DISSERTATION ON ASSESSMENT OF RED CELL DISTRIBUTION WIDTH IN PORTAL HYPERTENSION AND ITS CORRELATION WITH CHILD TURCOTTE PUGH SCORE AMONG PATIENTS WITH CHRONIC LIVER DISEASE.

Submitted in Partial Fulfillment of Requirements for

M.D.DEGREE EXAMINATION

BRANCH -1 INTERNAL MEDICINE

THE TAMIL NADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI

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APRIL – 2017

CERTIFICATE

This is to certify that the dissertation titled **"ASSESSMENT OF RED CELL DISTRIBUTION WIDTH IN PORTAL HYPERTENSION AND ITS CORRELATION WITH CHILD TURCOTTE PUGH SCORE AMONG PATIENTS WITH CHRONIC LIVER DISEASE"** is a bonafide work done **by Dr.D.JAYASUDHA**, Post graduate student, Institute of Internal Medicine, Madras Medical College, Chennai -03, in partial fulfillment of the University Rules and Regulations for the award of Degree of MD General Medicine (Branch – I), Internal Medicine, under our guidance and supervision, during the academic year 2014 – 2017.

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ACKNOWLEGEMENTS

At the outset, I would like to thank **Prof. Dr.M.K. MURALITHARAN, M.S., M.CH.,** Dean, Madras Medical College, for having permitted me to conduct the study and use the hospital resources.

I express my gratitude to **Prof. Dr.S. MAYILVAHANAN**, **M.D**., Director and Professor, Institute of Internal Medicine, for his inspiration, advice and guidance in this study.

I am indebted to my chief **Prof . Dr. R.PENCHALIAH, M.D**., Professor, Institute of Internal Medicine for his guidance and motivation throughout the study.

I am extremely thankful to Assistant Professors of Medicine **Dr.S. SIVARAM KANNAN. M.D., and Dr.D.DHAMODARAN. M.D.,** for guiding me with their corrections and prompt help rendered whenever approached.

In conclusion, I wish to thank all the professors, assistant professors and the technical staff in Institute of Internal Medicine

Last but not the least, I wish to thank all the patients without whom the study would have been impossible.

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ABBREVATIONS

ALD	-	ALCOHOLIC LIVER DISEASE
ALT	-	ALANINE AMINO TRANSFERASES
AST	-	ASPARTATE AMINOTRANSFERASE
CDT	-	CARBOHYDRATE DEFICIENT TRANSFERASE
CLD	-	CHRONIC LIVER DISEASE
CTP	-	CHILD TURCOTTE PUGH SCORE
EHPVO	-	EXTRAHEPATIC PORTAL VEIN OBSTRUCTION
GGT	-	GAMMA GLUTAMYL TRANSPEPTIDASE
HAV	-	HEPATITIS A VIRUS
HBV	-	HEPATITIS B VIRUS
HCV	-	HEPATITIS C VIRUS
HEV	-	HEPATITIS D VIRUS
HCC	-	HEPATOCELLULAR CARCINOMA
INR	-	INTERNATIONAL NORMALIZED RATIO
MCV	-	MEAN CORPUSCULAR VOLUME
MDB	-	MALLORY DENK BODIES
MELD	-	MODEL FOR END STAGE LIVER DISEASE
NAFLD	-	NON ALCOHOLIC FATTY LIVER DISEASE
NASH	-	NON ALCOHOLIC STEATO HEPATITIS
PT	-	PROTHROMBIN TIME
PV	-	PORTAL VEIN

RDW	-	RED CELL DISTRIBUTION WIDTH
RDW CV	-	RED CELL DISTRIBUTION WIDTH COEFFICIENT OF VARIATION
RDW SD	-	RED CELL DISTRIBUTION STANDARD DEVIATION
TB	-	TOTAL BILIRUBIN
WHO	-	WORLD HEALTH ORGANISATION

INTRODUCTION

INTRODUCTION

Chronic liver disease and its complications are regularly encountered in the medical wards. Regardless of the cause of the initial insult, fibrosis becomes the main component of chronic damage to the liver.

Hepatic fibrosis and its secondary complications are dynamic processes that in certain situations can be reversible, provided that the underlying insult has been removed.

One of the most common complication is portal hypertension. Direct consequences are ascites, splenomegaly, variceal bleeding, hepatorenal syndrome and portal hypertensive gastropathy. It is also implicated in spontaneous bacterial peritonitis, heatopulmonary syndrome, hepatic encephalopathy. The importance of portal hyertension and its complications is reflected by the fact that it is one of the common causes of death and liver transplantation in patients with chronic liver disease.

Knowledge of portal hyertension and its severity is very essential for assessment of progression of disease and prognosis. It also aids in determining the need for invasive procedure for diagnostic and

therapeutic intervention, optimisation of treatment, and to estimate its response.

Measuring HVPG is very ideal to diagnosis and to grade severity. But the drawback of this procedure is its invasiveness leading to complications. So, a simple, routinely available, cost effective method for severity assessment of portal hypertension would be attractive.

The most frequently ordered laboratory investigation is the complete blood count, which reports the cell counts along with their morphological indices. Red cell distribution width is an estimate of the variation of RBC size. Recent reports indicate that elevated RDW is associated with a higher risk of mortality. Impaired iron mobilisation, inflammatory stress, and various other factors leads to increased RDW. It has been found that in hepatic cirrhosis, expression of pro-inflammatory cytokines is regulated by ferritin. These cytokines increase the heterogenecity of RBC maturation and further impairment, which leads to an increase in RDW.

Child-Turcotte-Pugh score which indicates the severity of liver disease, has also been used to prognosticate patients with cirrhosis. Its five variables and three classes categorise the patients into mild, moderate and severe stages, thereby accounting for mortality risk.

This study aims to assess the severity of portal hypertension in chronic liver disease, using a simple haematological parameter, RDW, which is inexpensive, and to compare the same with Child Turcotte Pugh score.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

- To study the role of Red cell Distribution Width (RDW) in predicting the severity of portal hypertension in chronic liver disease

- To correlate Red cell Distribution Width with Child Turcotte Pugh score and portal Doppler.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Chronic Liver Disease and Cirrhosis:

Liver disease may pose a serious threat to the community because of its high prevalence worldwide and unfavorable outcome, which includes premature deaths from liver decompensation, cirrhosis, and HCC. Chronic liver disease and cirrhosis may occur to any people in the community regardless of age, sex or race. Mostly chronic liver disease (CLD) may lead to cirrhosis and this cirrhosis may eventually lead to several complications like ascites, portal hypertension, hepatic encephalopathy leading to a profound morbidity and mortality worldwide. However, the geographic variation plays a crucial role in determining the incidence and prevalence of hepatic diseases worldwide which is mainly based on the prevalence of causative factors in a particular environment. The major causative factors for the development of chronic liver disease eventually leading to cirrhosis are as follows: Viral hepatitis (mainly Hepatitis B,C), alcohol and NASH (non-alcoholic steatohepatitis). This again may split into 2 different classes like that alcohol and NASH are the leading causes of CLD among the developed countries while Viral hepatitis that too especially Hepatitis B is one of the major causative factors for CLD among the developing countries .(1)Other causes include hepatotoxins, immune-mediated liver injury,

Genetic abnormalities. One of the major complications of cirrhosis is portal hypertension which itself is a life-threatening condition. This review outlines the importance of chronic liver diseases and its impact on the development of portal hypertension globally and in India.(2–4)

Burden of CLD worldwide:

In 2001, an average estimate of around 771,000 people died because of CLD placing it as the 14th leading cause of death in the world scenario and 10th leading cause of death among the developed countries. In a global survey it has been estimated that around the year 2020, CLD may become the 12th leading cause of death in the world. The mortality rates were in the higher range in the mid-1970's due to the increased alcohol consumption mainly in the European and American countries. Later there was a declining phase around 1980's due to decrease in the alcohol consumption among the people. Recent reports suggest there was a steep increase in the mortality rates due to cirrhosis which was invariably due to overt increase in alcohol intake in the west and also in many developed countries. If we take into account the developing countries, the causative factor mainly being hepatitis B virus (HBV) infection. HBV is a global burden affecting 2 billion people of which around 350 million people were the chronic HBV patients. HBV is more prevalent in the Southeast Asia, china, Alaska, Peru, northwest Brazil.

Even though HBV plays a major role in the etiology of CLD, recently there has been an increasing trend in the development of NASH and non-alcoholic fatty liver disease (NAFLD). NAFLD is a condition which may range from simple hepatic steatosis to advance fibrosis and CLD. NASH leads to hepatic steatosis which is often missed in the diagnosis leading to mortality. NASH commonly occurs in patients with obesity, diabetes, and dyslipidemia. In Europe and America, there seems to be a rise in the incidence of NASH due to increase in the obese population in those countries. The estimated prevalence is around 3-35% and in North America around 26% of patients are diagnosed with hepatic steatosis. In other parts of the world, NASH ranges from 9-37%. It is estimated that around 90% of people with obesity have some form of fatty liver ranging from simple steatosis to severe forms of NASH that include cirrhosis. Patients with abnormal liver function tests with unknown etiology have been later diagnosed as NASH and this accounts for 30-40% of cases according to a survey.(4)

Burden of CLD in India:

In India, viral hepatitis is one of the most important causes for the development of CLD. Viral hepatitis is a major public health problem in India. This has also posed a significant economic burden to the country. Among the viruses hepatitis A (HAV) and E (HEV) plays a significant

role. It has been stated that almost 90% of people acquire anti-HAV antibodies during their adolescence itself and HEV affects the pregnant mothers and also it leads to fulminant hepatitis on co-infection with HBV. India has intermediate HBV endemicity of which 2%-4% comprises of the carrier population. HBV have found to be the major cause of CLD and HCC (hepatocellular carcinoma). Chronic HBV infection is acquired even before 5 years of age that too mainly through horizontal transfer. Vertical transmission of HBV has declined over the decades and it is found to be infrequent in the recent past. HBV genotypes A and D are prevalent in India, which shares the similarity of HBV strains in the west. HCV infection has a prevalence of around 1% and occurs predominantly through transfusion and the use of unsterile glass syringes. HCV genotypes 3 and 2 are prevalent in 60%-80% of the population. About 10%-15% of CLD was associated with HCV infection in India. In addition to this, there has been an increase in the incidence of Alcoholic liver disease (ALD) and NAFLD in the recent years.(3)

