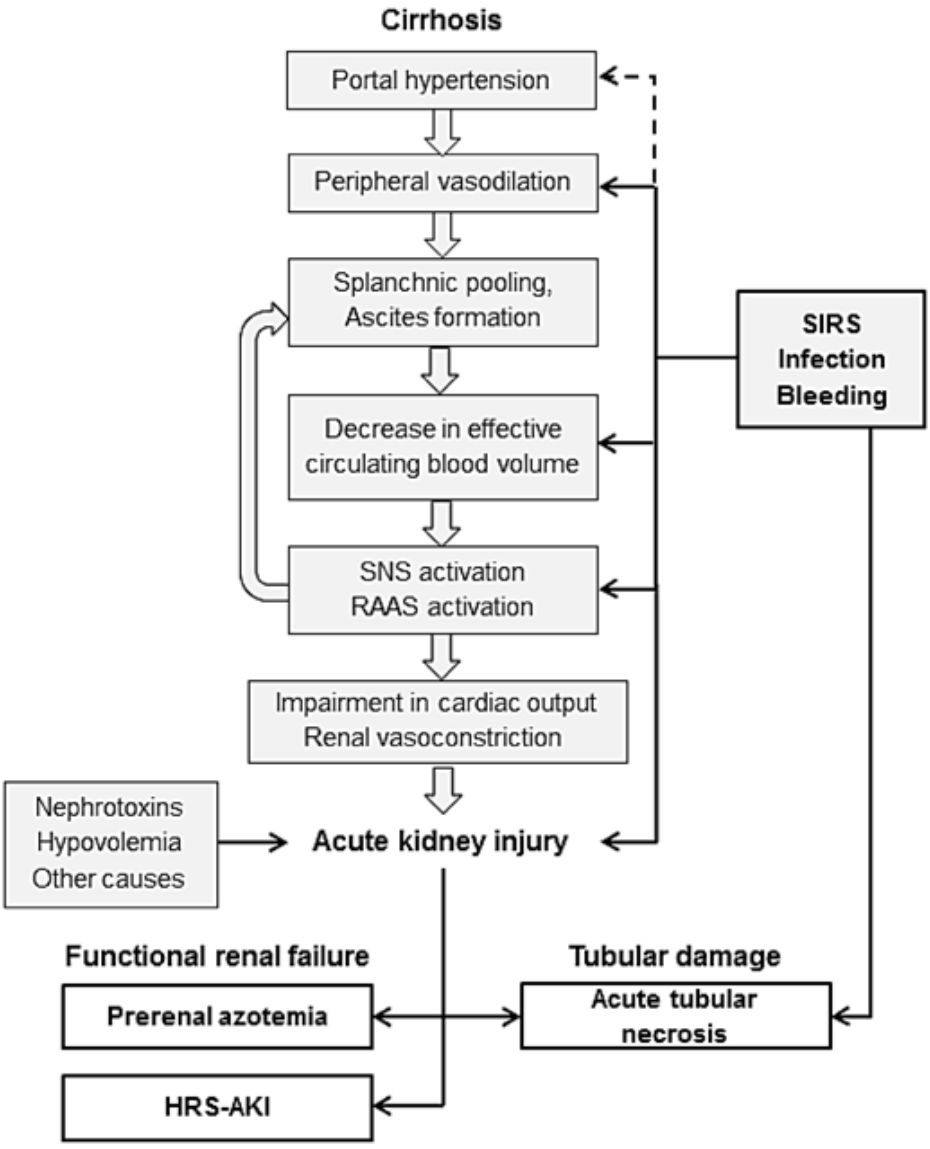


FIGURE 8: Pathophysiology of acute kidney injury (AKI) and hepatorenal syndrome (HRS) in decompensated cirrhosis. Broad arrows: vasodilation theory of ascites formation. Black arrows: 'inflammation theory' and further aspects of AKI development. Dashed line: impact of infections (i.e. spontaneous bacterial peritonitis) on portal hypertension. SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; SIRS, systemic inflammatory response syndrome; HRS-AKI, hepatorenal syndrome type of acute kidney injury.

HRS-AKI—the 'classical vasodilation theory'

The development of HRS-AKI is supposedly caused by intra-renal vasoconstriction due to circulatory dysfunction in decompensated cirrhosis. Indeed, the pathophysiology of HRS is closely linked to the development of ascites, which is considered a prerequisite for the development of HRS. In 1988, Schrier and colleagues proposed the peripheral arterial vasodilation hypothesis for ascites. According to this hypothesis, due to structural changes in the fibrotic tissue, intrahepatic vascular resistance is increased, causing portal hypertension and an overexpression of compensatory vasodilating factors.[88]The vasodilating factors accumulate in the splanchnic area and, in later stages, in the systemic circulation. This causes a pooling effect in the splanchnic vessels, leading to increased shear-wall stress and transudation of plasma into the abdominal cavity causing ascites. As a consequence, effective circulating blood volume and mean arterial pressure are decreased. This activates the sympathetic nervous system, initiating a hyperdynamic circulation, but also stimulating the renin-angiotensin-aldosterone system (RAAS). Excessive RAAS activation promotes water and sodium retention, thereby aggravating ascites formation via aldosterone and high levels of angiotensin II induce renal vasoconstriction.[89] In situations of hemodynamic stress such as in case of volume loss (e.g. due to diuretics, dehydration or gastrointestinal bleeding) or bacterial infections, RAAS activation and circulatory dysfunction may reach a point at which renal function can no longer be maintained and HRS-AKI ensues.

HRS-AKI as part of a multiorgan failure syndrome/systemic inflammatory response syndrome (SIRS) - a new hypothesis

There is increasing evidence that systemic inflammation also plays an important role in the development of complications of portal hypertension in cirrhosis. Until 2007,

sepsis was an exclusion criterion for HRS. However, in cirrhosis, renal dysfunction often develops secondarily to bacterial infections. SIRS and sepsis supposedly lead to renal blood flow redistribution, resulting in ischemia and subsequent tubular injury.

Toll-like receptor 4 (TLR4) is the main pattern-recognition receptor in the detection of inflammatory signals that has been identified to play an important role in the development of HRS-AKI in experimental models of cirrhosis. TLR4 is over expressed in kidney tissue and urine in patients with cirrhosis and AKI (including HRS-AKI patients) following an inflammatory insult. Endotoxins or lipopolysaccharides (LPS) are particles of the cell wall of Gram-negative bacteria and represent natural ligands to TLR4. LPS are strong pro-inflammatory factors by inducing TNF-α.[90]In cirrhosis, high levels of LPS (e.g. in case of spontaneous bacterial peritonitis [SBP] or sepsis) increase portal pressure and may induce hepatocyte death—thereby promoting hepatic decompensation. This may eventually lead to deterioration of the systemic circulation, shock and multiorgan failure, including HRS-AKI. Indeed, SBP and sepsis represent the most common precipitating events for HRS-AKI. Recent studies on terlipressin for treatment of HRS-AKI showed similar outcomes of patients with sepsis and SIRS-induced HRS-AKI treated with terlipressin, which indicates similarities in pathophysiology between patients with and without infections as triggers.

Besides cirrhosis, HRS-like AKI may also develop in acute settings, (i.e. acute or acute-on-chronic liver failure or steatohepatitis) due to excess liberation of pro-inflammatory cytokines or chemokines. These acute situations may also induce renal tubular damage due to upregulation of inflammatory mediators, chemokines and

cytokines that may directly cause renal damage and further induce circulatory dysfunction and worsening of systemic vasodilatation (Acute tubular necrosis, ATN). As a result, in contrast to HRS-AKI as functional renal failure, ATN may not respond to vasoconstrictor therapy.[91]

Structural changes in HRS-AKI

There is increasing evidence for structural renal changes at least in a subgroup of patients with end-stage liver diseases. Patients with cirrhosis and impaired renal function were reported to show glomerular, vascular and tubulo-interstitial pathologies even in the absence of proteinuria and hematuria. Patients with cirrhosis might suffer from specific renal pathologies associated with liver diseases such as IgA nephropathy in alcoholic cirrhosis or cryoglobulinemia in hepatitis C or other, non-cirrhosis-specific nephropathies (e.g. diabetic nephropathy). These renal pathologies should be screened for and treated adequately.

An important differential diagnosis for HRS-AKI is ATN. Next to pre-renal azotemia including HRS-AKI, ATN is the most common cause of AKI in cirrhosis. ATN is mainly caused by ischemic damage to the tubules following a hypotensive event, such as variceal bleeding or sepsis. Clinical presentation of ATN is often very similar to HRS and routine biomarkers are often unable to properly discriminate between these entities, especially in cirrhosis. Its prognosis is comparable to that of HRS-AKI.[92]

Management of AKI and specific treatment for HRS-AKI

Management of AKI in cirrhosis

The initial management of AKI should focus on early recognition and correction of potential trigger events and on preventing further hemodynamic deterioration. This includes careful review of all medications including over-the-counter drugs and

nephrotoxic agents (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]) need to be withdrawn. The use of drugs that may induce or aggravate arterial hypotension (e.g. vasodilators or non-selective beta-blockers [NSBBs]) should be carefully evaluated. In volume-depleted patients, diuretic therapy and/or lactulose should be withdrawn and plasma volume should be expanded with albumin, or blood transfusions in anemic patients due to gastrointestinal blood loss.

Since bacterial infections are the most common precipitant of AKI in cirrhosis, patients should be thoroughly screened for (e.g. by performing diagnostic paracentesis to rule in/out SBP). Early emperical antibiotic treatment should be initiated already on clinical suspicion and be based on local epidemiology and resistance patterns.[93]

In case of therapeutic response, which is defined as a decrease of sCr to a value within 0.3 mg/dL of baseline, patients should be followed closely for early detection of recurrent episodes of AKI. Follow-up assessment of sCr every 2–4 days during hospitalization and every 2–4weeks during the first 6 months after discharge is advised.

In case of stage 2 or 3 or progression to a higher AKI stage, patients need to be assessed for the presence of HRS-AKI and diuretics should be withdrawn immediately.[45] In addition, patients should receive plasma volume expansion with albumin for 2 consecutive days (1g per kg of body weight, maximum 100g/day).[45] Albumin is particularly beneficial in patients with SIRS or sepsis, since it has scavenging, anti-oxidant and endothelial-stabilizing functions in addition to its volume-expanding effect.[91]

Management of HRS-AKI and HRS type 2

Patients with AKI stages 2 and 3 who meet diagnostic criteria of HRS-AKI should be treated with vasoconstrictors (i.e. terlipressin, norepinephrine or midodrine plus octreotide) in combination with i.v. albumin.[45] Albumin should be administered initially with 1 g/kg body weight up to 100 g on the first day, then ongoing with 20–40 g/day, as it has been shown that the effects of i.v. albumin in the prevention and treatment of HRS are dose-dependent, with better results when higher cumulative doses were administered[98,99]. For prevention of HRS-AKI and HRS type 2, albumin should be administered in all large-volume paracenteses (>5 L, with 8 g/L of ascites removed), since it prevents post-paracentesis circulatory dysfunction, reduces the risk of renal dysfunction and might even improve survival.[94]

The vasopressin analogue terlipressin is the most intensively studied vasoconstrictor for the treatment of HRS-AKI and therefore commonly used in Europe. A bolus of terlipressin induces a statistically significant reduction in portal pressure over a 3- to 4-hour period and also increases mean arterial pressure. Terlipressin should be used with caution in patients with cardiovascular disease, since it may induce ischemia. Patients should be monitored for hyponatremia, which more commonly occurs in less advanced liver disease and (near-) normal baseline serum sodium levels. A recent study demonstrated fewer adverse events and lower total doses with equal efficacy by administering terlipressin via continuous intravenous infusion. Considering the costs and the pharmacodynamic profile of terlipressin, continuous infusion might be preferred over bolus administration. Although terlipressin has been consistently shown to improve renal function, its impact on survival is less clear.[95] Terlipressin is particularly beneficial in patients with SIRS or sepsis and might also prevent variceal bleeding during the period of discontinuation of NSBBs.

Norepinephrine (initial dose: 0.5 mg/hour; max. dose studied in randomized controlled trials: 3 mg/hour) is an equally effective and inexpensive alternative to terlipressin. A recent meta-analysis of four randomized–controlled trials (although at substantial risk of bias) demonstrated similar efficacy in terms of HRS reversal, when compared to terlipressin. The suggested therapy for type 2 HRS is similar; however, HRS type 2 commonly recurs after cessation of vasoconstrictor treatment.[96]

Complete response is defined by a decrease in sCr to a value within 0.3 mg/dL of baseline, while a regression of at least one AKI stage is considered as partial response.[45]If there is no response after 3 days of treatment, the vasoconstrictor dose should be increased. In non-responders, treatment should be discontinued after 14 days. In responders, longer treatment durations can be used as a bridging therapy to liver transplantation.

Due to poor prognosis, patients with HRS-AKI or HRS type 2 should be evaluated for liver transplantation as soon as possible. The insertion of a transjugular intrahepatic portosystemic shunt (TIPS) may represent a good bridging strategy to liver transplantation—especially in patients with HRS type 2. The TIPS improves both renal function and survival in patients with severe/refractory ascites most commonly associated with HRS type 2. Absolute contraindications for TIPS comprise cardiac insufficiency, pulmonary hypertension, uncontrolled systemic infections (this underlines the need to screen for SBP prior to TIPS) or sepsis and biliary obstruction, as well as anatomical abnormalities preventing TIPS implantation. Since liver dysfunction may deteriorate after TIPS, serum bilirubin >5 mg/dL and recurring spontaneous hepatic encephalopathy (HE) episodes represent (relative)

contraindications against TIPS for treatment of refractory ascites. Caution should generally be applied in patients with high MELD scores who may not benefit from TIPS implantation.[97]

Randomized–controlled trials have failed to demonstrate a survival benefit of renal replacement therapy (RRT) or extracorporeal liver support (ELS) for HRS-AKI and HRS type 2. Continuous RRT use may, however, be advantageous in patients who are hemodynamically unstable or at risk of elevated intracranial pressure. RRT and ELS should thus be restricted to patients who are eligible for liver transplantation. Combined liver and kidney transplantation should be considered in patients on RRT for more than 12 weeks.[98]

Future Perspectives

Novel urinary biomarkers are currently being explored for improved AKI diagnosis and will likely help in daily clinical practice to differentiate between the various forms of renal dysfunction in cirrhosis. The most frequently studied biomarker of renal dysfunction in cirrhosis is urinary neutrophil gelatinase-associated lipocalin (uNGAL). uNGAL is a urinary biomarker for tubular damage that facilitates the differentiation between functional and structural causes of renal failure in cirrhosis. Throughout the various studies, uNGAL levels correlated with renal damage. As such, uNGAL levels were high in patients with ATN and low in patients with prerenal azotemia, with levels in HRS-AKI in the intermediate range, helping to distinguish between the different entities of AKI in patients with cirrhosis. Besides uNGAL, other biomarkers such as interleukin 18 (IL-18), kidney injury molecule-1 (Kim-1) and liver-type fatty-acid binding protein were studied in patients with cirrhosis. In summary, all biomarkers for tubular damage were significantly increased in ATN as

compared non-ATN AKI to varying degrees. Similarly to uNGAL, IL18 as a mediator of inflammation is expressed in renal tubular cells and macrophages, and released into the urine in case of tubular injury. As a consequence, urinary levels are significantly higher in ATN than in HRS-AKI, where, due to the inherent inflammatory state, levels are still above those measured in pre-renal AKI or in patients without renal failure.[99]

At the moment, urinary biomarkers are still mainly tools for research purposes, as their costs are high, biochemical assays have not yet been introduced into standard laboratory testing and applicability in clinical practice is still unclear. Although study results appear promising, it is debatable whether or not the new biomarkers will find their way into routine examinations. Until then, physicians will have to rely on careful assessment of renal failure in order to correctly classify AKI.

To summarise, patients with cirrhosis are prone to developing AKI. The new ICA-AKI criteria provide a simple, but prognostically relevant staging system for AKI in cirrhosis based on relative increases in sCr. Potential triggers of AKI should be recognized and removed; this includes discontinuation of diuretics and nephrotoxic drugs, treatment of infections and gastrointestinal bleeding, and plasma expansion in case of hypovolemia. Vasopressors such as terlipressin and norepinephrine in combination with intravenous albumin represent the first-line therapy for HRS-AKI. While RRT does not improve outcome of patients with HRS-AKI, liver transplantation is considered an effective cure for HRS. Differential diagnosis of HRS-AKI from other forms of AKI, such as ATN, is often difficult. Specific biomarkers such as NGAL, KIM-1 or IL-18 may aid in the correct diagnosis of AKI in cirrhosis" but have not yet been introduced into clinical routine.

Chronic liver disease is associated with "primary and secondary kidney disease and impacts markedly on survival. The evaluation of kidney function and injury relies on the measurement of the concentration of serum creatinine, which is affected by the degree of liver disease and the analytical method employed. The integral role of creatinine concentration in the different classifications of AKI, chronic kidney disease and the survival predictive score, MELD, for chronic liver disease, confers large inaccuracies across this population, but currently offers the most cost-effective measure available. Hepatologists should perhaps use exogenous measures of kidney function and biomarkers, like cystatin C and the cystatin C-based equation for estimated GFR, more frequently, as these have been shown to be superior to creatinine. Improved assessment of the degree of residual kidney function may assist clinical decisions regarding risk of AKI, drug therapy in chronic liver disease, the tailoring of post-liver transplant immunosuppression regimens, and the allocation of organs for combined liver and kidney transplantation. Kidney injury biomarkers need further evaluation in the chronic liver disease population, but they seem likely to continue to perform well. Earlier diagnosis and implementation of currently established beneficial therapies seems to be pivotal in potentially reducing the severity of kidney injury and increasing survival outcomes"; whether this will be realized remains to be seen.

Rognant N et al in 2014[100] summarised that "early diagnosis of both acute kidney injury and chronic kidney disease and to reliable characterization of the renal status of the patient before performing a liver transplantation. Despite some limitations, the assay of serum creatinine (SCr) is universally used to estimate glomerular filtration rate (GFR) because of its wide availability, its simplicity and because it is inexpensive. Nevertheless, several reports show that the value of this assay to estimate

GFR is strongly challenged in cirrhotic patients, especially in patients with liver failure and/or severely impaired renal function. This has led to seek new alternatives to estimate more reliably the GFR in these patients. Although the reference methods, based on the utilization of exogenous markers, allow measuring GFR and thereby constitute the "gold standard" to evaluate renal function, they are not feasible in routine clinical practice. Several studies have shown that a cystatin C (CysC) based formula perform better than the SCr-based estimates in cirrhotic patients and the estimation of GFR by these formulas could therefore lead to optimize the management of the patients. A new estimate based on CysC has been recently developed using a large number of patients and the first results regarding the evaluation of its performance are promising, making this new formula the best candidate for a reference estimate of the renal function" in cirrhotic patients.

Das N et al in 2015[101]in a cross-sectional, observational studyassessed "the renal function in chronic liver diseases and find out the association of alteration of renal function with gradation of liver disease. (assessed by child-pugh criteria) and to find out the association of alteration of renal function among the cases of chronic liver disease of different aetiology". The authors found "Eighty six percent of the patients were male and the mean age of study population was 43.58 y, 68% patients suffered from alcoholic liver disease, followed by 14% patients had chronic Hepatitis-B, 10% patients developed acute kidney injury, 20% had hepato renal syndrome and 14% had IgA deposition. The distribution of serum urea and creatinine across the categories of Child Pugh classification tested by Mann-Whitney test and the distribution was statistically significant. The authors concluded that significant association was observed between severity of liver dysfunction" and certain parameters of renal dysfunction.

Francoz C et al in 2016[102] summarised that when "CKD is suspected, clearance of exogenous markers is the reference to assess glomerular filtration rate, as creatinine is inaccurate and cystatin C needs further evaluation. Recent biomarkers may help differentiate ATN from hepatorenal syndrome. Neutrophil gelatinase-associated lipocalin has been the most extensively studied biomarker yet, however, there are no clear-cut values that differentiate each of these conditions. Studies comparing ATN and hepatorenal syndrome in cirrhosis, do not include a gold standard. Combinations of innovative biomarkers are attractive to identify patients justifying simultaneous liver and kidney transplantation. Accurate biomarkers of underlying CKD are lacking and kidney biopsy is often contraindicated in this population. Urinary micro RNAs are attractive although not definitely validated. Efforts should be made to develop biomarkers of kidney fibrosis, a common and irreversible feature of CKD", whatever the cause. Biomarkers of maladaptative repair leading to irreversible changes and CKD after AKI are also promising.

Tsung-Hsing H et al in 2016[103] in aA "Nationwide Population-Based 3-Year Follow-up Study identified 44365 cirrhotic patients. RFI was identified in 2832 cirrhotic patients, including 1075 with acute renal failure (ARF) (169 with hepatorenal syndrome, HRS; 906 with non-hepatorenal syndrome, NHRS), 705 with chronic kidney disease (CKD), and 1052 with end stage renal disease (ESRD). After Cox proportional hazard regression analysis adjusted by gender, age, and comorbid disorders, the 30-day, 30 to 90-day, 90-day to 1-year, and 1 to 3-year mortality hazard ratios (HR) compared to the non-RFI group were: (ARF) 5.19 (4.70–5.74), 3.23 (2.76–3.77), 1.51 (1.26–1.81), and 1.35 (1.13–1.61), respectively; (CKD) 2.70 (2.30–3.18), 2.03 (1.66–2.49), 1.60 (1.34–1.90), and 1.26 (1.06–1.49), respectively; and (ESRD) 1.42 (1.17–1.72), 1.62 (1.35–1.94), 1.90 (1.68–2.15), and 1.67 (1.48–1.89),

respectively. Compared to NHRS, the 30-day, 30 to 90-day, 90-day to 1-year, and 1 to 3-year mortality HRs of HRS were 1.03 (0.80–1.32), 2.13 (1.46–3.11), 1.58 (0.90–2.75), and 2.51 (1.41–4.48), respectively, in cirrhotic patients with ARF. The authors concluded that the effects of CKD and ESRD on the mortality of cirrhotic patients are distributed equally in every survival stage, whereas the effect of ARF appears" only in the early stage. Compared to NHRS, HRS contributes to a higher mortality risk at the late survival stage.

Bucsics T et al in 2017[104] summarised that Renal dysfunction is a common complication of liver cirrhosis and of utmost clinical and prognostic relevance. Patients with cirrhosis are more prone to developing acute kidney injury (AKI) than the non-cirrhotic population. Pre-renal AKI, the hepatorenal syndrome type of AKI (HRS-AKI, formerly known as 'type 1') and acute tubular necrosis represent the most common causes of AKI in cirrhosis. Correct differentiation is imperative, as treatment differs substantially. While pre-renal AKI usually responds well to plasma volume expansion, HRS-AKI and ATN require different specific approaches and are associated with substantial mortality. Several paradigms, such as the threshold of 2.5 mg/dL for diagnosis of HRS-AKI, have recently been abolished and novel urinary biomarkers are being investigated in order to facilitate early and correct diagnosis and treatment of HRS-AKI and other forms of AKI in patients with cirrhosis.

Zhou F et al in 2017[105] in a retrospective analysis assessed the "prognostic accuracy of absolute serum creatinine (sCr) changes ('Delta-sCr') on the long-term outcomes in cirrhotic patients, and evaluate the performance of the 'Delta-sCr' approach to stage acute kidney injury (AKI), compared with the Kidney Disease Improving Global Outcomes (KDIGO) criteria. The authors found prevalence of AKI in cirrhotic

patients was 18.01% by the KDIGO criteria, and 25.22% by the ‘Delta-sCr’ system. On multivariable Cox hazard analysis, both of the two methods were independent predictive factors of death (‘Delta-sCr’ system: OR=2.911,p<0.001), (KDIGO criteria: OR=2.065, p<0.001). However, the ‘Delta-sCr’ system provided a modest improvement in classification over the KDIGO criteria with a net reclassification improvement (NRI) of 28.7% (p<0.001) and integrated discrimination improvement (IDI) of 7.5% (p=0.03). And the predictive value of the ‘Delta-sCr’ system could be significantly improved (p=0.006), when combined with age and MELD score. The authors concluded that Delta-sCr is associated” with the 1-year mortality. And the ‘Delta-sCr’ system may optimize the discrimination of risk prediction.

ABBREVIATION: ACE: angiotensin converting enzyme; ADQI: Acute Dialysis Quality Initiative; AKI: acute kidney injury; AKIN: Acute Kidney Injury Network; ATN: acute tubular necrosis; AUC: area under the curve; CKD: chronic kidney disease; CVVH: continuous veno-venous hemofiltration; GFR: glomerular filtration rate; HBV: hepatitis B virus; ICU: intensive care unit; IL: interleukin; KIM-1: urinary kidney injury molecule-1; KDOQI: Kidney Disease Outcome Quality Initiative; MDRD: Modification of Diet in Renal Disease; MELD: model for end stage liver disease; NGAL: neutrophil gelatinase lipocalin; NO: nitric oxide; OLT: orthotopic liver transplantation; RAA: renin-angiotensin-aldosterone; RIFLE: Risk; Injury; Failure; Loss; End-stage renal disease; sNGAL: serum neutrophil gelatinase lipocalin; UTI: urinary tract infection.

MATERIAL AND METHODS

A prospective cross sectional study was conducted among 65 patients to evaluate the assessment of renal function in chronic liver disease.

SOURCE OF DATA

Patients admitted in the medicine ICU/WARDS OF BLDE (Deemed to be University) Shri. B. M. Patil Medical College and Research Centre, Vijayapur and who fulfilled the inclusion criteria.

Patients attending the medicine OPD/ executive health check-up schemes who fulfilled the inclusion criteria

Study Duration:

November 2016 to August 2018.

Types of study:A Prospective cross sectional study

Sample size: 65 Patients

Sample size was calculated using the formula:

$$n= [z^2p(1-p)]/d^2$$

Where: Z = z statistic at 5% level of significance (0.95)

p = expected prevalence rate = 70%

d = margin of error = 5.5%

$$n= [0.95 \times 0.95 \times 0.7 (0.3)] / 0.055 \times 0.55 = 62.6$$

A sample size of 65 subjects will allow the study to assess the renal function in CLD with a confidence interval of ±10% with finite population correction.

INCLUSION CRITERIA

- Patients with Liver disease of more than 6 months duration of different etiology like Viral (Hepatitis B, Hepatitis C),
- Alcoholic chronic liver disease, Non alcoholic steatohepatitis, and Autoimmune (Wilson's disease, cryptogenic).
- Age > 18 years
- Of both sex

EXCLUSION CRITERIA

- Diabetes Mellitus
- Hypertension
- Chronic kidney disease
- Patients taking any nephrotoxic drugs

METHODOLOGY

The data was collected according to Performa in terms of details history, clinical examination and necessary investigations of the patients who fulfilled the inclusion criteria.

Investigations or interventions required in this study were routine standard procedures. Investigations included:

1. CBC
2. LIVER FUNCTION TEST
3. USG/ELASTOGRAPHY
4. URINE ROUTINE AND MICROSCOPY
5. RENAL FUNCTION TEST
6. FBS PPBS
7. PT, INR
8. HbsAg
9. HCV

The study was conducted after obtaining necessary permission from institutional ethics committee. The schedule was designed after consultation with the experts of general medicine and pre testing was done in the general medicine outdoor among 10 patients of chronic liver disease, who came for follow up.

Informed written consent in vernacular was obtained from each patient before inclusion in the study. The consent form was also approved by the institutional ethics committee.

Patients were interviewed about duration of the disease, presence of alcoholism, presence of yellowish discoloration of urine, vomiting of blood and passage of black stool. General survey was done to assess presence of anemia, jaundice, clubbing and oedema. The patients were also examined for presence of ascitis, hepato-splenomegaly, distented veins, everted umbilicus, spider naevi, palmar erythema, gynaecomastia, testicular atrophy, and bleeding manifestation to assess the severity of liver dysfunction.

Biochemical examination like blood for hemoglobin, total count, differential count, ESR, and fasting and post prandial sugar was done. Laboratory investigations like total bilirubin with conjugated and un-conjugated fraction, Alanine amino transferase, Aspartate amino transferase, Alkaline Phosphatase, total protein, albumin ,globulin, prothrombin time, HbSAg, Anti nuclear antibody, Anti-Liver Kidney Microsomal antibodies 1, 2 & 3 were done. Ascitic fluid was examined to assess the aetiology and severity of chronic liver disease. For assessment of kidney function serum urea, creatinine, seum sodium and potassium were examined.