Portal hypertension worldwide scenario:

Liver cirrhosis can progress from a preclinical phase which is usually prolonged over several years to a clinical phase with the development of ascites, encephalopathy, and variceal bleeding making the course of the disease much shorter and usually fatal. Portal

hypertension plays a vital role in this transition from pre-clinical to clinical stage of the disease. It is the major cause of bleeding-related mortality in case of cirrhotic patients. Portal hypertension occurs because of increase in the intrahepatic vascular resistance and also due to the resistance in the portal venous inflow. The notable clinical features are mainly splenomegaly and variceal bleeding. In this review, it deals mainly with the causative factors attributing to the development of portal hypertension by architectural distortion of vessels due to a primary pathology in the liver which may be a hepatic fibrosis of any etiology. The contributing factors may be viral hepatitis, alcoholic liver disease, NASH and any kind of hepatotoxic drugs or toxins which damages the liver and leading to progressive hepatic fibrosis and cirrhosis. Thus in a brief clinical context, oesophago-gastric varices are the most important collateral vessels in portal hypertension, which eventually ruptures resulting in severe bleeding manifestations, if the wall tension reaches a critical point. Bleeding is the leading cause of mortality in about one-third of cirrhotic patients. The reported prevalence of esophageal varices in cirrhotic patients ranges between 24% and 80%, with a mean of about 60%.(5) Also, the prevalence of varices among the compensated patients was found to be around 30% and for decompensated patients, it is about 60 %. In a study, it was found that cirrhosis was responsible for 51% of variceal bleeding and EHPVO (extra hepatic portal vein obstruction) for

34 % of variceal bleeding. However, mortality rates are more in cases of cirrhosis than in EHPVO. EHPVO is the leading cause of variceal bleeding in the west.(6) Hence in a case of portal hypertension, it is very essential to predict the indicators of portal hypertension at a very early stage to prevent mortality.(7) Endoscopic procedures to rule out portal hypertension were widely accepted for screening but being an invasive procedure it has its own limitations. Several non-invasive methods have been developed which has been further dealt in this review.

Portal hypertension in Indian context:

Portal hypertension (PHT) is defined “as an increase in portal pressure of >12 mmHg”. The diagnosis of esophageal varices by endoscopy is one of the important predictors of portal hypertension as another cause of esophageal varices is unknown. In India, a study conducted in a pediatric population has shown 76.5% cases of PHT were due to EHPVO and around 20% was due to cirrhosis. It has been shown that the risk of bleeding is much more with EHPVO than with cirrhosis. The risk of bleeding is 80% in EHPVO and 32% in cirrhosis.(8) Despite, the mortality related to variceal bleeding is much higher in cirrhosis as compared with EHPVO. Upper gastrointestinal bleeding (UGIB) is the most common gastroenterological emergency. Even though there were many major advances in diagnosis and treatment, UGIB remains a serious

problem in the routine clinical practice with a mortality of 3% to 14% in the recent years. Therefore, it is very important to guide the diagnosis towards a variceal or non-variceal bleeding even before performing an endoscopy.(9)

Alcohol and Chronic liver disease:

Alcohol is well-known hepatotoxin consumed worldwide resulting in morbidity and mortality of the community. Among those conditions affecting the community, alcoholic liver disease contributes to a greater extent which may vary from a simple steatosis to cirrhosis of the liver. Alcohol abuse has led to around 2.5 million deaths and 69.4 million annual disability adjusted life year. There is a strong association between the prevalence of cirrhosis and a country’s annual per capita alcohol consumption. The annual per capita consumption varies from one geographical region and the following graphs of WHO depicts the differences.

Figure 1: Proportion (%) of current drinkers, former drinkers, and life-time abstainers among the total population (15+ years) by WHO region and the world

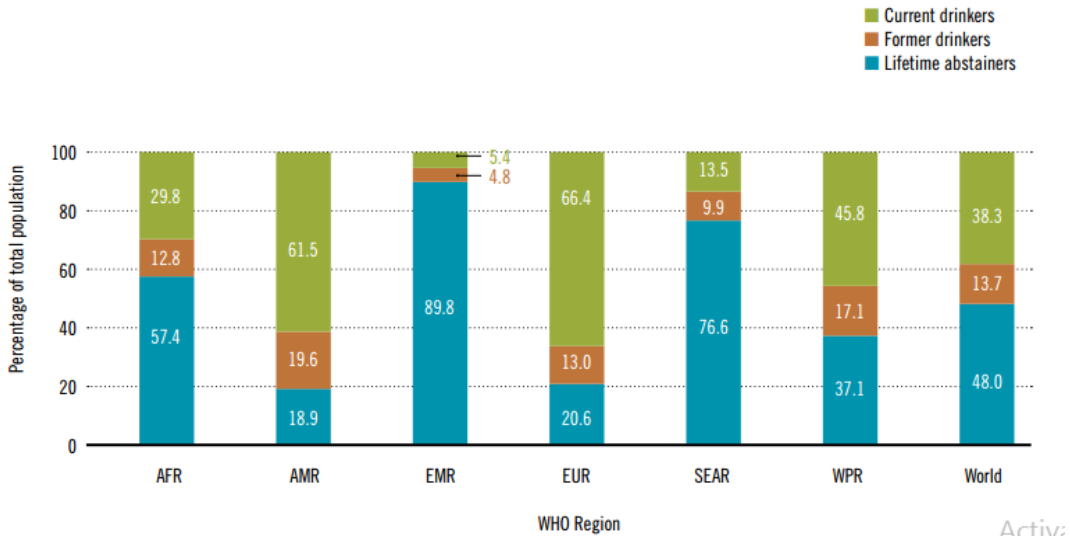


Figure 2: Five year change in recorded alcohol per-capita (15+ years) consumption, 2006-2010

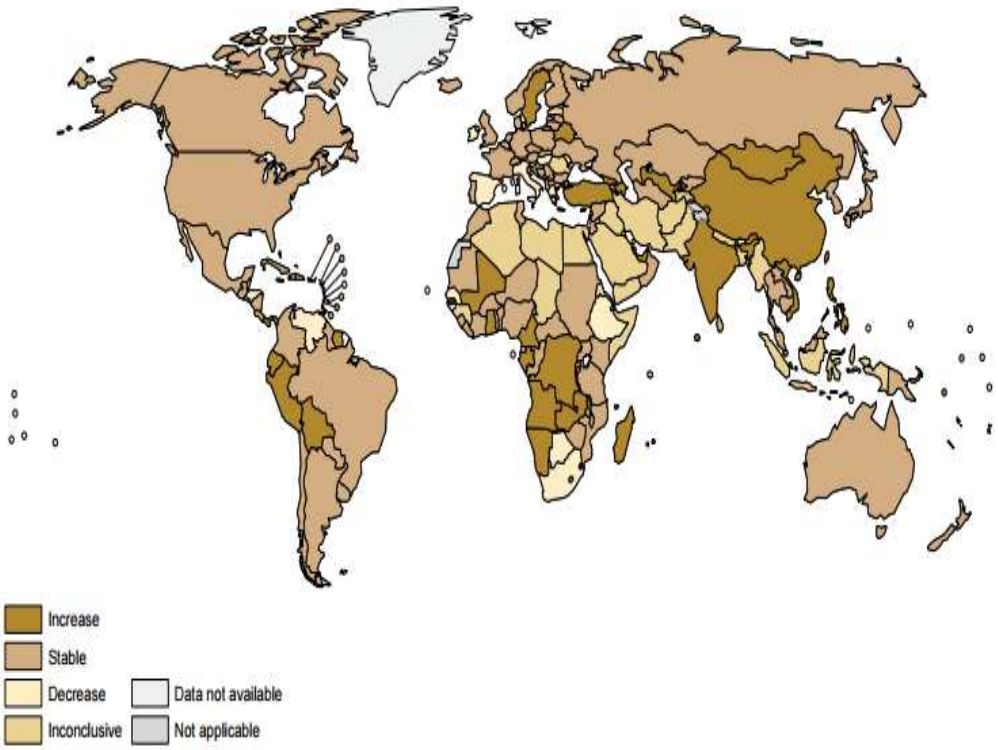
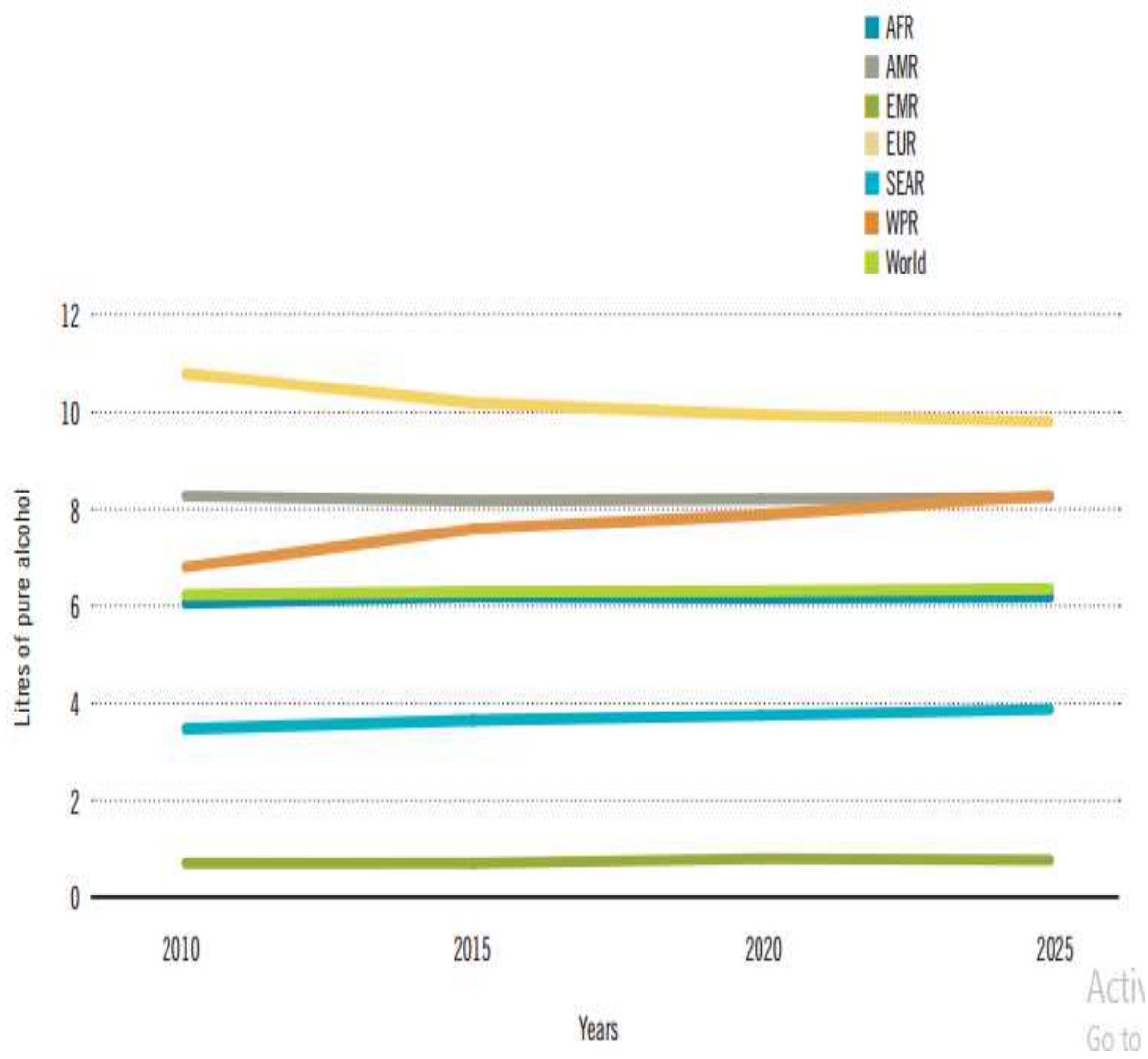