Radiographic examination like ultrasonography of upper abdomen and Kidney, Ureter, Bladder was done. Upper gastrointestinal endoscopy was done for detecting gastro-oesophagial varices, Routine and microscopic examination of urine, 24 h protein excretion and measurement of 24 h urine volume were also done.

STATISTICAL ANALYSIS

Quantitative data is presented with the help of Mean and Standard deviation. Qualitative data is presented with the help of frequency and percentage table. Association is assessed with the help of Fisher test, student 't' test and Chi-Square test. 'p' value less than 0.05 is taken as significant**.**

Pearson's chi-squared test

$$\mathrm{X}^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

Where X2 = Pearson's cumulative test statistic.

Oi = an observed frequency;

Ei = an expected frequency, asserted by the null hypothesis;

n = the number of cells in the table.

Results were graphically represented where deemed necessary.

Appropriate statistical software, including but not restricted to MS Excel, SPSS ver. 20 will be used for statistical analysis. Graphical representation will be done in MS Excel 2010.

OBSERVATIONS AND RESULTS

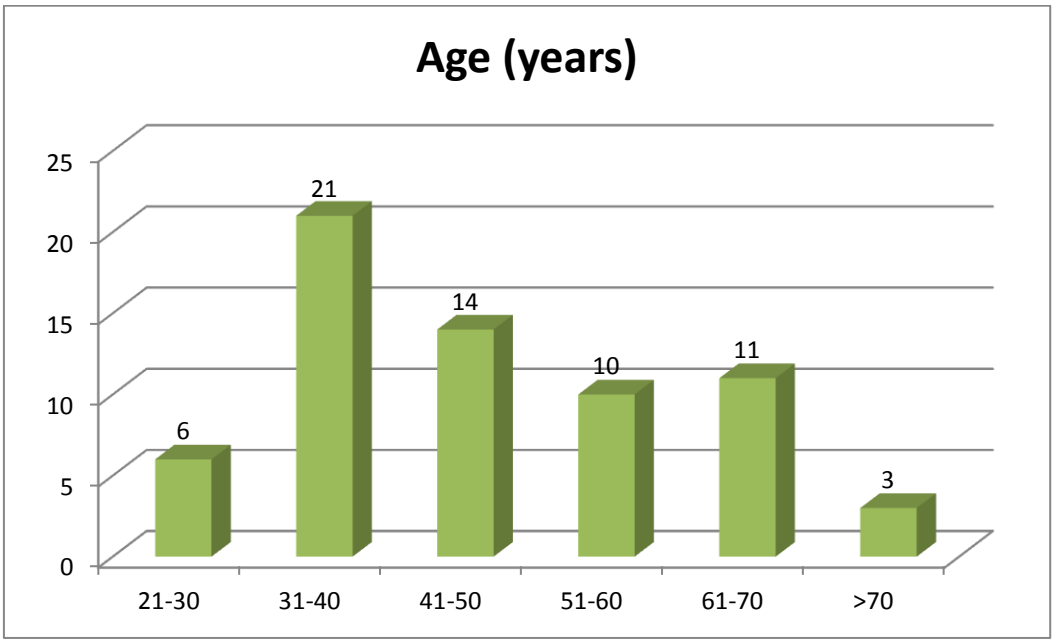
A prospective cross sectional study was conducted among 65 patients to evaluate the assessment of renal function in chronic liver disease.

Distribution of patients according to Age

Majority of the patients (32.4%) were in the age group of 31-40 years followed by 21.5% in the age group of 41-50 years, 16.9% in the age group of 61-70 years, 15.4% in the age group of 51-60 years, 9.2% patients in the age group of 21-30 years and 4.6% in the age group of >70 years. The mean age of the patients was 45.78 ± 13.19 years.

Table 7: Distribution of patients according to Age

Age	N	%
21-30	6	9.2%
31-40	21	32.4%
41-50	14	21.5%
51-60	10	15.4%
61-70	11	16.9%
>70	3	4.6%
Total	65	100%
Mean ± SD	45.78 ± 13.19	



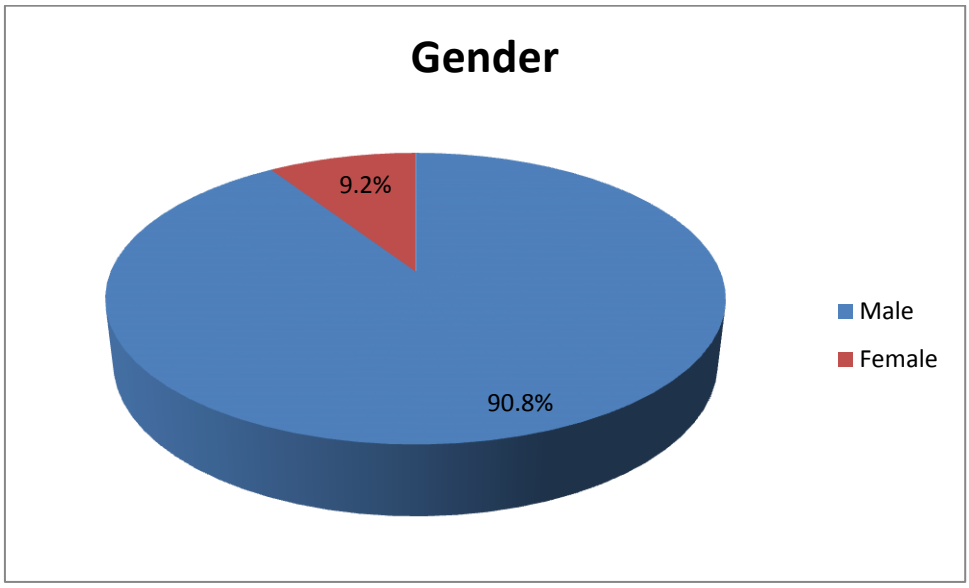
Graph 1 : Distribution of patients according to Age

Distribution of patients according to Gender

There was male preponderance (90.8%) whereas female patients constituted 9.2% of the study group.

Table 8: Distribution of patients according to Gender

Gender	N	%
Male	59	90.8%
Female	6	9.2%
Total	65	100%



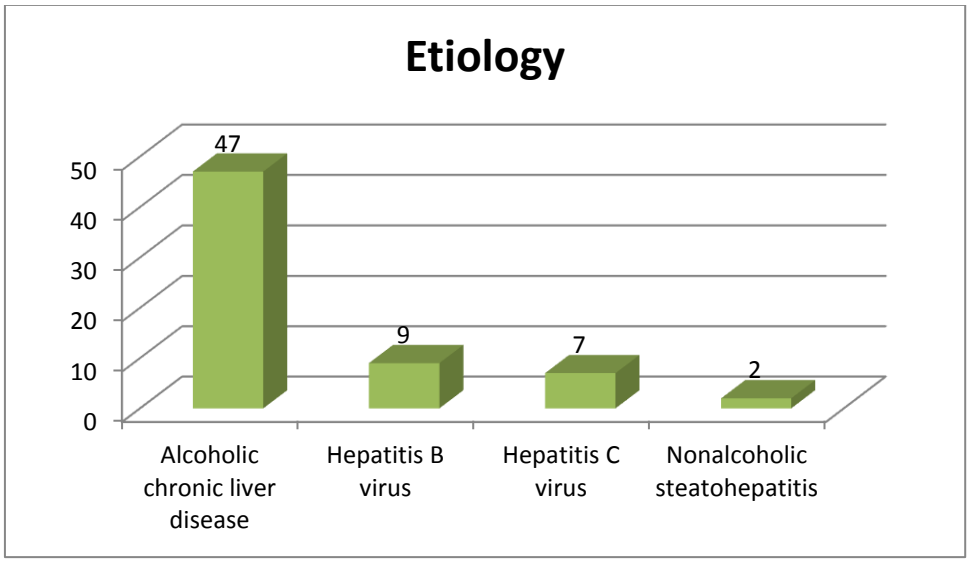
GRAPH 2: Distribution of patients according to Gender

Distribution of patients according to Etiology

47 (72.2%) patients suffered from Alcoholic liver disease while 9 (13.9%) and 7 (10.8%) patients had chronic Hepatitis-B and chronic Hepatitis-C respectively. 2 (3.1%) patients had Nonalcoholic steatohepatitis.

Table 9: Distribution of patients according to Etiology

Etiology	N	%
Alcoholic chronic liver disease	47	72.2%
Hepatitis B virus	9	13.9%
Hepatitis C virus	7	10.8%
Nonalcoholic steatohepatitis	2	3.1%
Total	65	100%



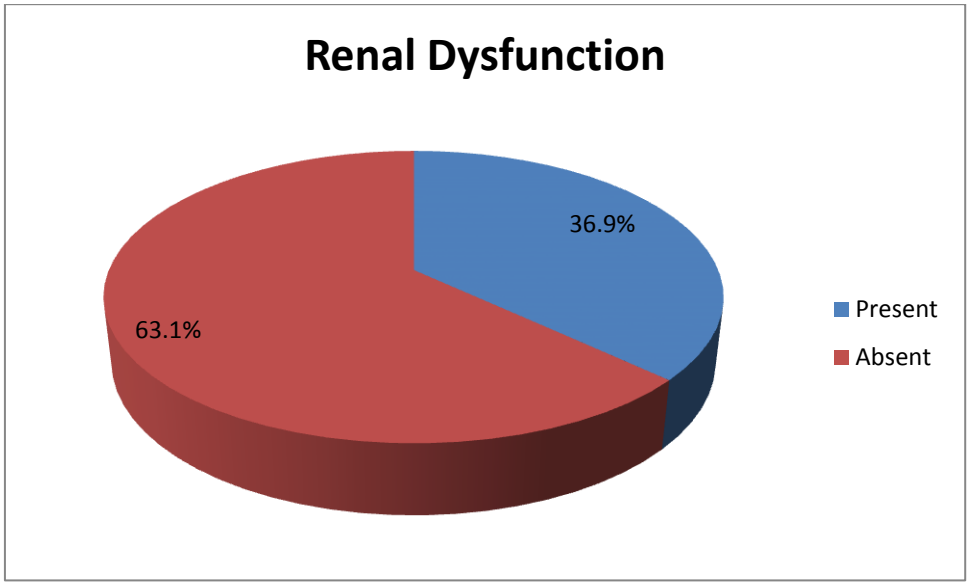
GRAPH 3 : Distribution of patients according to Etiology

Distribution of patients according to Renal Dysfunction

It was observed that 24 (36.9%) patients had renal dysfunction.

Table 10: Distribution of patients according to Renal Dysfunction

Renal Dysfunction	N	%
Present	24	36.9%
Absent	41	63.1%
Total	65	100%



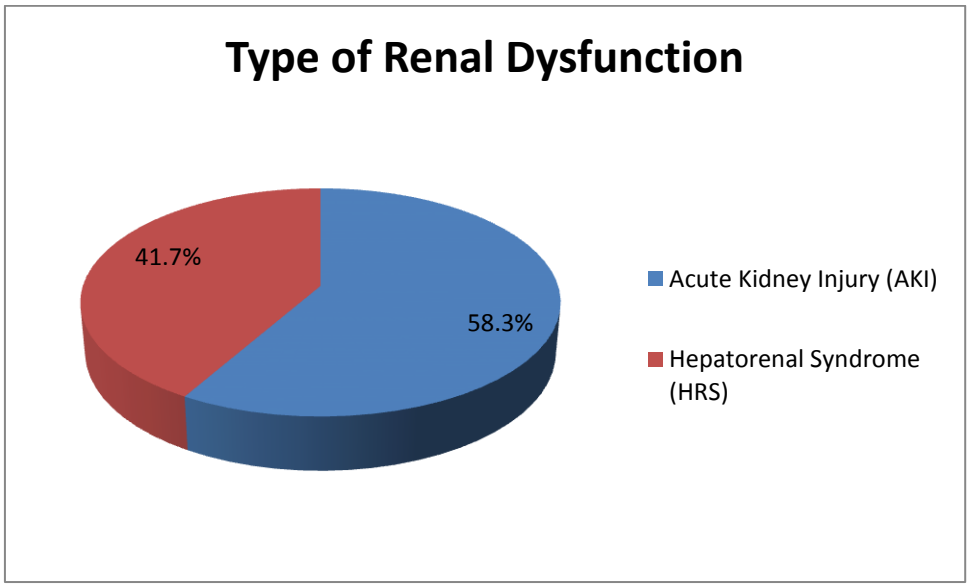
GRAPH 4 : Distribution of patients according to Renal Dysfunction

Distribution of patients according to Type of Renal Dysfunction (n=24)

The most common type of renal dysfunction was Acute Kidney Injury (58.3%) followed by Hepatorenal Syndrome (41.7%).

Table 11: Distribution of patients according to Type of Renal Dysfunction (n=24)

Type of Renal Dysfunction	N	%
Acute Kidney Injury (AKI)	14	58.3%
Hepatorenal Syndrome (HRS)	10	41.7%
Total	24	100%



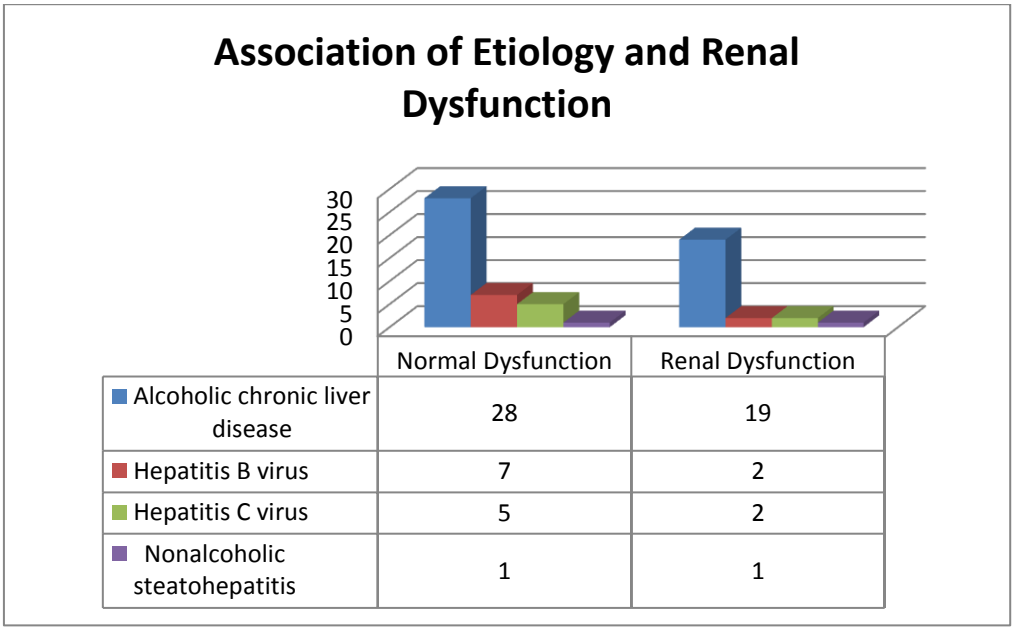
GRAPH 5 : Distribution of patients according to Type of Renal Dysfunction (n=24)

Association of Etiology and Renal Dysfunction

Majority of the cases of renal dysfunction (19 out of 24; 79.2%) were associated with chronic alcoholic liver disease. However there was no significant association between the etiology and renal dysfunction as per Chi-Square test (p>0.05).

Table 12: Association of Etiology and Renal Dysfunction

Etiology	Normal Dysfunction		Renal Dysfunction		Chi-Square Value	p Value
	N	%	N	%		
Alcoholic chronic liver disease	28	43.1%	19	29.2%	1.426	>0.05
Hepatitis B virus	7	10.8%	2	3.1%		
Hepatitis C virus	5	7.7%	2	3.1%		
Nonalcoholic steatohepatitis	1	1.5%	1	1.5%		
Total	41	63.1%	24	36.9%		



GRAPH 6 : Association of Etiology and Renal Dysfunction

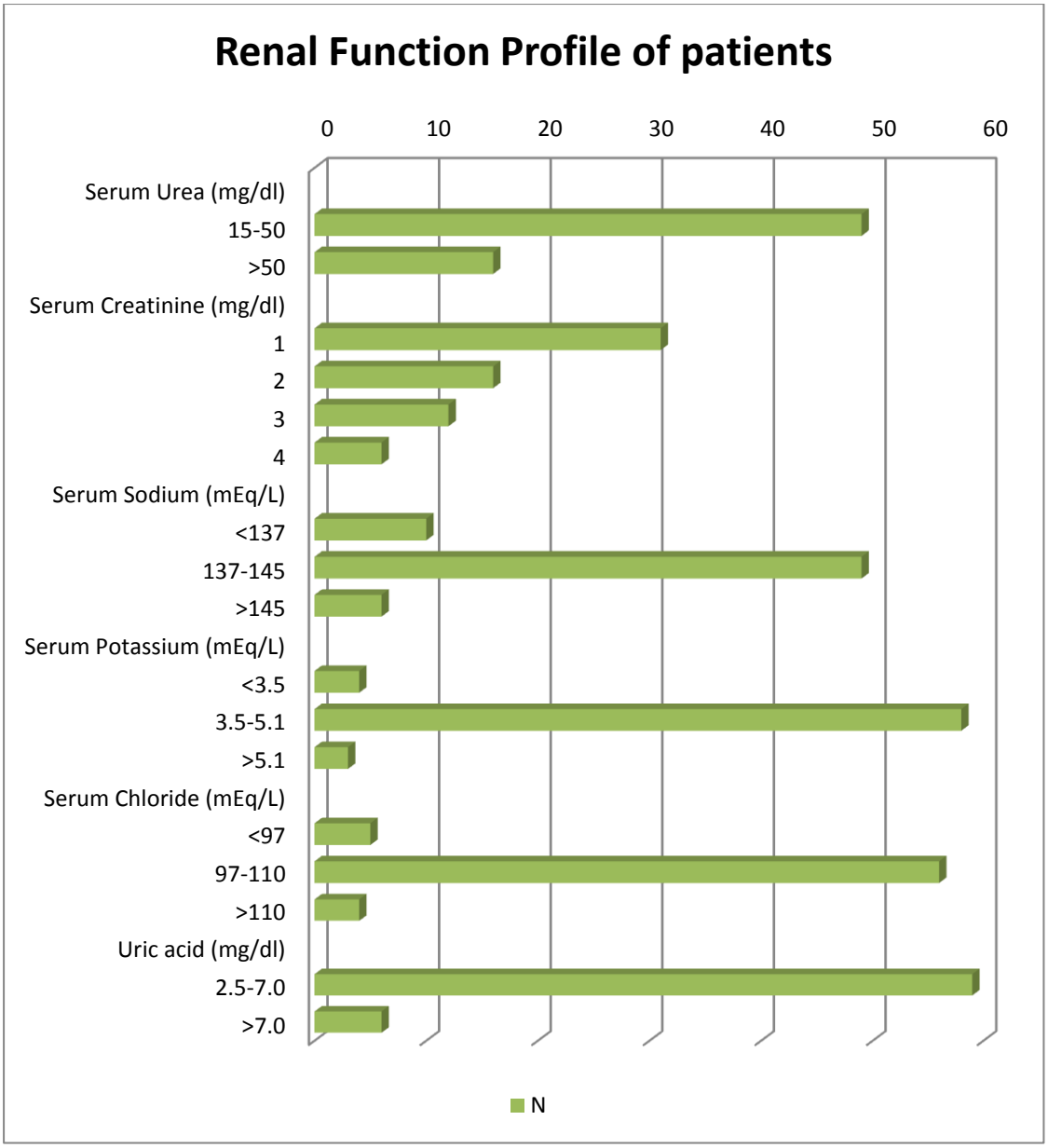
Renal Function Profile of patients

49 (75.4%) patients had serum urea in the range of 15-50 mg/dl while 31 (47.8%) patients had serum creatinine level of 1 mg/dl. 49 (75.4%) patients had serum sodium level in the range of 137-145mEq/L while 58 (89.3%) patients had serum potassium in the range of 3.5-5.1mEq/L. 56 (86.2%) patients had serum chloride level in the range of 97-110mEq/L while 59 (90.8%) patients had uric acid level in the range of 2.5-7.0 mg/dl.

Table 13: Renal Function Profile of patients

Parameters	N	%
Serum Urea (mg/dl)		
15-50	49	75.4%
>50	16	24.6%
Serum Creatinine (mg/dl)		
1	31	47.8%
2	16	24.6%
3	12	18.4%
4	6	9.2%
Serum Sodium (mEq/L)		
<137	10	15.4%
137-145	49	75.4%
>145	6	9.2%
Serum Potassium(mEq/L)		
<3.5	4	6.1%
3.5-5.1	58	89.3%

>5.1	3	4.6%
Serum Chloride(mEq/L)		
<97	5	7.7%
97-110	56	86.2%
>110	4	6.1%
Uric acid(mg/dl)		
2.5-7.0	59	90.8%
>7.0	6	9.2%



GRAPH 7 : Renal Function Profile of patients

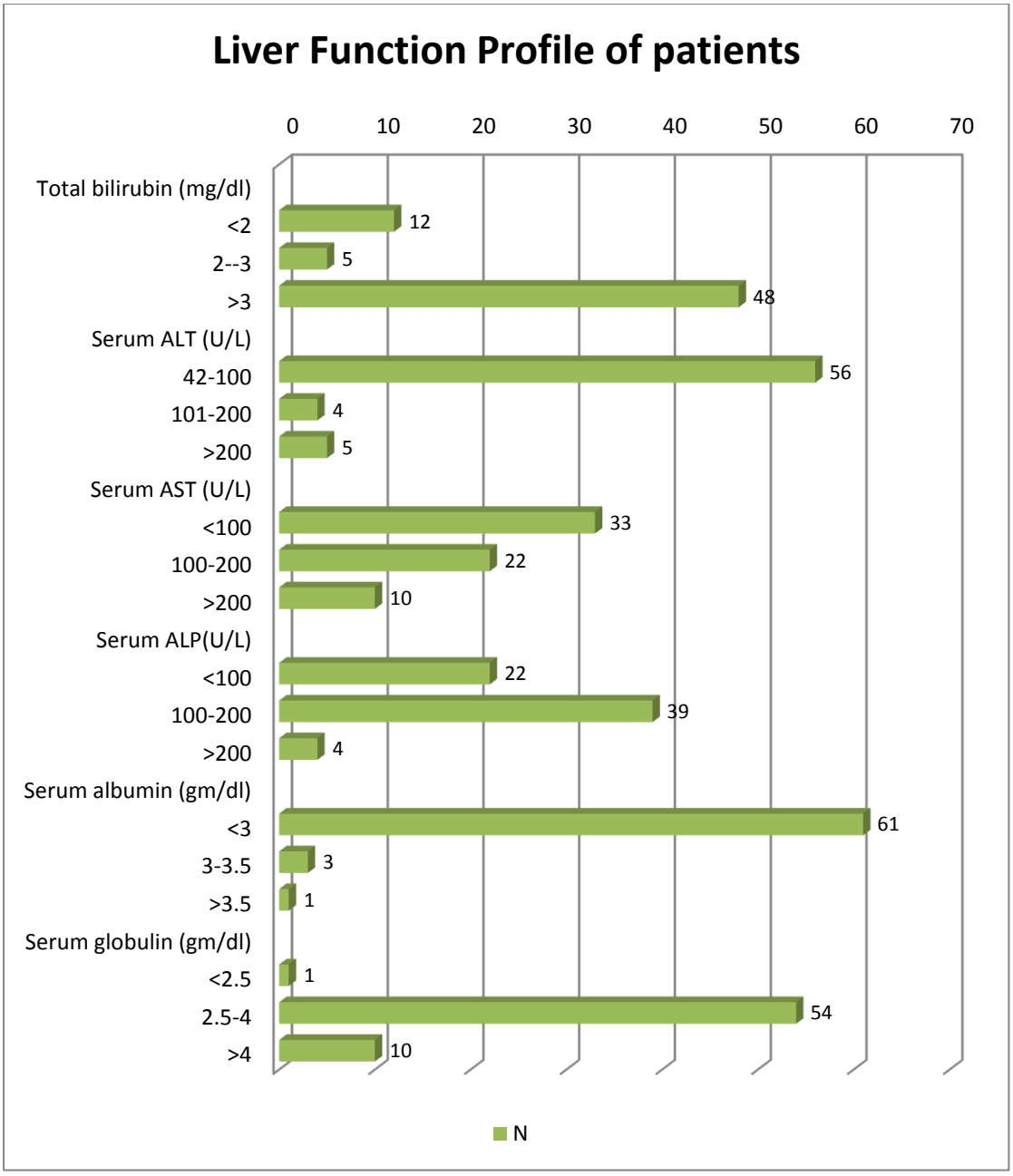
Liver Function Profile of patients

48 (73.7%) patients had total bilirubin level >3 mg/dl while 56 (86.2%) patientshad serum Alanine amino transferase (ALT) <100u/L.33 (50.8%) patients had serum Aspartate amino transferase (AST) <100 u/L and39 (60.1%) patientshad serum Alkaline phosphatase (ALP) within the range of 100-200 u/L. 61 (93.8%) had serum albumin level <3gmdl while 54 (83.1%) patients had serum globulin in the range of 2.5-4 gm/dl.

Table 14: Liver Function Profile of patients

Parameters	N	%
Total bilirubin (mg/dl)		
<2	12	18.5%
2-3	5	7.8%
>3	48	73.7%
Serum ALT(U/L)		
<100	56	86.2%
100-200	4	6.1%
>200	5	7.8%
Serum AST(U/L)		
<100	33	50.8%
100-200	22	33.8%
>200	10	15.4%
Serum ALP(U/L)		
<100	22	33.8%
100-200	39	60.1%
>200	4	6.1%

Serum albumin(gm/dl)		
<3	61	93.8%
3-3.5	3	4.6%
>3.5	1	1.5%
Serum globulin(gm/dl)		
<2.5	1	1.5%
2.5-4	54	83.1%
>4	10	15.4%



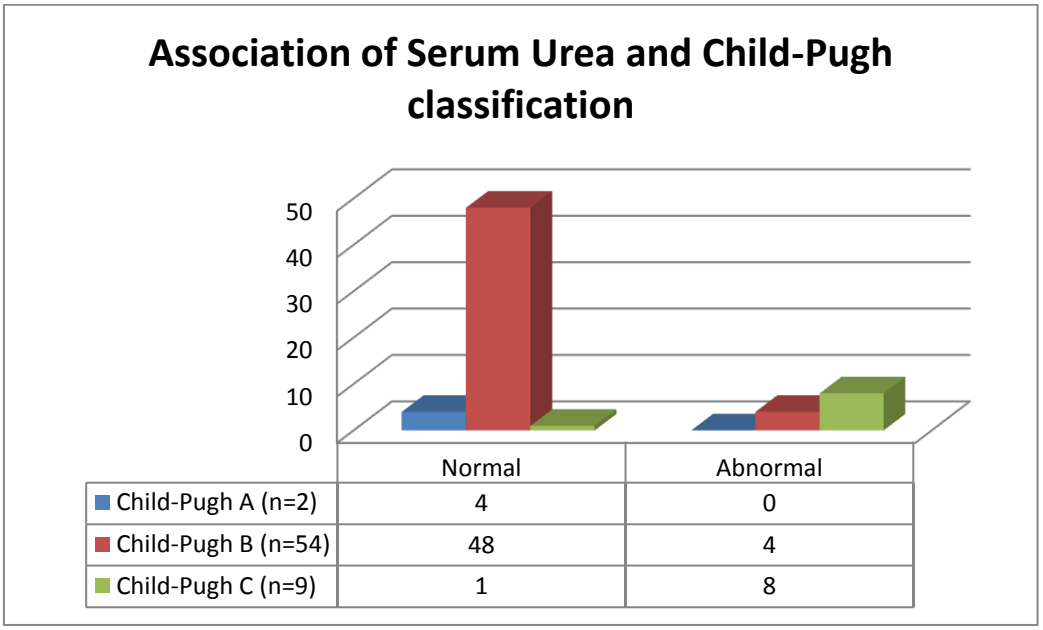
GRAPH 8 : Liver Function Profile of patients

Association of Serum Urea and Child-Pugh classification

It was observed that there was significant increase in abnormal value of serum urea with increase in the severity of liver disease as per Chi-Square test (**p<0.05**).