Figure 3: Total alcohol per capita (15+ years) consumption by WHO region, 2010-2025



On a broader perspective, Alcoholic liver disease may progress as a fatty liver (simple steatosis) followed by alcoholic hepatitis, hepatic fibrosis, and finally to cirrhosis. Alcoholic hepatitis may not develop in all the persons who consume agreater quantity of alcohol. It has been suggested that among 90% of heavy drinkers only a smaller proportion of people (around 10-35%) might develop severe complications with the worst prognosis. Even the duration, frequency, amount of alcohol consumption as well as the type of alcohol consumed may decide the prognosis of ALD. Recent meta-analysis results suggest an average of 25 grams of pure alcohol consumption may lead to the development of cirrhosis (higher risk) when compared to non-drinkers. Despite this, only an average of around 10-20% people (80g pure alcohol consumption) have the risk of ending up with cirrhosis.(10) Gender also plays an important role in the development of cirrhosis, women are more prone for cirrhosis than men even with shorter duration of alcohol consumption. The mechanism that has been postulated for this is as follows:

- Lower total body water content in females than males
- Lower activity of gastric alcohol dehydrogenase
- Higher body fat content

Genetic factors like change in the DNA coding region in CD14 and a newer genotype PNPLA3 rs738409 (G/G) was associated with cirrhosis.(11)

Viral hepatitis and CLD:

It has been estimated that around 240 million people across the globe were found to be infected with Hepatitis B virus (HBV) and those people were at a greater risk of developing hepatic decompensation and cirrhosis in future. Before the implementation of the Hepatitis B virus vaccination program, the Asian-Pacific region was categorized into 3 zones based on HbSAg prevalence. They are as follows:

- High-prevalence zones (8%) which include mainland China, the Hong Kong, Taiwan, Korea, Mongolia, Philippines, Thailand, Vietnam and south pacific islands
- Intermediate-prevalence zones (2–8 %) which include central Asia, the Indian subcontinent, Indonesia, Malaysia, and Singapore
- Low-prevalence zones (<2 %) which includes Australia and New Zealand(12)

In the recent years, the incidence of HBV have significantly decreased due to the global HBV vaccination programs and even in India reports suggests that the incidence of HBV was around 3.7% among the pregnant females in the year 1987 which was overtly reduced to 1.1% in recent years. Some of the important definitions regarding HBV infection which is helpful for understanding the disease progress and also in the management of the patients suffering from the disease were described below

- Chronic HBV infection: “HBsAg seropositive status beyond 6 months”
- Chronic hepatitis B: “Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. It can be subdivided into HBeAg-positive and HBeAg-negative chronic hepatitis B”

Hepatic decompensation: “Significant liver dysfunction as indicated by raised serum bilirubin (more than 2.5 times the upper limit of normal) and prolonged prothrombin time (prolonged by more than 3 s), or INR>1.5 or occurrence of complications such as ascites and hepatic encephalopathy” HBV has 8 genotypes (A-J) and among those 8 genotypes, A&D were found to be commonly occurring genotypes in India. Genotype C infections possess a higher frequency of BCP

A1762T/G1764A mutation than genotype B. Genotype D-infected patients had a higher prevalence of BCP A1762T/G1764A mutation with more progressive liver disease than those with genotype A infection. On the treatment perspective, genotype A has shown a favorable response to IFN-A treatment when compared to genotype D patients. One of the peculiar and rare presentations of HBV is Occult hepatitis B (OBI) infection. OBIcan be coined when there is detectable HBV DNA in serum and/or liver in patients who are tested negative for serum HBsAg by the most sensitive commercial assays. The prevalence of OBI across the globe was estimated around <1% to 18% and there also consensus that the range may be underestimated as the diagnosis of OBI was certainly difficult in the clinical practice.(12) The mechanism which leads to OBI still remains as inconclusive. However, there are few postulations for the development of OBI and they are listed below:

- Mutations in viral genomes, mainly over the surface gene (e.g., G145R) as a result of which the surface antigen cannot be detected
- Replication of HBV at an extremely slower rate because of which the surface antigen might be expressed only at undetectable levels

- More range of diversities found among the nucleoside and amino acid composition of OBI when compared to other chronic HBV types.

These properties are of paramount importance because the undiagnosed cases of OBI may lead to the development of severe hepatic decompensation amidst with cirrhosis and cirrhosis-related complications like portal hypertension and hepatic encephalopathy resulting in a significant morbidity and mortality to the community. According to several studies in the recent past, almost all OBI patients were found to have normal liver function tests and very few or no necro-inflammation and fibrosis in the histopathology of liver. Despite, OBI may be the causative factor for the development of cirrhosis and hepatocellular carcinoma. It was also suggested that in most of the cases where OBI was found to the etiology of liver cirrhosis, nearly in all cases co-infection with hepatitis C were evident. Studies also suggest that in the overall incidence of cryptogenic liver cirrhosis OBI constitutes around 4.8-40% of the cases. Thus in the management of chronic liver diseases, emphasis on OBI was much needed for the good prognosis of patients.

Impact of Occult HBV in India:

India lies in the intermediate zone of HBV prevalence and around 40 million people are affected by HBV. The newer and recent entity was occult HBV infection which goes unnoticed in the clinical practice. The cause of acute liver failure in around 47% of patients in India is unknown. In this 458 patients were taken into analysis and out of which 216 acute liver failure patients etiology was unknown in nature. 41% of these patients were found to be positive for HBV DNA screened through polymerase chain reaction. The patients who are chronically infected with hepatitis B virus were considered to be the reservoirs of HBV infections while the occult HBV cases may be due to the occurrence of several mutations inside the carriers. These mutations may alter the immune-reactivity of several HBV proteins and might also alter the HbSAg titers in those patients which lead to seronegativity among OBI patients. Out of 591 patients 56 patients were found to be HbsAg negative with quantifiable significant HBV DNA titers.(13) The genome sequence analysis was performed in these patients in an Indian based study and the results are as follows:

- Eight patients were found to be affected by genotype A and 6 patients with genotype D

- The changes observed in the regulatory region with some possible alterations in the proportion of large and small nuclear proteins of HBV DNA may result in the undetectable levels of HbSAg in the serum of the patients.

Diagnostic aspects of CLD:

The important area of this review begins with the diagnostic aspects of Chronic Liver Disease. The diagnosis of a CLD can be broadly classified into 2 different categories as:

Non-invasive techniques

Invasive techniques

These techniques can be applied to various etiologies of CLD notably Alcoholic liver disease, viral hepatitis (HBV & HCV), miscellaneous causes.