Table 15: Association of Serum Urea and Child-Pugh classification

Classification	Normal		Abnormal		Chi-Square Value	p Value
	N	%	N	%		
Child-Pugh A (n=2)	4	7.5%	0	-	29.60	**<0.05**
Child-Pugh B (n=54)	48	90.6%	4	33.3%		
Child-Pugh C (n=9)	1	1.9%	8	66.7%		
Total	53	100%	12	100%		



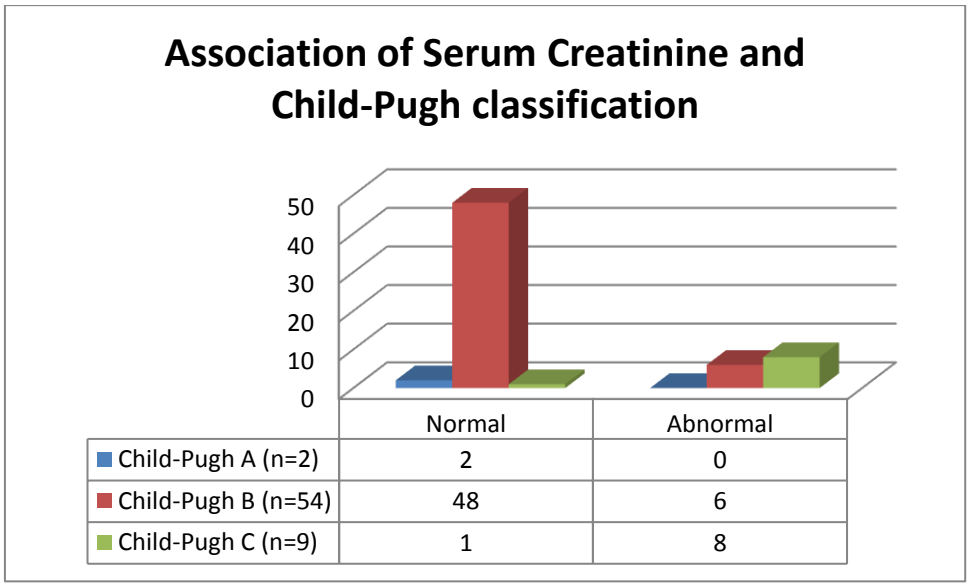
GRAPH 9 : Association of Serum Urea and Child-Pugh classification

Association of Serum Creatinine and Child-Pugh classification

It was observed that there was significant increase in abnormal value of serum creatinine with increase in the severity of liver disease as per Chi-Square test (**p<0.05**).

Table 16: Association of Serum Creatinine and Child-Pugh classification

Classification	Normal		Abnormal		Chi-Square Value	p Value
	N	%	N	%		
Child-Pugh A (n=2)	2	3.6%	0	-	26.773	**<0.05**
Child-Pugh B (n=54)	48	94.6%	6	42.9%		
Child-Pugh C (n=9)	1	1.8%	8	57.1%		
Total	51	100%	14	100%		



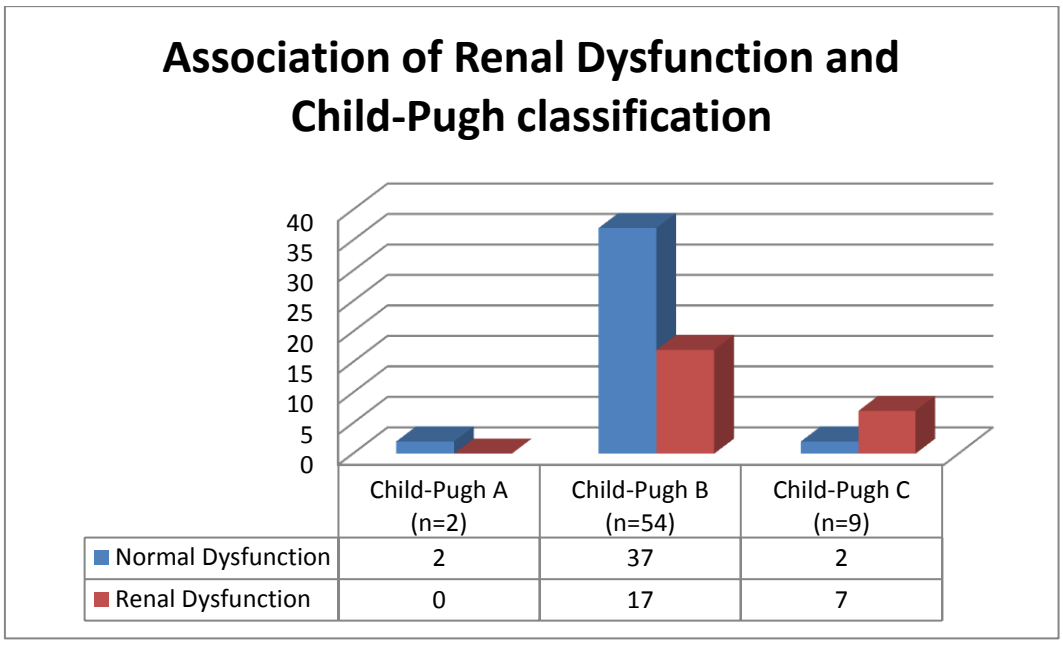
GRAPH 10 : Association of Serum Creatinine and Child-Pugh classification

Association of Renal Dysfunction and Child-Pugh classification

2 (4.9%) patients each corresponded to Child–Pugh A class and Child–Pugh C class while 37 (90.2%) patients corresponded to Child–Pugh B class.There was significant increase in renal dysfunction with increase in the severity of liver disease as per Chi-Square test (**p<0.05**).

Table 17: Association of Renal Dysfunction and Child-Pugh classification

Classification	Normal Dysfunction		Renal Dysfunction		Chi-Square Value	p Value
	N	%	N	%		
Child-Pugh A (n=2)	2	4.9%	0	-	11.504	**<0.05**
Child-Pugh B (n=54)	37	90.2%	17	70.8%		
Child-Pugh C (n=9)	2	4.9%	7	29.2%		
Total	41	100%	24	100%		



GRAPH 11: Association of Renal Dysfunction and Child-Pugh classification

DISCUSSION

A prospective cross sectional study was conducted among 65 patients in department of medicine Shri. B. M. Patil Medical College Hospital and Research Centre Vijayapur to evaluate the assessment of renal function in chronic liver disease.

The prevalence of CLD has been increasing since last few years which can both be attributed to early diagnosis and an increased incidence[106]. One of the major concerns associated with CLD is its unrelenting course, as no therapies have been found to prevent its progression to advanced stages which are marked by fibrosis and cirrhosis as final outcome.

Advancement of liver disease is generally associated with various consequences such as PHTN(Portal Hypertension), upper GI bleed, ascites and SBP(Spontaneous bacterial peritonitis). Deranged liver physiology has a profound effect on the homeostatic mechanisms of the body affecting various other organs, including lungs and kidneys.

Importance of renal involvement in CLD has long been recognized by many workers[32,107]. Renal dysfunction has been recently emphasized by Choi et al. in a retrospective study ,where they concluded that renal derangement in CLD was not an uncommon phenomenon[108]. Renal failure in patients with CLD, particularly with advanced liver disease, seems to be common; however, the exact incidence is unknown and is probably underestimated. This may be explained by the fact that patients with cirrhosis tend to have falsely low SCr levels due to decreased hepatic

creatinine synthesis and decreased skeletal muscle mass[86]. ARF in patients with cirrhosis frequently accompanies complications such as bacterial peritonitis, sepsis or hypovolemia from gastrointestinal bleeding, excessive diuretic therapy or administration of nephrotoxic drugs/contrast agents[109]. The probability of the occurrence of HRS in patients with cirrhosis and ascites at 1and 5 years is 18% and 39%, respectively, with mortality approaching 100% in type 1 HRS without specific therapy .The median survival time in these patients without liver transplantation was only 12 days after diagnosis in onestudy[26]. However, this seems to have improved with terlipressin and albumin therapy. The development of ARF in patients with advanced liver disease has significant prognostic importance[110]. In patients with cirrhosis admitted to hospital with acute upper gastrointestinal hemorrhage, development of ARF forms an independent predictive factor for death[19]. There is considerable evidence that ARF in cirrhosis is primarily related to disturbances in circulatory function, mainly a reduction in systemic vascular resistance as a result of primary arterial vasodilatation in the splanchnic circulation, triggered by PHTN[56]. Furthermore, an intrinsic defect in cardiac performance termed cirrhotic cardiomyopathy lead to attenuated cardiac function, also contribute to renal dysfunction in cirrhotics particularly when exposed to stressful events like sepsis[111].

The diagnosis of ARF in cirrhosis is traditionally made by a 50% increase in sCr with setting a fixed sCr threshold of $\geq$1.5mg/dl[31]. However, final consensus has not been reached yet on classification of cirrhosis-AKI. In the last decade, several attempts have been made. In 2002, the ADQI Working Group developed RIFLE criteria for AKI. Subsequent evidence that even small increase in sCr (as small as 0.3mg/dl)also

has a negative impact on survival led to a modification of the RIFLE criteria called AKIN[112].

More recently, the KDIGO criteria have been developed to reach a consensus drawing consolidating elements of both RIFLE and AKIN on staging AKI[113]. Whether these criteria improve the traditional criterion (a final threshold value for sCr of 1.5mg/dl) in terms of a better prediction of mortality is still a matter of debate[114].

In the present study, majority of the patients (32.4%) were in the age group of 31-40 years followed by 21.5% in the age group of 41-50 years, 16.9% in the age group of 61-70 years, 15.4% in the age group of 51-60 years, 9.2% patients in the age group of 21-30 years and 4.6% in the age group of >70 years. The mean age of the patients was 45.78 ± 13.19 years. There was male preponderance (90.8%) whereas female patients constituted 9.2% of the study group. This is similar to the studies of Aggarwal HK et al[115], Mohan J et al[116], Das N et al[101] and Zhou F et al[105].

Aggarwal HK et al[115] study assessing the incidence and relationship of various factors for different types of renal failure in cirrhotic patients found mean age of patients was 46.12±11.33 years, with arange of 20–70 years. Ninety-six patients were males with only four females.

Mohan J et al[116] retrospective study analyzing the profile of renal dysfunction in patients with cirrhosis found mean age of patients was 48.32 ± 10.19 years. Of these, majority were male (95% (95/100)) and females were 5% (5/100).

Das N et al[101] cross-sectional, observational study assessing the renal function in chronic liver diseases found mean age of the patients were 43.58 years and majority of patients were male.

Zhou F et al[105] retrospective analysis assessing the prognostic accuracy of absolute serum creatinine (sCr) changes ('Delta-sCr') on the long-term outcomes in cirrhotic patients found median age of the patients was 55.68±12.56 years, and 63.06% (n=210) of the patients were male.

In our study, 47 (72.2%) patients suffered from Alcoholic liver disease while 9 (13.9%) and 7 (10.8%) patients had chronic Hepatitis-B and chronic Hepatitis-C respectively. 2 (3.1%) patients had Nonalcoholic steatohepatitis. This is comparable to the studies of Das N et al[101], Aggarwal HK et al[115], Mohan J et al[116] and Zhou F et al[105].

Das N et al[101] cross-sectional, observational study assessing the renal function in chronic liver diseases reported most common cause of chronic liver disease was alcohol followed by Hepatitis B and Hepatitis C.34 (68%) patients suffered from Alcoholic liver disease,7 (14%) patients had chronic Hepatitis-B, 3 (6%) patients had chronic Hepatitis-C, 3 (6%) patients had Non alcoholic fatty liver disease, 2 (4%) patients had Wilson's Disease and 1 (2%) patients had autoimmune hepatitis.

Aggarwal HK et al[115] study assessing the incidence and relationship of various factors for different types of renal failure in cirrhotic patients reported major etiology to be alcohol (n=88) and all the patients in this group were males. Other etiologies included cryptogenic (n=5), hepatitis B (n=4), hepatitis C (n=2) and alcohol with hepatitis B

(n=1). Icterus was present in 59 patients; 60 patients had clinically evident ascites with almost half of the patients having fluid thrill whereas, UGI bleed was present in 41 patients and 26 patients had features of hepatic encephalopathy (HE).

Mohan J et al[116] retrospective study analyzing the profile of renal dysfunction in patients with cirrhosis reported most common etiology of cirrhosis was alcohol 85% (85/100), followed by Hepatitis B (11% (11/100)) and C virus (4% (4/100)). Renal dysfunction was observed in 33.3% (5/15) of cirrhotic cases with viral etiology. There is no significant association between the etiologies of cirrhosis and renal disorders ($p = 0.25$).

Zhou F et al[105] retrospective analysis assessing the prognostic accuracy of absolute serum creatinine (sCr) changes ('Delta-sCr') on the long-term outcomes in cirrhotic patients reported most common etiology of cirrhosis was HBV infection (n=232, 69.7%), followed by miscellaneous (n=40,12%), Alcohol (n=30, 9%), Cholestasis (n=17, 5.1%), and Autoimmune (n=14, 4.2%).

It was observed in our study that 24 (36.9%) patients had renal dysfunction. The study of Mohan J et al[17] analyzing the profile of renal dysfunction in patients with cirrhosis found renal diseases prevalance in 22% (22/100) of cirrhotic patients.

The most common type of renal dysfunction in our study was Acute Kidney Injury (58.3%) followed by Hepatorenal Syndrome (41.7%). This is concordant to the studies of Bucsics Tet al[104], Mohan J et al[116] and Zhou F et al[105].

Bucsics Tet al[104] study summarized that Renal dysfunction is a common complication of liver cirrhosis and of utmost clinical and prognostic relevance. Patients with cirrhosis are more prone to developing acute kidney injury (AKI) than the non-

cirrhotic population. Pre-renal AKI, the hepatorenal syndrome type of AKI (HRS-AKI, formerly known as 'type 1') and acute tubular necrosis represent the most common causes of AKI in cirrhosis.

Mohan J et al[116] retrospective study analyzing the profile of renal dysfunction in patients with cirrhosis reported most common type of renal dysfunction in liver cirrhotic cases was AKI, present in 12% (12/100) of patients followed by HRS(7%, 7/100) and CKD (3%, 3/100).

Zhou F et al[105]retrospective analysis assessing the prognostic accuracy of absolute serum creatinine (sCr) changes ('Delta-sCr') on the long-term outcomes in cirrhotic patients, and evaluating the performance of the 'Delta-sCr' approach to stage acute kidney injury (AKI), compared with the Kidney Disease Improving Global Outcomes (KDIGO) criteria reported prevalence of AKI in cirrhotic patients was 18.01% by the KDIGO criteria, and 25.22% by the 'Delta-sCr' system.