ALCOHOLIC LIVER DISEASE (ALD):

Initially to diagnose a case of ALD using clinical and relevant biochemical parameters it must be ensured that there is no other etiology was associated with CLD in such patients of heavy alcohol consumption. Moreover to diagnose a case of ALD could be a challenging one as there is no clear cut confirmatory diagnostic tool to focus on ALD. Adding to

this the patients may be completely devoid of any symptomatology pertinent to ALD, no obvious clinical signs suggestive of early ALD or early cirrhosis and there may also be normal liver function tests. Moreover, the coexisting comorbidities like obesity and diabetes may be a confounding factor in the development of NAFLD and there may also be some patients who fail to attend the clinical setting despite continuous heavy alcohol consumption. All these factors have placed ALD, a condition of a chronic progressive liver disease. Generally suspicion of ALD should arise if there is evidence of prolonged alcoholic consumption and the laboratory values are suggestive of increase in the liver enzymes notably if the AST (aspartate aminotransferase) was significantly greater when compared to ALT (Alanine aminotransferase) along with the examination findings such as hepatomegaly, apparent clinical signs of CLD, imaging studies like radiological picture in favor of hepatic steatosis or fibrosis/cirrhosis. It also includes patients who have undergone a liver biopsy in the recent past and the reports were suggestive of features of macro-vesicular steatosis or cirrhosis. As already discussed patients with ALD may or may not have increased levels of liver enzymes because the severity of ALD does not have a significant correlation with the severity of the hepatic injury. However, the pattern of increase in the liver enzymes i.e. serum transaminases plays a significant role in the diagnosis of hepatic injury related to alcohol

consumption. Aspartate aminotransferases may increase around 3 folds greater when compared to Alanine aminotransferases (ALT). There is also a significant rise of GGT (Gamma-glutamyltranspeptidases) in patients with ALD.(14) Nevertheless, it is important to exclude other causes related to hepatic dysfunction and of some of the conditions sharing the similarity in differential diagnosis were chronic viral hepatitis, autoimmune hepatitis, hemochromatosis and drug-related hepatotoxicity. In such conditions where the etiology cannot be concluded with the laboratory tests invasive tests like Liver biopsy is warranted. In the initial workup, primary investigations such as complete blood counts, serum liver enzymes like ALT, AST, ALP, GGT, bilirubin, albumin and INR need to be checked. If there is evidence of any hepatocellular injury patient should be screened for HbSAg, HbcAG, HBC antibody titers in order to rule out viral hepatitis. Serum GGT, AST, ALT, mean corpuscular volume (MCV) and carbohydrate-deficient transferrin (CDT) were the most common biomarkers to be screened if an alcoholic liver disease was the provisional diagnosis. Antibody titers also play a role in the diagnosis of alcoholic liver disease. IgA to IgG ratio is increased in the case of an alcoholic liver disease. GGT is a non-specific marker for an alcoholic liver disease because there are conditions like obesity, advanced age, also in some liver diseases like fatty liver as well as the hepato-biliary disorder, carcinoma of liver and in a certain drug like phenytoin,

there was a rise in the levels of GGT. There is also another marker for chronic alcoholism which is more sensitive than GGT is carbohydrate-deficient transferrin (CDT). CDT was nothing but the transferrin that has lower bonding with carbohydrates and can rise with alcohol consumption. However, there is no single biomarker which has both adequate sensitivity and specificity in order to detect the chronic alcohol abuse. Even though there are many markers for the alcoholic liver disease the way of diagnosing ALD can be a combinatorial approach which can be done by combining screening questionnaire with the diagnostic markers that can be an optimistic tool for the accurate diagnosis of ALD. Ethyl glucuronide (EtG), ethyl sulfate (EtS) and phosphatidylethanol (PEth) were the newer diagnostic markers used in the clinical out-patient departments to monitor the alcohol abstinence in individuals treated for ALD.

Somehow, notable inter-individual variability in phosphatidyl ethanol (PEth) levels have been observed in the clinical research studies which may pose a confusion in the reliability of PEth levels for determining chronic alcoholism further it may limit the utility of PEth levels in the identification of relapse cases from alcohol abstinence. Serum cytokeratin-18, a recent marker identified to detect apoptosis of the hepatocyte in liver disorders and it was one of the most promising

tools in the diagnosis of NASH and that too in combination with Fibroblast Growth Factor (FGF-21), it possesses a greater sensitivity in the diagnosis of ALD. Currently, the available imaging modalities for diagnosing ALD were USG of liver, Fibroscans, CT scan and MRI. In alcoholic liver disease (ALD), hepatic steatosis was one of the major pathology found in patients with ALD.(14) Non-contrast CT helps in diagnosing hepatic steatosis at an early stage. Some of the recent developments in the CT scan are as follows:-\

- Liver to spleen attenuation ratio
- Controlled attenuation parameters with transient elastography help to find the features of hepatic steatosis and also in the process of quantification of steatosis
- In CT scan >10 HU was highly predictive of hepatic steatosis. MRI of liver in case of ALD shows the following features such as an enlarged caudate lobe, visualization of the right posterior hepatic notch and smaller size regenerative nodules. Acoustic radiation force impulse and magnetic resonance elastography are the latest developments in the imaging modalities and have been used for measuring the liver stiffness for the purpose of quantifying hepatic steatosis. However, if it was demanded as a single Gold standard test for diagnosing liver fibrosis eventually

liver biopsy is the only diagnostic tool currently available to stage the disease progression. This is very important often in clinical practice because the stage of simple steatosis to alcoholic steatohepatitis (ASH) may significantly impair the prognosis in patients with ALD. The typical histopathological findings are listed below

- Centrilobulated accentuated steatosis
- Hepatocyte ballooning insidiously associated with Mallory-Denk bodies Steatosis and alcoholic steatohepatitis (ASH) are the most common predictors in the diagnosis of ALD and it also implies the chronic alcohol abuse. Some of the other clinical and demographical factors associated with the development of ALD involve the patients with continuous alcohol consumption, advancing age groups, chronic smokers, cirrhosis with increased child pughTurcott score, and also concomitant chronic viral hepatitis infection.

Viral hepatitis:

Viral hepatitis due to hepatitis B and C is a dreadful condition which has to be diagnosed more precisely not only to diagnose the patient's disease condition but also to decide the therapeutic strategy for starting an anti-viral regimen in patients with viral hepatitis. Even though

invasive procedures like liver biopsy was one of the standard investigatory procedure for evaluating patients with viral hepatitis and to find the level of tissue damage starting from a simple steatosis to a massive fibrosis. Ishak and METAVIR were one of the significant combinatorial assessments along with fibrosis clinically. The clinically relevant endpoints are as follows:

- If METAVIR score is more than 2 and Ishak score is more than 3 for fibrosis, it indicates that patients were in need of antiviral therapy for either hepatitis B or C.
- If METAVIR is score than 4 and Ishak score is around 5-6 then it implicates that patient was progressing from fibrosis to cirrhosis and it indicates that patients were in need of monitoring for the complications pertaining to portal hypertension as well as hepatocellular carcinoma Liver biopsy as such it has several limitations on its own and also it is an invasive procedure with apparent inter as well as intraobserver variations in the purview of histopathological examination. Recently American guidelines for obtaining a liver biopsy specimen specifies that only a 16 gauge needle should be used along with 11 complete portal tracts for a tissue length of 2-3 cm in size.(15,16) But to accustom with such a precise

technique, it is possible for only a few clinical expertise in this field. After the invention of novel invasive methods for assessing liver fibrosis and in addition to that even the treatment strategy may be planned according to that, moreover, it is also useful in monitoring the patient response to anti-viral therapy. The non-invasive techniques also aid in prognosis of the patients.

A series of biochemical tests are performed in order to confirm the diagnosis of viral hepatitis and they are as follows:

- Liver function tests include both direct and indirect bilirubin, serum transaminases which include alanine aminotransferases (ALT), aspartate aminotransferase (AST), AST/ALT ratio, gamma-glutamyltranspeptidase (GGT), alkaline phosphatase, albumin, albumin/globulin ratio, prothrombin time
- Lipid profile includes the levels of triglycerides, total cholesterol, low-density lipoprotein, and high-density lipoprotein
- Other tests include blood urea nitrogen, creatinine, alpha-fetoprotein.
- Most importantly marker of hepatitis virus plays a significant role both in diagnosis and prognosis of the disease. They are

HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, HBV-DNA anti-HCV, HCV RNA

Among the non-invasive tests available for chronic hepatitis C (CHC) infection, the first non-invasive technique used in the diagnosis was the Fibrotest, which is a group of essential diagnostic parameters comprising of haptoglobin, alpha 2-macroglobulin, g-glutamyltransferase (GGT), apolipoprotein A1 and total bilirubin

¬Forns' score and the APR index are the newer modalities. In Forns' score, the components were age, GGT, cholesterol, platelets, and pro-thrombin, whereas APR index includes AST and platelets. Furthermore, other newer models have been developed which includes the ELF-score, heap-score, and the fibro meter

¬ Measurement of liver stiffness: Transient elastography: FibroScan is used (results may range from 2.5 to 75kPa) Acoustic radiation force impulse imaging: Acuson 2000 Virtual Touch Tissue Quantification (results may range from 0.5 to 4.4 meters/sec) Magnetic resonance elastography (results may range from 0.5 to 10 kPa).(15)(17)

Table: Common non-invasive diagnostic indices for viral hepatitis(15)

Hepatitis B serum biomarkers	Hepatitis C serum biomarkers
Hui-score: 3.148+0.167*BMI+0.888*bilirubin -0.151*albumin-0.19*platelet	Fibrotest: a2 macroglobulin, GGT, apo-lipoprotein A1, haptoglobin, total bilirubin, age and gender.
Zeng score: 13.995+3.220*log(a2 macroglobulin)+3.096*(age)+ 2.254*log(GGT)+2.437*log(hyaluronate)	Forn index: 7.811- 3.131*ln(platelet count)+0.781*ln(GGT)+3.467*ln(age)-0.014(cholesterol) AST to platelet ratio(APRI) score

Prospects and limitations of non-invasive diagnostic modalities:

Serum biomarkers:

Prospects:

- Easily affordable and available at low cost
- Results can be reproducible even at different settings
- Highly applicable indeed well-validated techniques are available

Limitations:

- Results are sometimes non-specific with the given liver pathology
- Stages of cirrhosis are difficult to diagnose and reliable results cannot be obtained
- Less specific when compared with TE (transient elastography)

Transient elastography:

Prospects:

- Higher prognostic significance in case of cirrhosis
- Easily learned technique and available as an out-patient procedure
- Results are obtained rapidly and it is easier to learn the technique

Limitations:

- Difficult to differentiate the intermediate stages of fibrosis
- Chances of obtaining false positive results may be possible in cases of acute hepatitis, extra-hepatic cholestasis
- Lower applicability in cases with obesity and ascites

ARFI

Prospects:

- Higher applicability when compared to TE in cases of obesity and ascites
- Can be operated with the help of a normal ultrasound machine

Limitations:

- Quality of the tests is not reliable
- Cannot be applied to differentiate the intermediate stages of fibrosis
- Narrow range in the depiction of values

MR elastography:

Prospects:

- Whole examination of liver may be possible with MR elastography
- Higher applicability when compared with TE in cases of fibrosis
- Can be operated with a regular MRI machine

Limitations:

- More time-consuming procedure
- Highly expensive and not affordable to all patients
- Not applicable in cases hemosiderosis and other iron overload states

Portal Hypertension:

Portal hypertension is one of the common and most important complications that arise as a sequel of chronic liver disease of any etiology. However, fibrosis tends to remain as the main component in terms of severity and prognosis of portal hypertension. In the current era of advanced diagnostics and treatment modalities even there is a chance of reversal mechanisms favoring prognosis of the disease. Thus in a case of portal hypertension which is mostly arising out of a consequence of long-standing hepatic fibrosis, it may be reversible if the cause of hepatic fibrosis being removed. In due course of time, there may be a chance of regression of the disease. Henceforth, it is of paramount importance to accurately determine the prognosis and severity of fibrosis which may eventually lead to portal hypertension. Therefore, an accurate estimation of the extent of damage due to fibrosis and PHT is important to evaluate the disease state and prognosis and probably this will be the most important milestone in revolutionizing the treatment strategy of portal

hypertension. Being heterogenic in nature, portal hypertension and cirrhosis were to be diagnosed at an early point of time. One of the most promising invasive diagnostic tools in the diagnosis of portal hypertension was HVPG (hepatic venous portal gradient) and it is currently the gold standard technique. The HVPG is measured as a difference between the following 2 parameters

Wedged hepatic venous pressure (WHVP) :

It is a direct relation to the pressure formed in the hepatic sinusoids. This is done by the process of occluding the hepatic vein which will result in the cessation of blood flow leading to the formation of a static column of blood. It also provides an accurate measurement of portal pressure which was already been demonstrated in cases of alcoholic hepatitis and viral hepatitis.

Free hepatic venous pressure (FHVP):

FHVP is measured by the process of pressure estimation in a non-occluded hepatic vein. HVPG may be a better prediction tool to provide valuable information about the future morbidity and mortality risk associated with portal hypertension. Moreover, this can also be an indirect tool in the assessment of liver parenchymal function and in

addition it may also be a supportive tool in the correlation of the degree of histological fibrosis associated with chronic liver pathology.

Non-invasive:

Non-invasive studies associated with the diagnosis of portal hypertension are very few in number. The literature search also shows very limited techniques available for this purpose. Some of the important serum biomarkers currently available are listed below

- Serum laminin levels,
- Serum hyaluronic acid
- Procollagen type ⅢpropeptideStudies have shown that laminin and hyaluronic acid levels in the serum were found to correlate with the extent of liver damage. Studies have shown that in cases of portal hypertension and esophagealvarices, laminin and hyaluronic acid levels correlate with the disease severity. In clinical application perspective, the role of non-invasive biomarkers when compared to the invasive biomarkers lag behind in the aspect of diagnosis and treatment of the disease condition. In summary, noninvasive laboratory markers are still inadequatein assessing the degree of fibrosis especially in PHT, and accurate broader validations in various clinical situations are needed. Imaging modalities like Doppler US indices which

include the measurable parameters like PV blood volume, effective portal liver perfusion mean or maximum PV velocity, portal blood flow, PV congestion indexand resistance indices of arteries in the spleen and the liver may help in the better diagnosis of liver pathology. Pulsed wave Doppler may aid in the determination of the changes observed in the following vessels

- Proper hepatic arteries
- Portal vein and
- Hepatic vein (HV).

Among the three vessels, HV waveform seems to be more promising in the depiction of data for the future prognostic score for assessing the severity of portal hypertension. Here comes a parameter of significance namely damping index (DI). The damping index was nothing but a formula which is calculated by dividing the minimum velocity by the maximum velocity of the downward hepatic venous flow. This damping index has a reasonable sensitivity and specificity in the prediction of portal hypertension with a greater accuracy. Despite, measurement of values by the assessment of Doppler may be influenced by several patient-related factors. Doppler measurement is influenced by many patient-related factors which include respiratory movements of the

patient and the meal timings, as well as inter-observer variations. (5,18,19)

Besides, collateral pathways, hepatic steatosis, and inflammation may also contribute to the variability in the assessment of portal hypertension. Contrast-enhanced ultrasound (CEUS) imaging was one of the emerged newer techniques in the diagnostic arena. As of now, there are only two US elastography techniques currently in use to measure the liver stiffness (LS). They are as follows:

- Shear-wave based elastography: includes Transient elastography (TE), commonly called as fibro scan. It is the most widely used and a clinically validated tool in the diagnostic perspective of CLD. Other techniques were acoustic radiation force imaging (ARFI) and supersonic shear wave elastography (SSWE)
- Real-time elastography.
- Shearwave based elastography includes TE (commonly called as fibroscan), which is the most widely evaluated and used technique followed by acoustic radiation force impulse (ARFI) imaging, and supersonic shear wave elastography (SSWE).

Patients with portal hypertension in a consistent show the alteration in the following lab parameters low platelet counts, anemia, an increase in INR, AST >2xUNL, ALT >2xUNL, elevated bilirubin and GGT levels. However, if we take into account of the complications pertaining to portal hypertension the major role being played by portal hypertensive gastropathy (PHG) which is generally a complex secondary change seen in the gastric mucosa. PHG may be an important causative and a provocative factor in the development of acute or chronic hemorrhage. Thus endoscopic procedures although being invasive in nature, it is the deciding diagnostic modality for treating as well as monitoring the patient outcome in the case of portal hypertension.(19) This can be done with several prognostic markers and scores namely child-pughTurcott score (CPT), MELD score and their correlation with fibro tests which all together can improve the quality of patient care in portal hypertension.

Non-invasive markers and its current aspects in Liver diseases:

The liver is the gateway for gut products to enter into systemic circulation. As a result, it is more exposed to potential toxins and injury. Recent longitudinal studies have shown that mainly the presence of fibrosis and its severity in liver biopsy is the single most important predictor of outcome in chronic liver diseases.

Hepatic stellate cells and myofibroblasts are the main sources of liver fibrosis. Insult to liver leads to cytokines production and activation of hepatic stellate cells, thereby causing liver inflammation which advances to irreversible changes and scarring.

Liver biopsy is the gold standard for assessment and quantification of liver fibrosis. Major drawbacks of liver biopsy are due to its invasiveness which engenders pain and significant complications, poor patient acceptance, considerable cost, sampling errors. These factors have lead to an increased interest in the identification of non-invasive of markers of liver fibrosis.

The availability of accurate non-invasive tests enables us to screen large cohorts and to assess the true burden of liver disease in general population.

Non-invasive tests are safe, easy to perform, reproducible and inexpensive.

For chronic liver disease or cirrhosis, non-invasive markers can be broadly divided into radiological and serum biomarkers.

In this review, we intend to describe RDW (red cell distribution width) as a non-invasive biomarker and to correlate its severity with chronic liver disease and portal hypertension.(20)

NON-INVASIVE SEROLOGICAL MARKERS

Characteristics of ideal non-invasive serological markers include- It should be

- Quick to perform and analyze.
- Inexpensive and reproducible.
- Able to differentiate between distinct entities eg. Inflammation and fibrosis.
- Not affected by impairment in liver fibrosis.
- Able to predict and track disease progress or regress

When evaluating biomarkers, one should ensure consistency in assessment and evaluation, and also the need for simple and robust classification systems.

Non-invasive biomarkers of liver fibrosis are broadly divided into two classes:

Class I markers –

They are direct markers of fibrosis. These reflect the molecular pathogenesis and extracellular matrix turnover of liver.They are categorized into enzymatic markers, collagen markers, glycoproteins, matrix metalloproteinases, and glycosaminoglycans.

Class II markers –

They indirectly reflect the activity of extracellular matrix of the liver and also the extent of fibrosis. These include – aspartate aminotransferase(AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT)

In addition, they also include the markers of synthetic function as follows: prothrombin time (PT/INR), bilirubin levels, haptoglobin and albumin levels in the serum, Apolipoprotein A1, a2-macroglobulin, ceruloplasmin, transferrin and hepcidin levels.(20)

Other indirect markers such as platelet count, other hematological indices, a1-antitrypsin, ferritin, and certain adipokines have also been included in this exhaustive list of tests.

PLATELETS IN LIVER FIBROSIS

Recent studies state that platelets have the beneficial role in liver fibrosis through reduced expression of TGF-beta, a pro-fibrogenic cytokine and increased expression of matrix metallo-proteinases. Platelets also mediate inflammatory reaction after liver injury. Thus, platelets play the dual role in both liver fibrogenesis and regeneration.

Mean platelet volume (MPV), a sign of inflammation, indicates platelet size. Platelet distribution width (PDW) is the degree of variation in platelet size.(21)

Due to splenic sequestration in CLD, the life cycle of platelets becomes shorter. This, in turn, leads to increased production in bone marrow, thereby increasing young platelets in circulation. And so there would be an increase in MPV and PDW levels.

INDICES OF LIVER FIBROSIS/ CIRRHOSIS

Certain indices or scores with indirect parameters have shown to be good predictors of fibrosis and cirrhosis.

- Fibrotest – includes alpha2 macroglobulin, apoA1, bilirubin, GGT, haptoglobin, AST to platelet ratio index (APRI).

- Enhanced liver fibrosis (ELF) test- includes hyaluronic acid, tissue inhibitor of MMP-1, procollagen type III, propeptide.
- NAFLD fibrosis score- age, BMI, DM/IGT, platelet count, albumin, AST/ALT ratio.
- Plasma Cytokeratin -18 fragment, which indicates the apoptosis of liver cells, is the marker of NASH
- Hepascore – age, sex, alpha-2-macroglobulin, hyaluronate, bilirubin, GGT
- Forns index – age, GGT, cholesterol, platelets
- FIB-4 – age, ALT, AST, platelets(18)

RBC STATUS IN LIVER DISEASES

Among the several hematological complications in liver disease, macrocytic anemia is one of the common features. Macrocytosis in liver diseases can be associated with normoblasts or megaloblastic marrow based on pathogenesis and severity of the liver disease.Extensive studies of RBC mass and plasma volume in cirrhosis have reported an expanded plasma volume, low hematocrit, reduced RBC survival.A major cause of anemia in cirrhosis is hemolysis by an enlarged spleen, which sequesters and destroys RBC. This, in turn, leads to the macro-normoblasts bone marrow.