It was observed in the present study that majority of the cases of renal dysfunction (19 out of 24; 79.2%) were associated with alcoholic chronic liver disease. However there was no significant association between the etiology and renal dysfunction as per Chi-Square test ($p>0.05$).

Mohan J et al[116] retrospective study analyzing the profile of renal dysfunction in patients with cirrhosis reported no statistically significant difference in renal parameters in different etiologies of liver cirrhosis.

In our study, 49 (75.4%) patients had serum urea in the range of 15-50 mg/dl while 31 (47.8%) patients had serum creatinine level of 1 mg/dl. 49 (75.4%) patients had serum

sodium level in the range of 137-145mEq/L while 58 (89.3%) patients had serum potassium in the range of 3.5-5.1mEq/L. 56 (86.2%) patients had serum chloride level in the range of 97-110mEq/L while 59 (90.8%) patients had uric acid level in the range of 2.5-7.0 mg/dl.

48 (73.7%) patients had total bilirubin level >3 mg/dl while 56 (86.2%) patients had serum Alanine amino transferase (ALT) <100u/L.33 (50.8%) patients had serum Aspartate amino transferase (AST) <100 u/L and39 (60.1%) patients had serum Alkaline phosphatase (ALP) within the range of 100-200 u/L. 61(93.8%) had serum albumin level <3gmdl while 54 (83.1%) patients had serum globulin in the range of 2.5-4 gm/dl. Similar observations were noted in the studies of Aggarwal HK etal[115] and Das N et al[101].

Aggarwal HK et al[115] study assessing the incidence and relationship of various factors for different types of renal failure in cirrhotic patients reported at the time of presentation, 37 patients had renal dysfunction with RFIs indicating a pre-renal type of renal failure in 30 patients, whereas intrinsic renal disease in six patients and structural renal damage was found in only one patient. Five patients had features suggestive of HRS. Patients with PHTN as marked by PVD of ≥13mm and/or ascites had higher incidence of renal dysfunction. Patients with other forms of decompensation such as jaundice, upper gastro-intestinal bleed and HE were prone to develop renal derangements as compared to their counterparts. Infection in the form of SBP and/or sepsis predisposed patients to develop renal dysfunction.

Das N et al[101] cross-sectional, observational study assessing the renal function in chronic liver diseases reported 39 patients (78%) had Serum total protein 6 gm/dl.

Forty seven patients (94%) had Serum albumin level <3gmdl. Forty one patients (82%) had serum urea within the range of 15-40 mg/dl. Nine patients (18%) had serum urea > 41 mg/dl. Forty patients (80%) on day 1 had serum creatinine level 1 mg/dl, and 40 patients (80%) had serum creatinine level on day 3 as1 mgdl.66% patients had serum bilirubin level > 2mg/ 20 patients (40%) had Serum AST within the range of 42-100 u/L. Thirty five patients(70%) had Serum Alanine amino transferase (ALT) < 100 u/L 15 patients(30%) had Serum Alkaline phosphatase (ALP) < 100 u/L. Thirty three patients (66%) had Serum ALP within the range of 100-200 u/L. Two patients (4%) had Serum ALP > 200 u/L.

It was observed in the present study that there was significant increase in abnormal value of serum urea and serum creatinine with increase in the severity of liver disease as per Chi-Square test (**p<0.05**). 2 (4.9%) patients each corresponded to Child–Pugh A class and Child–Pugh C class while 37 (90.2%) patients corresponded to Child–Pugh B class.There was significant increase in renal dysfunction with increase in the severity of liver disease as per Chi-Square test (**p<0.05**). This is similar to the studies of Mohan J et al[116], Das N et al[101], Al-Mamun A et al[117] and Fornari F et al[118].

Mohan J et al[116] retrospective study analyzing the profile of renal dysfunction in patients with cirrhosis reported out of the one hundred patients, sixteen patients (16%, 16/100) corresponded to Child–Pugh C class, 80% (80/100) to B class, and only 4% (4/100) were class A. There is an increase in the number of renal disorder with increase in the severity of cirrhosis. In the cirrhotic patients with higher severity of cirrhosis (Child Pugh class B and C), renal dysfunction was developed much more (OR=3.37; CI=1.08-10.5; P = 0.03).

Das N et al[101] cross-sectional, observational study assessing the renal function in chronic liver diseases reported distribution of serum urea and creatinine, according to the severities of liver disease as per Child Pugh classification, was statistically significant, but serum creatinine level on day 1 and day 3 was not found to be significantly distributed among different aetiologies of chronic liver disease.

Al-Mamun A et al[117]study reported no statistically significant relation between Child-Pugh score and serum creatinine. Fornari F et al[118] study showed 30% of patients with cirrhosis had gall stones, risk of developing stones most strongly associated with Child's grade C & alcoholic cirrhosis with a yearly incidence of about 5%.

SUMMARY

A prospective cross sectional study was conducted among 65 patients in department of medicine Shri. B. M. Patil Medical College Hospital & Research Centre Vijayapur to evaluate the assessment of renal function in chronic liver disease. The following observations were noted:

1. Majority of the patients (32.4%) were in the age group of 31-40 years followed by 21.5% in the age group of 41-50 years, 16.9% in the age group of 61-70 years, 15.4% in the age group of 51-60 years, 9.2% patients in the age group of 21-30 years and 4.6% in the age group of >70 years. The mean age of the patients was 45.78 ± 13.19 years.

2. There was male preponderance (90.8%) whereas female patients constituted 9.2% of the study group.

3. 47 (72.2%) patients suffered from Alcoholic liver disease while 9 (13.9%) and 7 (10.8%) patients had chronic Hepatitis-B and chronic Hepatitis-C respectively. 2 (3.1%) patients had Nonalcoholic steatohepatitis.

4. It was observed that 24 (36.9%) patients had renal dysfunction.

5. The most common type of renal dysfunction was Acute Kidney Injury (58.3%) followed by Hepatorenal Syndrome (41.7%).

6. Majority of the cases of renal dysfunction (19 out of 24; 79.2%) were associated with alcoholic chronic liver disease. However there was no significant association between the etiology and renal dysfunction as per Chi-Square test ($p>0.05$).

7. 49 (75.4%) patients had serum urea in the range of 15-50 mg/dl while 31 (47.8%) patients had serum creatinine level of 1 mg/dl. 49 (75.4%) patients had serum sodium level in the range of 137-145mEq/L while 58 (89.3%) patients had serum potassium in the range of 3.5-5.1mEq/L. 56 (86.2%) patients had serum chloride level in the range of 97-110mEq/L while 59 (90.8%) patients had uric acid level in the range of 2.5-7.0 mg/dl.

8. 48 (73.7%) patients had total bilirubin level >3 mg/dl while 56 (86.2%) patients had serum Alanine amino transferase (ALT) <100u/L.33 (50.8%) patients had serum Aspartate amino transferase (AST) <100 u/L and39 (60.1%) patients had serum Alkaline phosphatase (ALP) within the range of 100-200 u/L. 61 (93.8%) had serum albumin level <3gmdl while 54 (83.1%) patients had serum globulin in the range of 2.5-4 gm/dl.

9. It was observed that there was significant increase in abnormal value of serum urea with increase in the severity of liver disease as per Chi-Square test (**$p<0.05$**).

10. It was observed that there was significant increase in abnormal value of serum creatinine with increase in the severity of liver disease as per Chi-Square test (**p<0.05**).

11. 2 (4.9%) patients each corresponded to Child–Pugh A class and Child–Pugh C class while 37 (90.2%) patients corresponded to Child–Pugh B class. There was significant increase in renal dysfunction with increase in the severity of liver disease as per Chi-Square test (**p<0.05**).

CONCLUSION

Physicians involved in the care of patients with cirrhosis have become even more interested in the assessment of renal function and creatinine was shown to be astrong prognostic marker. However, in cirrhosis, there is still a gap between serum creatinine and renal function. Serum creatinine and the widely used creatinine-based equations must be interpreted with caution.

This study emphasizes the fact that we should be more vigilant when treating Chronic Liver Disease (CLD) patients, regarding their renal function, as proper screening, prevention and treatment of renal dysfunction can decrease morbidity and mortality.

Patient need to be cautioned about the poor liver condition and further added complication of renal function for which they need to have regular follow-up and treatment.

BIBLIOGRAPHY

1. http://www.ner.vse.cz//wiki/index.php/Chronic liver disease last accessed on 13.5.2012 .
2. SlackA, Yeoman A, Wendon J. Renal Dysfunction in Chronic liver disease. Critical Care. 2010;14:214.
3. Betrosiun AP, Agarwal B, Douzinas EE. Acute renal dysfunction in liver disease. World J Gastroenterol. 2007;13(42):5552–59.
4. Eren Z, Kantaru G. Assessment of renal functions in patients with liver disease: which one is correct? BANTAO Journal. 2010;8(1):9–12.
5. Gines P, Schrier GP. Renal failure in cirrhosis. N Engi J Med. 2009;361: 1279–90.
6. Caronia S, Taylor K, Pagliaro L et al. Further evidence for an association between non-insulin-dependent-diabetes mellitus and chronic hepatitis C virus infection. Hepatology. 1990;30:1059–63.
7. Kalaitzakis E, Rosengren S, Skommevik T. Björnsson ecoronary artery disease in patients with liver cirrhosis. Dig Dis Sci. 2010;55(2):467–75.
8. Chantler C, Haycock GB. Estimation of glomerular filtration rate from height/plasma creatinine ratio. Arch Dis Child. 1983;58(9):754–55.
9. Sabry AA, Sobh MA, Irving WLet al. Original Article A comprehensive study of the association between hepatitis C virus and glomerulopathy. 2002; 239–45.
10. Alessandria C, Ozdogan O, Guevara M et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. Hepatology 2005;41: 1282–9.

11. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology 2002;35:1179–85.
12. Wiesner R, Edwards E, Freeman R et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–6.
13. Wong F. Recent advances in our understanding of hepatorenal syndrome. Nat Rev Gastroenterol Hepatol 2012;9:382–91.
14. Gerbes AL. Liver cirrhosis and kidney. Dig Dis 2016;34:387–90.
15. Piano S, Rosi S, Maresio G et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol 2013;59:482–9.
16. Follo A, Llovet J, Navasa M et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994;20:1495–501.
17. Hampel H, Bynum GD, Zamora Eet al. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. Am J Gastroenterol 2001;96:2206–10.
18. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology 2008;48:2064–77.
19. Cárdenas A, Ginès P, Uriz J et al. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. Hepatology 2001;34(4):671–6.
20. Tsien CD, Rabie R, Wong F. Acute kidney injury in decompensated cirrhosis. Gut 2013;62:131–7.

21. Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol 2011;9:260–5.
22. Fagundes C, Barreto R, Guevara M et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. J Hepatol 2013;59:474–81.
23. Nadim MK, Kellum JA, Davenport A et al. Hepatorenal syndrome: the 8th international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2012;16:R23.
24. Kellum JA, Levin N, Bouman Cet al. Developing a consensus classification system for acute renal failure. Curr Opin Crit Care 2002;8(6):509–14.
25. Bern MM. Hepatorenal syndrome: study of clinical characteristics in a large series. South Med J 1973;66:775–8.
26. Ginès A, Escorsell A, Ginès P et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229–36.
27. Francoz C, Glotz D, Moreau Ret al. The evaluation of renal function and disease in patients with cirrhosis. J Hepatol 2010;52:605–13.
28. Fernández J, Navasa M, Planas R et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818–24.
29. Schwabl P, Bucsics T, Soucek K et al. Risk factors for development of spontaneous bacterial peritonitis and subsequent mortality in cirrhotic patients with ascites. Liver Int 2015;35:2121–8.

30. Salerno F, Gerbes A, Ginès Pet al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007;56:1310–18.
31. Wong F. The evolving concept of acute kidney injury in patients with cirrhosis. Nat Rev Gastroenterol Hepatol 2015;12:711–19.
32. Flint A. Clinical report on hydro-peritoneum, based on an analysis of forty-six cases. Am J Med Sci 1863;45:306–39.
33. McCorkle H, Howard FS. Severe trauma of the liver with 'hepatorenal syndrome'. Ann Surg 1942;116:223–30.
34. Perl AF. Hepatorenal syndrome with recovery. Canad MAJ 1947;57:290–2.
35. Heyd CG. The liver and its relation to chronic abdominal infection. Ann Surg 1923;79:55–77.
36. Gordon C. Complications after gallbladder surgery. Ann Surg 1937;105:1–8.
37. Furtwaengler A. Diffuse rindennekrose beider nieren nach leberruptur. Krankheitsforschung 1927;4:349.
38. Orr TG, Helwig FC. Liver trauma and the hepatorenal syndrome. Ann Surg 1939;110:682–92.
39. Reynolds TB, Lieberman FL, Redeker AG. Functional renal failure with cirrhosis: the effect of plasma expansion therapy. Medicine (Baltimore) 1967;46:191–6.
40. Ariyan S, Sweeney T, Kerstein M. The hepatorenal syndrome: recovery after portacaval shunt. Ann Surg 1975;181:847–9.
41. Mullane JF, Gliedman ML. Development of renal impairment in Laennec's cirrhosis. Ann Surg 1971;174:892–901.

42. Orloff MJ. Effect of side to side portacaval shunt on intractable ascites, sodium excretion, and aldosterone metabolism in man. Am J Surg 1966;112:287–98.

43. Earley LE. Presentation of diagnostic criteria of the hepatorenal syndrome. In: Bartoli E, Chiandussi L (eds). Hepatorenal Syndrome . Padova: Piccin Medical Books, 1979.

44. Arroyo V, Ginès P, Gerbes A et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis: International Ascites Club. Hepatology 1996;23:164–76.

45. Angeli P, Ginès P, Wong F et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62:986–74.

46. Bircher J, Benhamou JP, McIntyre Net al. Oxford Textbook of Clinical Hepatology. 2nd Edition. Oxford University Press; 1999. Schuppan and Afdhal Page 9

47. Schaffner H, Popper H. Capillarization of the sinusoids. Gastroenterology 1963;44:339–42.

48. Wanless IR, Nakashima E, Sherman M. Regression of human cirrhosis. Morphologic features and the genesis of incomplete septal cirrhosis. Arch Pathol Lab Med 2000;124:1599–607.

49. National Center for Health Statistics. US Department of Health and Human Services, Centers for Disease Control and Prevention; Hyattsville, MD: 2005. Series 13

50. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 2006;43(2 Suppl 1):S99–S112.