Anaemia in liver disease is described as Spur cell hemolytic anemia due to the changes in lipid composition of RBC membrane, leading to the characteristic RBC morphology. In liver disease, 30% increase in membrane lipids correlates with membrane surface area, thereby increasing MCV. This also causes decreased membrane fluidity and flexibility which gives osmotic resistant property, so that the lifespan of RBCs are prolonged againstfrequent splenic sequestration.(22)

RBC in alcoholism

Alcohol, being the most common pathogenetic agent may induce disturbed erythropoiesis and decrease RBC survival. Blood picture in alcohol abuse with or without liver disease is macrocytosis along with reticulocytosis and folate deficiency.RBC membrane changes are also partly due to plasma lipid changes like reduced plasma level of apoAII, which participates in cholesterol transport.

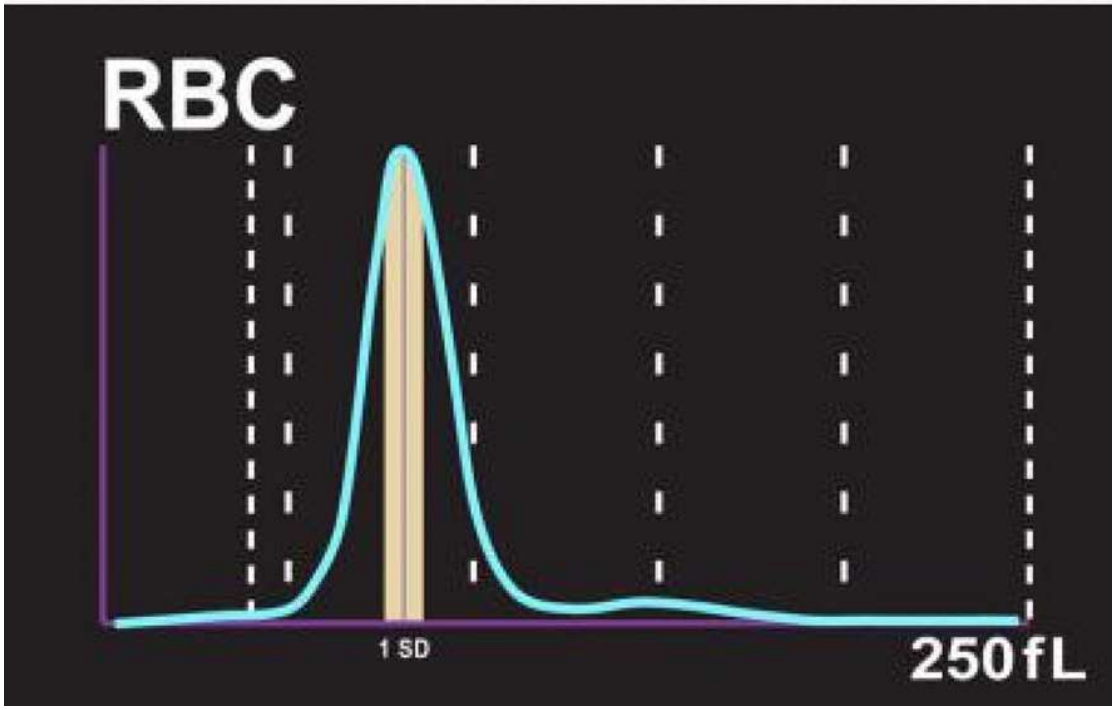
In acute alcohol ingestion, alcohol or acetaldehyde suppress erythropoiesis leading to decreased bone marrow cellularity and vacuolization of RBC. In chronic alcohol abuse, malnutrition and folate deficiency leads to megaloblastichematopoiesis. Morphologically they are spur cells, macrocytic target cells and discocytes due to increased lipid structural order in RBC membrane. In alcoholic liver disease, serum

vitamin B12 did not change. Folate depletion occurs due to malnutrition and antifolate action of alcohol by increasing urinary folate excretion. Macrocytosis due to alcoholic liver disease rapidly recovers during abstinence from alcohol stating that peripheral RBC picture is due to alcohol, malnutrition, and folate deficiency.(22)

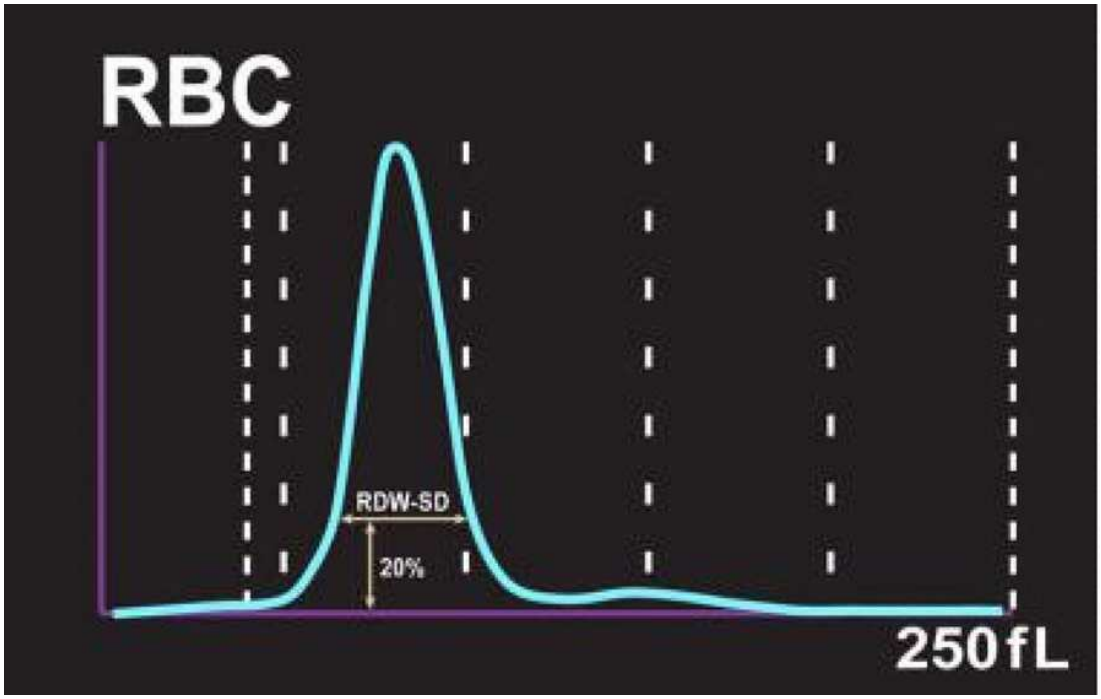
RED CELL DISTRIBUTION WIDTH

RDW is a morphological marker of heterogenicity of RBC size. It is a measure of anisocytosis, helpful in the differential diagnosis of anemia.The standard size of RBC is 6-8 microns in diameter. Higher RDW values commonly indicate more variation in size. Depending on the hematological analyzer instrument, RDW can be reported as coefficient of variation (CV) and standard deviation (SD).

- RDW – CV:



RDW SD:



- RDW CV is the measure of the deviation of the RBC volume width, usually, refers to the width of the volume curve.
- RDW-CV measurement is derived from 1SD divided by MCV times 100%. So it is affected by RBC size.Formula for calculation-
- RDW-CV (%) = 1 standard deviation of RBC volume/MCV x 100%
- RDW-SD is the measurement of the width of RBC size distribution histogram.(23)
- For measuring RDW SD, calculate the width (in fL) at the 20% height level of RBC size distribution histogram. So this parameter is not influenced by RBC size.

- Reference range of RDW

- RDW-SD : 39 – 46 fL

- RDW- CV : 11.6 – 14.6 %

- RDW is easily available as a part of complete blood count and so it incurs no additional cost.

Table: Comparison of RDW, MCV with disease conditions

RDW	**MCV**	**CONDITIONS**
NORMAL	LOW	ANAEMIA OF CHRONIC DISEASE, HETEROZYGOUS THALASSEMIA,, HB E TRAIT
NORMAL	HIGH	APLASTIC ANAEMIA, CLD, ALCOHOL, CHEMOTHERAPY, ANTIVIRALS

NORMAL	NORMAL	ANAEMIA OF CHRONIC DISEASE, ACUTE BLOOD LOSS/ HEMOLYSIS
HIGH	LOW	IRON DEFICIENCY, SICKLE CELL, BETA THALASSEMIA
HIGH	HIGH	FOLATE/ B12 DEFICIENCY, IMMUNE HEMOLYTIC ANAEMIA, CLD, MDS, CYTOTOXIC CHEMOTHERAPY
HIGH	NORMAL	EARLY IRON, B12, FOLATE DEFICIENCY, DIMORPHIC ANAEMIA, SICKLE CELL DISEASE, CLD, MDS.

- Anaemia with normal RDW is seen in thalassemia. Therefore Mentzer index should be done to confirm it.

- MENTZER INDEX = MCV (fL) / RBC count (million per microL)

- In Thalassemia, it is less than 13. In iron deficiency anemia, it is more than 13.(24)

RDW IN CLD

- Elevated RDW is associated with an increase in all-cause mortality. This can be explained by the fact that chronic inflammation and oxidative stress cause elevation in RDW. There is also a positive association between inflammation and oxidative stress with the advancement of fibrosis in liver disease.Elevated RDW occurs in conditions of ineffective erythropoiesis, increased RBC destruction, also in blood transfusions.

- Inflammation may increase RDW as it

- Impairs iron metabolism.

- Inhibits production or response to erythropoietin.

- Shortens RBC survival.

- Pro-inflammatory cytokines might suppress erythropoietin gene expression, inhibit proliferation of erythroid progenitors, downregulates erythropoietin receptor expression.

- Oxidative stress will increase the fragility of RBCs, decrease the erythroid maturation and RBC lifespan. Therefore raises RDW.Previous studies state that elevated RDW is correlated with conditions like hypertension, cardiovascular diseases, irritable bowel syndrome,

microalbuminuria due to low antioxidant nutrients in these conditions.(25)

NON-INVASIVE RADIOLOGICAL TECHNIQUES

- Greyscale& Doppler Ultrasound are simple and inexpensive to study and follow-up patients with CLD.