51. Smith HJ. The Kidney: Structure and Function in Health and Disease. London, England: Oxford University Press, 1964, pp v–vii.

52. Ruiz-del-Arbol L, Monescillo A, Arocena Cet al. Circulatory function and hepatorenal syndrome in cirrhosis. HEPATOLOGY 2005;42:439-447

53. Munoz SJ. The hepatorenal syndrome. Med Clin NorthAm2008;92:813-837.

54. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. HEPATOLOGY 2006;43:S121-S131.

55. Dimeski G, McWhinney B, Jones Bet al. Extent of bilirubin interference with Beckman creatinine methods. Ann Clin Biochem 2008;45:91-92.

56. Schrier RW, Arroyo V, Bernardi Met al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. HEPATOLOGY 1988;8(5):1151- 1157.

57. Dudley FJ, Kanel GC, Wood LJet al. Hepatorenal syndrome without avid sodium retention. HEPATOLOGY 1986;6:248-251.

58. Krag A, Moller S, Henriksen JHet al. Terlipressin improves renal function in patients with cirrhosis and ascites without hepatorenal syndrome. HEPATOLOGY 2007;46:1863-1871.

59. Davis CL, Feng S, Sung Ret al. Simultaneous liver-kidney transplantation: evaluation to decision making. Am J Transplant 2007;7:1702-1709.

60. Wiest R, Tsai MH, Groszmann RJ. Octreotide potentiates PKC-dependent vasoconstrictors in portal-hypertensive and control rats. Gastroenterology 2000;120:975-983.

61. Lim JK, Groszmann RJ. Vasoconstrictor therapy for the hepatorenal syndrome. Gastroenterology 2008;134:1608-1611.

62. Moreau R, Lebrec D. Diagnosis and treatment of acute renal failure in patients with cirrhosis. Best Pract Res Clin Gastroenterol 2007;21:111-123.

63. Perz JF, Armstrong GL, Farrington LAet al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45:529–538. doi: 10.1016/j.jhep.2006.05.013.

64. Bash LD, Astor BC, Coresh J. Risk of incident ESRD: A comprehensive look at cardiovascular risk factors and 17 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis. 2010. in press .

65. Appel G. Viral infections and the kidney: HIV, hepatitis B, and hepatitis C. Cleve Clin J Med. 2007;74:353–360. doi: 10.3949/ccjm.74.5.353.

66. Russell RT, Pinson CW. Surgical management of polycystic liver disease. World J Gastro. 2007;13:5052–5059.

67. Snanoudj R, Durrbach A, Gauthier E. Changes in renal function in patients with familial amyloid polyneuropathy treated with orthotopic liver transplantation. Nephrol Dial Transpl. 2004;19:1779–1785. doi: 10.1093/ndt/gfh063.

68. Swan SK. The search continues-an ideal marker of GFR. Clin Chem. 1997;43:913–914.

69. Tomlanovich S, Golbetz H, Perlroth Met al. Limitations of creatinine in quantifying the severity of cyclosporine-induced chronic nephropathy. Am J Kidney Dis. 1986;8:332–337.

70. Takabatake T, Ohta H, Ishida Yet al. Low serum creatinine levels in severe hepatic disease. Arch Intern Med. 1988;148:1313–1315. doi: 10.1001/archinte.148.6.1313.

71. Cholongitas E, Shusang V, Marelli L. Review article: renal function assessment in cirrhosis - difficulties and alternative measurements. Aliment Pharmacol Ther. 2007;26:969–978.

72. Mandall MS, Lindenfield J, Tsou MYet al. Cardiac evaluation of liver transplant candidates. World J Gastro. 2008;12:3445–3451.

73. Skulzacek PA, Szewc RG, Nolan CRet al. Prediciton of GFR in liver transplant candidates. Am J Kidney Dis. 2003;42:1169–1176.

74. Proulx NL, Akbari A, Garg AXet al. Measured creatinine clearance from timed urine collections substantially overestimates glomerular filtration rate in patients with liver cirrhosis: a systematic review and individual patient meta-analysis. Nephrol Dial Trans. 2005;20:1617–1622. doi: 10.1093/ndt/gfh839.

75. Woitas RP, Stoffel-Wagner B, Flommersfeld S. Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. Clin Chem. 2000;46:712–715.

76. Poge U, Gerhardt T, Stoffel-Wagner Bet al. Calculation of glomerular filtration rate based on cystatin C in cirrhotic patients. Nephrol Dial Transpl. 2006;21:660–664.

77. Bolignano D, Coppolino G, Campo S. Urinary neutrophil gelatinase-associated lipocalin (NGAL) is associated with severity of renal disease in proteinuric patients. Nephrol Dial Transpl. 2008;23:414–416. doi: 10.1093/ndt/gfm541.

78. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1–266.

79. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 2002;40:221–226.

80. Takeuchi M, Fukuda Y, Nakano Iet al. Elevation of serum cystatin C concentrations in patients with chronic liver disease. Eur JGastroenterol Hepatol 2001;13:951–955.

81. Rivolta R, Maggi A, Cazzaniga Met al. Reduction of renal cortical blood flow assessed by Doppler in cirrhotic patients with refractory ascites. Hepatology 1998;28:1235–1240.

82. Platt JF, Marn CS, Baliga PKet al. Renal dysfunction in hepatic disease: early identification with renal duplex Doppler US in patients who undergo liver transplantation. Radiology 1992;183:801–806.

83. Elia C, Graupera I, Barreto R et al. Severe acute kidney injury associated with non-steroidal antiinflammatory drugs in cirrhosis: a case-control study. J Hepatol 2015;63:593–600.

84. Tandon P, James MT, Abraldes JGet al. Relevance of new definitions to incidence and prognosis of acute kidney injury in hospitalized patients with cirrhosis: a retrospective population-based cohort study. PLOS 2016;11:1–15.

85. Mandorfer M, Bota S, Schwabl P et al. Nonselective β blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology 2014;146:1680–90.e1.

86. Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. Am J Kidney Dis 2003;41(2):269–78.

87. Stevens LA, Schmid CH, Greene T et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int 2009;75:652–60.

88. Hu LS, George J, Wang JH. Current concepts on the role of nitric oxide in portal hypertension. World J Gastroenterol 2013;19:1707–17.

89. Epstein M, Berk DP, Hollenberg NK et al. Renal failure in the patient with cirrhosis: the role of active vasoconstriction. Am J Med 1970;49:175–85.

90. Wang JB, Wang HT, Li LP et al. Development of a rat model of D-galactosamine/lipopolysaccharide induced hepatorenal syndrome. World J Gastroenterol 2015;21:9927–35.

91. Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. J Clin Exp Hepatol 2014;4:302–11.

92. Allegretti AS, Ortiz G, Wenger J et al. Prognosis of acute kidney injury and hepatorenal syndrome in patients with cirrhosis: a prospective cohort study. Int J Nephrol 2015;2015:1–9.

93. Jalan R, Fernandez J, Wiest R et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014;60:1310–24.

94. Ginés P, Tilo L, Arroyo V et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988;94:1493–502.

95. Boyer TD, Sanyal AJ, Wong F et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with

cirrhosis and hepatorenal syndrome type 1. Gastroenterology 2016;150: 1579–89.

96. Rodriguez E, Pereira GH, Sola et al. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: effects on kidney function and transplantation outcomes. Liver Transplant 2015;21:1347–54.

97. Feyssa E, Ortiz J, Grewal K et al. MELD score less than 15 predicts prolonged survival after transjugular intrahepatic portosystemic shunt for refractory ascites after liver transplantation. Transplantation 2011;91:786–92.

98. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53:397–417.

99. Puthumana J, Ariza X, Belcher JMet al. Urine interleukin 18 and lipocalin 2 are biomarkers of acute tubular necrosis in patients with cirrhosis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016 Dec 21. pii: S1542-3565(16)31231-9.

100. Rognant N and Lemoine S. Evaluation of renal function in patients with cirrhosis: where are we now? World Journal of Gastroenterology. 2014, 20(10):2533-2541.

101. Das N, Bhattacharyya A, Paria B et al. Study on Assessment of Renal Function in Chronic Liver Disease. J Clin Diagn Res. 2015 Mar; 9(3): OC09–OC12.

102. Francoz C, Nadim MK, Durand F. Kidney biomarkers in cirrhosis. J Hepatol. 2016 Oct;65(4):809-824.

103. Tsung-Hsing H, Chorng-Jang L, Chih-Wei Tet al. The Effect of Renal Function Impairment on the Mortality of Cirrhotic Patients: A Nationwide Population-Based 3-Year Follow-up Study. PLoS ONE 11(9): e0162987. https://doi.org/10.1371/journal.pone.0162987
104. Bucsics T and Krones E. Renal dysfunction in cirrhosis: acute kidney injury and the hepatorenal syndrome. Gastroenterology Report, 2017, Volume 5, Issue 2, Pages 127–137.
105. Zhou F, Luo Q, Han Let al. Evaluation of Absolute Serum Creatinine Changes in Staging of Cirrhosis-Induced Acute Renal Injury and its Association with Long-term Outcomes. Kidney Blood Press Res 2017;42:294-303
106. Nobili V, Carter-Kent C, Feldstein AE. The role of lifestyle changes in the management of chronic liver disease. BMC Med. 2011;9(1):70.
107. Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. Lancet. 1956;271(6953):1121–1125.
108. Choi YJ, Kim JH, Koo JK et al. Prevalence of renal dysfunction in patients with cirrhosis according to ADQI-IAC working party proposal. Clin Mol Hepatol. 2014;20(2):185–191.
109. Eckardt KU. Renal failure in liver disease. Intensive Care Med. 1999;25(1):5–14.
110. Betrosian AP, Agarwal B, Douzinas EE. Acute renal dysfunction in liver diseases. World J Gastroenterol. 2007;13(42):5552–5559.
111. Mandell M-S. Cardiac evaluation of liver transplant candidates. World J Gastroenterol. 2008;14(22):3445–3451.

112. Wong F: Definition and Diagnosis of Acute Kidney Injury in Cirrhosis. Dig Dis 2015;33:539-547.
113. Lameire N: The definitions and staging systems of acute kidney injury and their limitations in practice. Arab J Nephrol Transplant 2013;6:145-152.
114. Wong F: Treatment to improve acute kidney injury in cirrhosis. Curr Treat Options Gastroenterol. 2015;13:235-248.
115. Aggarwal HK, Jain D, Singla S et al. Assessment of renal functions in patients of chronic liver disease, Renal Failure, 2015;37(9):1457-1463.
116. Mohan J, Narayanasamy K, Ramalingam S et al. Clinical profile of renal dysfunction in cirrhotic liver. International Journal of Biomedical Research. 2016; 7(2): 073-076.
117. Al-Mamun A, Mashud G, Karim F et al. serum creatinine levels unrelated to Child-Pugh status in uncomplicated cirrhosis of liver with ascites.Euroasian J Hepato-Gastroenterol. 2013;3(1):36-38.
118. Fornari F, Imberti D, Squillante MM et al. Incidence of gall stones in a population of patients with cirrhosis. J Hepatol. 1994;20:797.

ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

6/2016
06/10/16

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 04/10/2016 *at* 3-00pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title "Study of renal function in chronic Liver Disease"

Name of P.G. student Pankaj Kumar Saksena
General Medicine

Name of Guide/Co-investigator Dr R.C. Bidari
Professor of Medicine

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE,BIJAPUR-586 103

RESEARCH INFORMED CONSENT FORM

TITLE OF THE PROJECT : "TO STUDY OF RENAL FUNCTION TEST IN CHRONIC LIVER DISEASE"

PG GUIDE : DR. R. C. BIDRI

PG STUDENT : DR. PANKAJ KUMAR SAKSENA

PURPOSE OF RESEARCH:-

BENEFITS:-

I understand that my participation in this study will help the investigator to diagnose the disease better and will help in the management of the disease.

PROCEDURE:- I understand that relevant history will be taken and I will undergo detailed clinical examination after which necessary investigations will be done and accordingly treatment will be given.

RISK AND DISCOMFORTS:-

I understand there is no risk involved and I will experience no pain during the procedures performed.

CONFIDENTIALITY:-

I understand that medical information produced by this study will become a part of my hospital records and will be subjected to the confidentiality and privacy regulation of the said hospital. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file.

If the data are used for publication in the medical literature or for teaching purposes no names will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand I may see the photographs, videotapes and hear the audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:-

I understand that I may ask more questions about the study at any time Concerned. The researcher is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which may influence my continued participation.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:-

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in this study at any time without prejudice. I also understand that the researcher may terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician, if this is appropriate.

INJURY STATEMENT:-

I understand that in the unlikely event of injury to me resulting directly from my participation in this study and if such injury were reported promptly, then medical treatment will be available to me, but no further compensation will be provided. I understand that by my agreement for my participation in this study, I am not waiving any of my legal rights.

I have explained to (patient's / relevant guardian's name) the purpose of the research, the procedures required, and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Investigator / P. G. Guide Date

I confirm that …….(Name of the PG guide / chief researcher) has explained to me the research, the study procedures that I undergo and the possible risks and discomforts as well as benefits that I may experience. I have read and I understand this consent form. Therefore, I agree to give my consent for my participation as a subject in this research project.

_____ _____

Participant / guardian Date

_____ _____

Witness to signature Date

B.L.D.E. (Deemed to be University) SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR.