CONVENTIONAL ULTRASONOGRAM

- Ultrasound is well established, widely available, cost-effective modality for diagnosis of cirrhosis. Certain characteristic changes in sonography detect the progression of fibrosis in CLD.

- LIVER- coarse appearance or nodularity of liver parenchyma, hepatomegaly, hypertrophy of caudate lobe (which is the ratio of caudate lobe to right lobe). Most direct sign of advanced fibrosis is hepatic surface nodularity detected by the linear probe.

- SPLEEN- In the supine position, with the 2-5MHz curvilinear transducer placed in coronal plane posteriorly in left lower intercostal space, spleen size is measured. Then the plane of section is swept posterior to anterior and with various inspiratory degrees, an entire volume of the spleen is calculated.

- Characteristics of normal spleen –

- Average length of the adult spleen is 12cm.

- Parenchyma is homogeneous with uniform mid to low echogenicity.

In Portal hypertension – Spleen size is >13cm in cephalocaudal measurement and more echogenic than normal.

Table: Comparison of various diagnostic modalities in respect to sensitivity and specificity(18)

	SENSITIVITY	**SPECIFICITY**	**AUC**
CAUDATE HYPERTROPHY	**84%**	**100%**	**94%**
2 COMPONENT SCORE	**82.2%**	**79.9%**	**80.4%**
7 COMPONENT SCORE	**78.7%**	**80.1%**	**80.2%**

AUC- Area under the curve, the measure of accuracy.

2 Component score- includes nodularity, portal velocity.

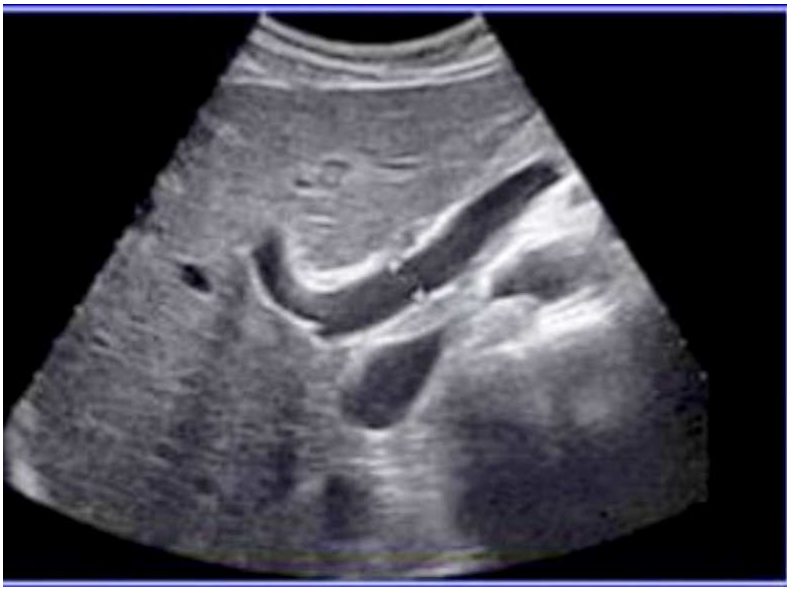
7 Component score- includes liver size, caudate hypertrophy, echogenicity, nodularity, portal vein diameter, portal velocity, spleen size.

DRAWBACKS OF ULTRASONOGRAM

- Subjective and operator dependent.
- Sensitivity and specificity for liver fibrosis are low.
- Does not correlate with the histological stage of fibrosis obtained from liver biopsy.

PORTAL DOPPLER STUDY

In liver fibrosis, regional hepatic and systemic hemodynamic changes are essential. Doppler US can detect these hemodynamic changes in pre-cirrhotic stages itself. Pulsed wave doppler is used to determine changes in waveforms of vessels – hepatic arteries, portal vein, hepatic veins.(26)

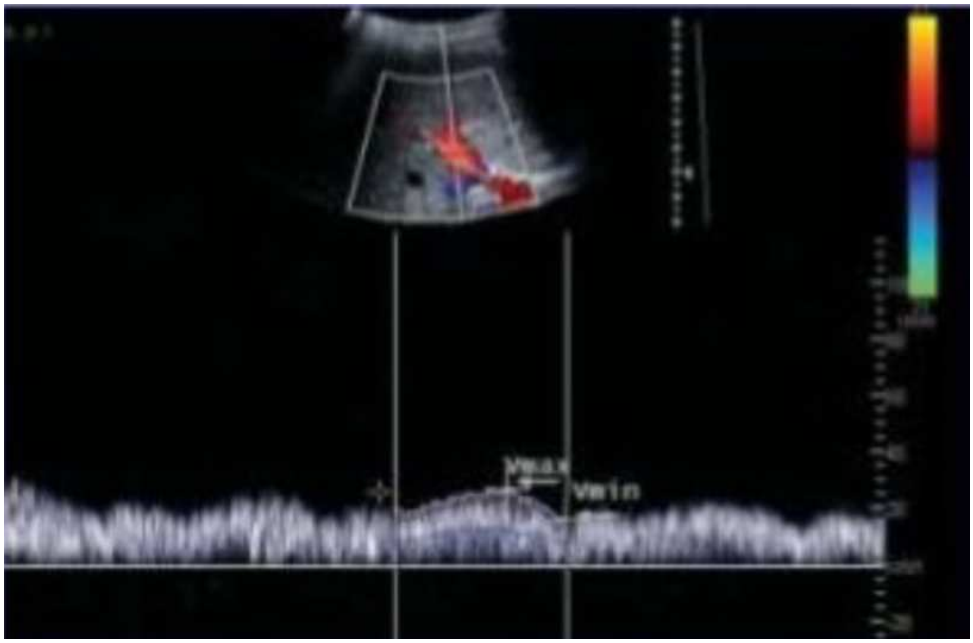


[. Portal vein diameter measurement at crossing of IVC]

PORTAL VEIN DIAMETER MEASUREMENT- Left portal vein is visualized by oblique, cranially placed subxiphoid view. Right and main portal vein are seen in the saggitalplane.Normally at the point of IVC crossing, portal vein diameter is <13mm in quiet respiration. If it is increased, portal hypertension is most likely.

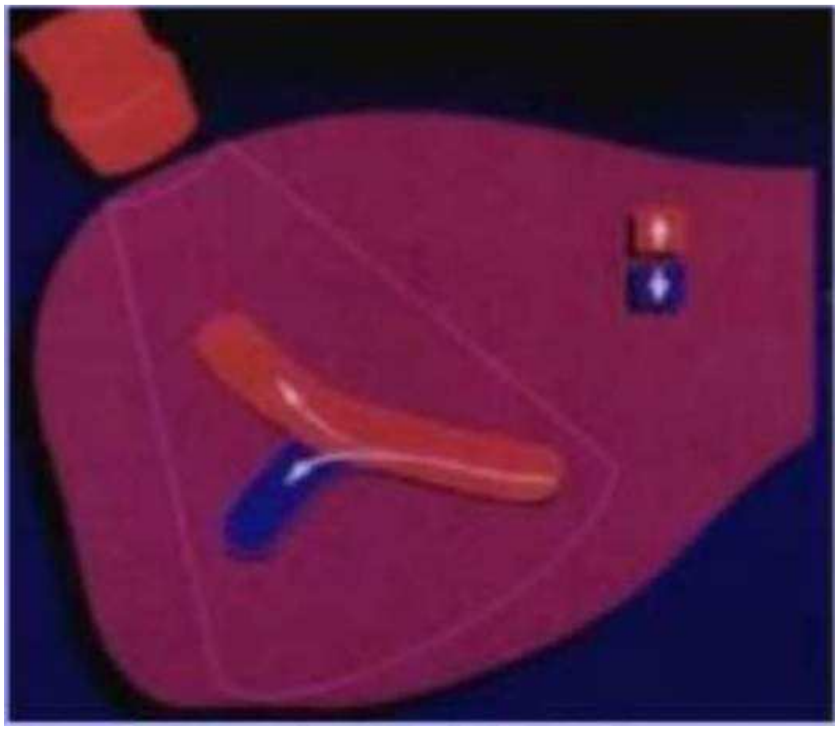
In many studies, this measurement is taken into account for portal hypertension

PORTAL VEIN VELOCITY- Normal portal mean velocity is 15-18cm/sec. It varies with respiratory and cardiac activity with an undulating appearance of waveforms. This is reduced in portal hypertension.

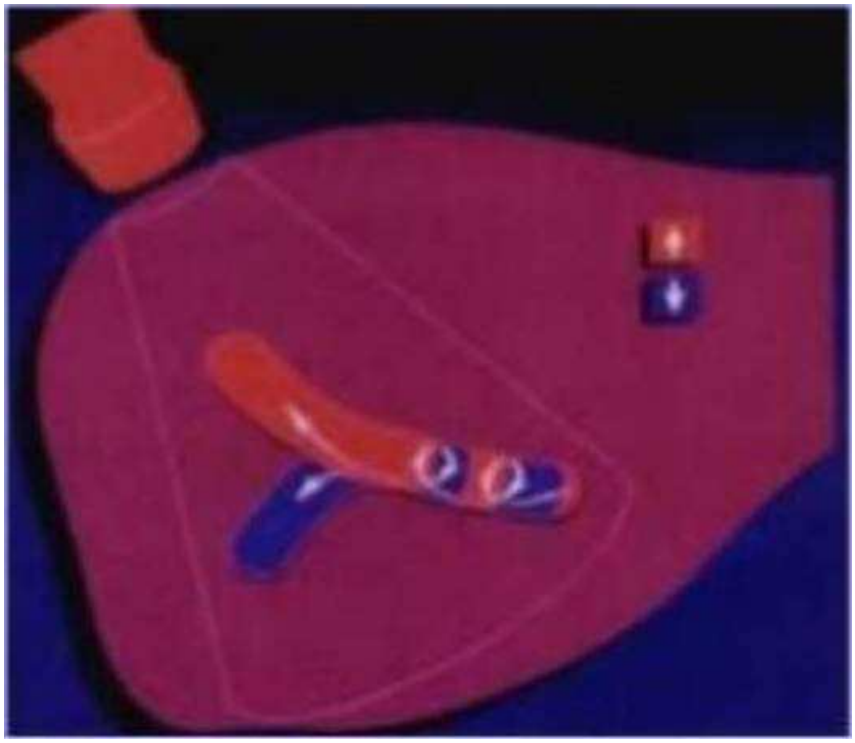


[This shows portal vein velocity measured using Vmax and Vmin]

FLOW PATTERN- It is detected by spectral and colordoppler. Normal flow in the portal vein is hepatoportal i.e. towards the liver with the postprandial increase in splanchnic circulation. In cirrhosis, obstruction of hepatic venulesand sinusoids occurs (mainly by fibrosis). Also, arterio-portal and portosystemicshunting adds to the reversal of flow. Hence hepatomegaly flow is seen in portal hypertension.(27)



[Laminar flow / hepatopetal flow]



[Helical flow / bidirectional flow]

- COLLATERALS FORMATION- Portosystemic collaterals are formed due to the opening of normally collapsed ones. This is seen in portal hypertension. Examples- splenorenal, umbilical, coronary, gastroepiploic.