DEPARTMENT OF MEDICINE

CASE PROFORMA

Name : IP number:

Age: Sex:

Address : Occupation :

Date of Admission : Date of discharge:

Chief Complaints :

SYMPTOMS

1 Fatigue and weight loss	Yes/No
2 Anorexia and flatulent dyspepsia	Yes/No
3 Abdominal pain	Yes/No
4 Jaundice	Yes/No
5 Swelling of legs and abdomen	Yes/No
6 Loss of libido	Yes/No
7 Fever	Yes/No
8 Alteration of bowel habit	Yes/No
9 Malena	Yes/No

10 Haemetamesis	Yes/No
11.Flapping tremor	Yes/No

Past history

Treatment History

Personal History

Physical Examination:

On Examination :

VITALS:

Temperature:

Pulse:

Respiratory rate:

Blood pressure:

GENERAL CONDITION:

Pallor:	Yes/ No
Icterus:	Yes/ No
Cynosis:	Yes/No
Clubbing:	Yes/No
Lymphadenopathy:	Yes/No
Edema:	Yes/No
Pt condition on discharge	Improved/Worsened/same/Expired

SYSTEMIC EXAMINATION

P.A:

C.V.S:

R.S:

C.N.S:

PROVISIONAL DIAGNOSIS :

FINAL DIAGNOSIS :

KEY TO MASTER CHART

A - Absent

P - Present

Y - Yes

N - No

M - Male

F - Female

ALD - Alcoholic liver diseases

HBV - Hepatitis B Virus

HCV - Hepatitis C Virus

AKI - Acute kidnry injury

HRS - Hepatorenal syndrome

NRD - No renal dysfunction

MASTER CHART

				Clinical Features												Renal Functions Test						Liver Function Test							
Serial Number	In/Out patient Number	Sex	Age(Year)	Fatigue and Weight loss	Abdomenal pain	Jaundice	Swelling of legs and Abdomen	Fever	Malena	Hematemesis	Pallor	Icterus	Pitting Edema in lower limb	Flapping tremor	Etiology	Blood Urea(mg/dl)	Serum Creatinine(mg/dl)	Serum Sodiun (mEq/L)	Serum Potassium (mEq/L)	Serum chloride (mEq/L)	Uric Acid(mg/dl)	Total Bilirubin(mg/dl)	SGOT(AST) (U/L)	SGPT(ALT) (U/L)	Alk.Phosphate (U/L)	Serum albumin (gm/dl)	Serum globulin	Renal Dysfunction	Type of Renal Dysfunction
1	3148	M	38	N	N	Y	Y	N	N	N	Y	Y	Y	A	ALD	18	0.6	138	4	101	5	3.2	198	84	154	1.9	3.5	A	NRD
2	13557	M	37	N	Y	Y	Y	N	N	Y	Y	Y	Y	A	ALD	15	0.5	140	3.6	110	3.5	4	109	32	133	2.5	3.9	A	NRD
3	10999	M	78	N	Y	Y	Y	N	Y	N	Y	Y	Y	A	ALD	38	1.1	138	4.2	98	4.8	3.5	90	40	102	2.1	3.8	A	NRD
4	36737	M	56	N	Y	Y	Y	N	N	N	Y	Y	Y	A	ALD	50	3.5	141	4.2	113	4.6	7.8	170	79	98	2.2	4.2	P	HRS
5	11973	M	39	N	N	Y	Y	N	Y	N	Y	Y	Y	P	ALD	98	2.5	137	4.6	103	2.6	5.35	144	75	85	0.8	2.5	P	AKI
6	648	M	32	N	N	Y	Y	N	Y	N	Y	Y	Y	A	ALD	46	5.8	127	3.2	100	4.2	17.7	75	24	109	2	3.4	P	HRS
7	41912	M	30	N	Y	Y	Y	N	N	Y	Y	Y	Y	A	ALD	31	1.3	137	3.6	97	5.1	4.3	108	56	202	2.5	5.1	A	NRD
8	24740	M	75	Y	N	Y	Y	Y	N	N	Y	Y	Y	A	ALD	84	2.6	148	3.7	91	8.1	3.4	101	50	90	2	3.9	P	AKI
9	11073	M	35	N	Y	Y	Y	N	Y	Y	Y	Y	Y	P	ALD	55	2.9	131	3.9	101	4.8	5.4	615	201	177	2.5	4	P	HRS
10	41911	M	70	N	Y	Y	Y	Y	N	N	Y	Y	Y	A	HBV	38	0.6	140	3.5	81	4.1	1.7	97	21	99	2.9	3.4	A	NRD
11	39365	F	58	Y	Y	Y	Y	Y	N	N	Y	Y	Y	A	HBV	50	2.5	132	3.5	101	5.1	4.4	82	69	258	2.6	3.5	P	HRS
12	15388	M	60	N	N	Y	Y	N	N	N	Y	Y	N	A	ALD	35	0.9	139	4.9	98	4.5	1.9	87	42	92	2	5.1	A	NRD
13	3222	M	47	N	Y	Y	Y	N	N	Y	Y	Y	Y	A	ALD	41	0.7	137	3.6	110	3.2	5.1	93	60	117	2.5	3.3	A	NRD
14	1583	M	60	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	A	ALD	42	3.1	142	5.1	82	4.2	6.5	104	31	118	2.1	3.1	P	HRS
15	22815	M	35	N	N	Y	Y	N	N	N	N	Y	Y	A	ALD	40	0.6	137	3.5	99	4.1	16.9	101	29	109	1.5	3.5	A	NRD
16	3217	M	59	N	N	Y	Y	N	Y	N	Y	Y	Y	A	ALD	86	1.9	115	4.8	82	4.1	6.5	91	36	72	2	3.5	P	AKI
17	39791	M	42	N	N	Y	Y	N	N	N	Y	Y	Y	A	ALD	18	0.6	137	3.5	109	7	15.1	106	24	156	2.5	3.1	A	NRD

18	5832	M	50	N	N	Y	Y	N	Y	N	Y	Y	Y	A	ALD	22	1	140	3.7	98	6.2	9.4	85	36	110	2.9	3.8	A	NRD
19	5433	M	43	N	N	Y	Y	N	N	N	Y	Y	Y	A	ALD	16	0.6	137	3.6	99	2.6	4.5	152	34	131	1.9	3	A	NRD
20	17335	M	45	N	Y	N	Y	N	N	N	Y	Y	Y	A	ALD	24	1.3	138	4.3	97	2.8	5.9	76	21	84	2.1	4.6	A	NRD
21	5315	M	32	Y	Y	Y	Y	N	Y	N	Y	Y	Y	A	HBV	18	0.6	139	3.8	98	3.1	1.8	149	87	155	1.7	3.2	A	NRD
22	5818	M	65	N	N	Y	Y	N	N	N	Y	Y	Y	A	HCV	42	0.8	137	4.1	110	3.2	13.5	108	52	118	1.8	2.9	A	NRD
23	12975	M	32	N	N	Y	Y	N	N	N	Y	Y	Y	A	ALD	35	0.6	139	5.7	100	2.8	3.3	91	28	140	2	3.1	A	NRD
24	6801	M	36	N	N	N	Y	Y	N	N	N	A	Y	A	ALD	20	0.9	138	3.9	103	7	0.9	42	21	112	1.9	3.8	A	NRD
25	20897	M	54	N	N	Y	Y	N	Y	N	Y	Y	Y	P	ALD	132	2.2	125	4.2	101	7.6	2.9	208	102	70	2.5	3.6	P	AKI
26	1674	M	40	N	N	Y	Y	N	N	N	N	Y	Y	A	ALD	16	0.6	140	3.5	98	4.1	4.1	88	40	90	2.5	4.1	A	NRD
27	10996	M	35	N	N	Y	Y	N	Y	N	Y	N	Y	A	ALD	30	0.6	137	4.1	110	3.4	1.5	73	39	118	1.8	3.4	A	NRD
28	11581	M	55	N	Y	Y	Y	Y	N	N	Y	Y	Y	P	HCV	79	5.4	154	4.1	104	8.4	7.9	43	39	40	2.4	3	P	AKI
29	5666	M	75	N	N	Y	Y	N	N	N	Y	Y	Y	A	HBV	26	0.8	141	4.8	101	4.7	6.8	55	82	84	2	4.5	A	NRD
30	1077	M	68	N	N	Y	Y	N	N	Y	Y	Y	Y	A	ALD	42	1.2	142	4.2	102	3	5.9	210	109	110	1.5	3.4	A	NRD
31	16593	M	30	N	N	Y	Y	N	N	N	N	Y	Y	A	ALD	40	0.6	137	4.2	108	4	4.5	216	114	115	3	3.2	A	NRD
32	1156	M	50	N	N	Y	Y	N	N	N	N	Y	Y	A	ALD	34	1.1	138	4	99	3.1	2.8	60	38	85	2.6	3.1	A	NRD
33	6752	M	39	N	Y	Y	Y	Y	N	N	Y	Y	Y	A	ALD	18	2.9	139	3.9	88	7.7	9.3	366	61	105	1.6	3.5	P	HRS
34	10399	M	49	N	N	Y	Y	N	Y	N	Y	Y	Y	A	ALD	70	1.8	145	3.4	105	4.2	3.5	101	68	173	2.5	3.9	P	AKI
35	7688	M	65	N	Y	Y	Y	Y	N	N	Y	N	Y	A	HCV	29	1.1	137	3.9	98	5.7	1.8	102	58	192	2.2	3.5	A	NRD
36	25443	M	29	N	N	Y	Y	N	N	N	Y	Y	Y	A	ALD	32	0.8	140	4.2	108	2.9	12.2	145	93	110	3.1	2.8	A	NRD
37	20966	M	45	Y	Y	Y	Y	N	Y	N	Y	Y	Y	P	ALD	17	0.7	141	4	97	4.2	10	155	55	65	1.5	4.1	A	NRD
38	25321	F	65	N	Y	N	Y	Y	N	N	Y	A	Y	A	HBV	26	0.6	138	3.9	99	2.7	1.4	54	31	82	2.8	3.1	A	NRD
39	22691	M	50	N	N	Y	Y	N	Y	N	Y	Y	Y	A	ALD	42	1.2	145	4.6	109	5.4	2.1	91	28	148	2.1	3.9	A	NRD
40	9054	M	42	N	N	Y	Y	Y	N	N	N	Y	Y	A	HCV	40	1.2	137	4	110	4.2	5.2	88	71	110	1.8	2.7	A	NRD
41	36072	M	47	N	Y	Y	Y	N	N	N	N	Y	Y	P	ALD	185	2.4	128	5	97	14	4.1	87	40	90	2.5	3.8	P	AKI
42	11013	M	37	N	Y	Y	Y	N	N	N	Y	Y	Y	A	ALD	80	1.8	147	2.5	90	2.6	5.2	615	210	118	2.5	2.9	P	AKI
43	25689	F	65	N	Y	Y	Y	N	N	N	Y	Y	Y	A	HBV	40	0.8	141	4	109	3	4.9	80	70	110	2	3.1	A	NRD
44	2559	M	40	N	Y	Y	Y	Y	Y	N	Y	Y	Y	A	HCV	98	2.1	148	5.4	103	12	5.4	52	75	113	2.1	3.6	P	AKI

45	25655	M	64	N	N	N	Y	N	N	N	N	N	Y	A	ALD	30	0.6	137	4.5	108	3.2	0.5	98	33	190	2.6	4	A	NRD
46	22914	M	24	N	Y	Y	Y	N	Y	N	Y	Y	Y	P	NASH	54	2.3	149	1.8	102	7.4	3.1	88	50	45	2	3.5	P	HRS
47	21567	M	35	N	N	Y	Y	N	N	N	Y	Y	Y	A	ALD	50	2.6	125	4.6	104	3.2	16	105	16	123	2.1	3.8	P	HRS
48	4092	M	60	Y	Y	N	Y	N	Y	N	Y	N	Y	A	ALD	30	0.7	140	4.3	100	4.2	1.2	99	44	99	2.7	3.5	A	NRD
49	25573	M	52	N	N	Y	Y	N	N	Y	Y	Y	Y	P	ALD	47	2.8	138	4.1	113	4.9	3.2	87	33	60	2.9	2.7	P	HRS
50	5335	M	54	N	N	Y	Y	N	N	N	Y	Y	Y	A	ALD	30	1	142	3.8	105	5.1	6.2	64	21	98	3.6	3.8	A	NRD
51	9309	F	68	N	Y	Y	Y	Y	N	N	Y	Y	Y	A	HCV	40	0.7	141	3.6	98	3.3	3.8	151	110	188	2.7	2.4	A	NRD
52	42253	M	45	N	Y	Y	Y	N	Y	N	Y	Y	Y	A	ALD	94	1.9	148	3.5	104	6.8	23.4	306	258	110	2.3	3.1	P	AKI
53	18779	M	67	N	N	Y	Y	Y	Y	N	Y	N	Y	A	HBV	30	0.7	137	4.5	101	5.2	1.9	40	36	131	3.3	3.5	A	NRD
54	24109	F	65	Y	Y	Y	Y	N	N	N	Y	Y	Y	A	NASH	25	1.1	138	3.9	98	4.3	6.9	92	50	118	2.1	4.1	A	NRD
55	24315	M	40	N	Y	Y	Y	Y	Y	N	Y	Y	Y	A	HBV	176	1.6	127	5.1	102	15	3.4	251	60	376	2.2	2.9	P	AKI
56	25211	M	36	N	N	Y	Y	N	N	N	Y	Y	N	A	ALD	40	0.6	137	4.7	110	3.2	9.5	122	59	97	2.2	4.3	A	NRD
57	26118	F	28	N	Y	Y	Y	Y	N	N	Y	Y	Y	A	HBV	36	1	139	4	105	3.4	18.9	473	202	156	2.8	3.9	A	NRD
58	39968	M	38	N	Y	Y	Y	Y	N	N	Y	N	Y	A	HCV	45	1.2	138	4.1	112	4.2	1.8	67	52	182	1.8	3.5	A	NRD
59	19418	M	64	N	N	Y	Y	N	Y	N	Y	Y	Y	A	ALD	195	3.3	142	5.6	120	5.8	2.9	84	43	46	1.7	3.4	P	AKI
60	41987	M	35	N	Y	Y	Y	N	Y	N	Y	Y	Y	A	ALD	40	2.8	138	3.6	82	5.4	16.9	158	56	152	2.5	3.4	P	HRS
61	35882	M	38	N	Y	Y	Y	N	N	Y	Y	Y	Y	A	ALD	127	3	110	3.4	97	7.2	22	488	203	235	2	2.8	P	AKI
62	10995	M	42	N	N	Y	Y	N	N	N	Y	Y	Y	A	ALD	25	0.7	137	3.5	99	4.2	0.4	98	44	138	1.2	3.4	A	NRD
63	20651	M	45	N	N	Y	Y	N	Y	N	Y	Y	Y	A	ALD	116	4.5	129	5	103	4.5	7.5	115	51	70	1.7	3.8	P	AKI
64	29191	M	38	N	N	Y	Y	N	N	N	Y	Y	Y	A	ALD	50	0.6	141	3.6	101	3.4	3.4	105	78	110	1.9	3.6	A	NRD
65	28434	M	28	N	N	Y	Y	N	N	N	Y	Y	Y	A	ALD	46	0.7	138	4	98	3.2	2.6	85	29	130	2.5	4.5	A	NRD