- FLOW PATTERN IN HEPATIC VEINS – Doppler waveforms are recorded with end-expiration breath holding, to a minimum of 5 seconds

- Blue waveform – flow away from the probe

- Red waveform – flow towards the ultrasound probe

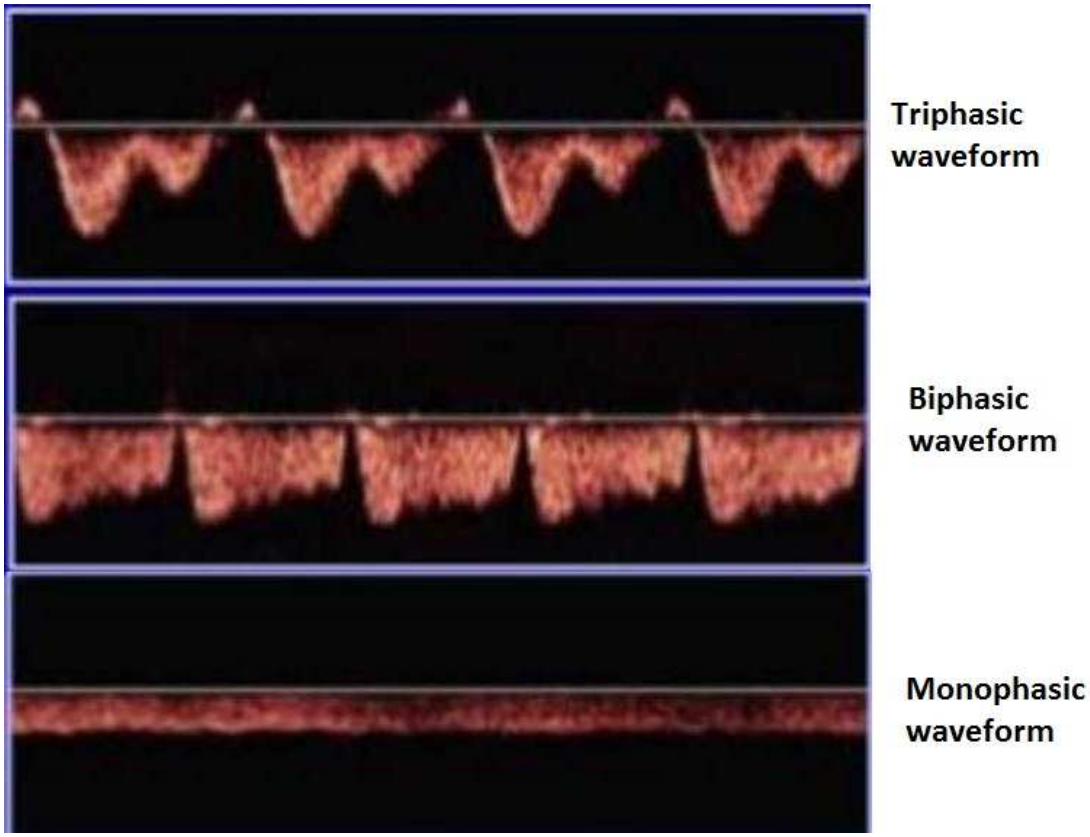
- Classification of hepatic vein waveforms

1. Triphasic – flow reversed in at least one phase

2. Biphasic – flow not reversed with or without decreased phasic oscillations

3. Monophasic – flat, with or without fluttering

Flow pattern in a normal right hepatic vein is triphasic. In a case of fibrosis, it will be mono or biphasic.



Doppler wave forms

DAMPING INDEX (DI) = Minimum velocity/ Maximum velocity of downward hepatic vein flow. It correlates with severity of CLD

SENSITIVE MARKERS OF PORTAL HYPERTENSION are

- Portal vein diameter >13mm.
- Absence of respiratory variations in splenic and mesenteric veins.

PORTAL VEIN THROMBOSIS can be detected as non-visualisation of the portal vein or cavernous transformation with extensive collateral networks.

DRAWBACKS OF DOPPLER STUDY

- It is influenced by patient-related factors like respiration, timing of meals.
- Observer variability.
- Equipment differences.
- Certain factors contribute to variability in measurements such as collateral pathways, hepatic steatosis, inflammation.

USEFUL DOPPLER ULTRASOUND INDICES

- □ Portal vein blood volume
- □ Portal blood flow
- □ Mean or peak portal vein velocity

- □ Congestion index of portal vein
- □ Resistance indices of arteries in liver and spleen
- □ Effective portal liver perfusion

CHILD TURCOTTE PUGH SCORE:

Parameter	Numerical score		
	1	**2**	**3**
Ascites	None	Slight	Moderate/severe
Encephalopathy	None	Slight/moderate	Moderate/severe
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds in increased)	1-3	4-6	>6
INR	<1.7	1.7-2.3	>2.3

□ Total numerical score

o 5-6 - Child Class A

o 6-9 - Child Class B

o 10-15 - Child Class C

Note: Higher class indicates greater severity

 Child-Pugh score was proposed by Child and Turcotte to predict the risk of surgery for patients who are undergoing portosystemic shunt surgery in case of variceal bleeding

 Its primary version includes ascites, hepatic encephalopathy, nutritional status, total bilirubin, and albumin. This is modified by Pugh et al by including PT/INR and excluded nutritional status from the score. This score is widely used for assessment of severity of liver disease. So this score assesses the prognosis of cirrhotic patients. Also, liver graft allocation is performed based on the severity of liver disease, which is determined by the CTP score. Time spent on the waiting list is also taken into account(28)

 Main advantages of CTP – widely adopted, ease of use and its simplicity

Rating of mortality following abdominal surgery in patients with cirrhosis:

 Child A – 10%

 Child B – 30-31%

- Child C – 76-82%
- Class A – surgery can be undertaken
- Class B – optimization of medical condition is required before surgery
- Class C – surgery better avoided

DRAWBACKS OF CTP:

- The two variables – namely ascites and hepatic encephalopathy – are subject
- Variations occur in physicians judgement, and with diuretic and lactulose use, in determining the above
- INR does not reflect coagulopathy sufficiently and therefore the liver function

MODEL FOR END-STAGE LIVER DISEASE [MELD] SCORE:

- MELD was primarily created for predicting the survival of these patients who are undergoing TIPS/ This version fo the score included the etiology for liver cirrhosis, which was later found to

be unnecessary.Now, this score incorporates 3 variables, namely total bilirubin, creatinine and INR

- Formula for MELD score= 9.57 x loge (creat) + 3.78 x loge (total bilirubin) + 11.2 x loge (INR) + 6.43(29)

- Working range – 6 to 40

- This score correlates with mortality of patients undergoing hepatic resection, abdominal procedures and cardiac surgery other than liver transplantation.It is used to prioritize allocation of donor organs for transplantation of liver. Thus, recently developed MELD score is used for rationalization of liver graft allocation and predicts mortality

Advantage of MELD:

- In the background of cirrhosis, presence of a renal failure is an independent risk factor for mortality. But CTP score does not include this parameter.

Thus MELD score was elaborated which encompasses the level of serum creatinine for assessing the survival rate. So MELD score is superior to CTP.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY CENTRE

Institute of Internal Medicine, Madras Medical college and Rajiv Gandhi Government General Hosital, Chennai.

DURATION OF STUDY

6 months

STUDY DESIGN

Observational study (Prospective)

SAMPLE SIZE

100 Patients

INCLUSION CRITERIA

- Age – adults <60 years
- Gender – Male
- Patients with symptomatic liver disease for > 6 months duration
- Portal hypertension due to hepatic cause.

EXCLUSION CRITERIA

- Malignancy
- Patients on medications that impair red cell production or destruction
- Anaemia due to nutritional deficiencies/ hemolysis
- Patients with cardiovascular disease
- Patients with renal failure
- Chronic bedridden patients

DATA COLLECTION AND METHODS

Chronic liver disease patients with portal hypertension admitted in male medical wards of RGGGH are subjected to detailed history taking, clinical examination and other parameters with RDW measured.

In patients in male medical wards with portal hypertension secondary to chronic liver disease are selected for clinical study as per inclusion/exclusion criteria.

Patients are subjected to thorough history taking, clinical examination after obtaining consent. Blood samles are collected from each patient and sent for

- Complete hemogram including Hb, red cell count, WBC count, DC, platelet count, red cell distribution width, RBC and platelet indices
- Peripheral smear
- Liver function tests
- PT, INR, aPTT
- USG abdomen
- Portal vein doppler
- Child Pugh score calculated using serum bilirubin, albumin, PT, ascites, hepatic encephalopathy

INVESTIGATION DETAILS

- Complete hemogram – Automated analyser
- Serum bilirubin – Diazo method
- Serum albumin – Bromo cresol green method
- PT, INR – ISI of thromboplastin reagents
- USG abdomen, Portal vein Doppler

SPONSORSHIP

No

CONFLICT OF INTEREST

None

OBSERVATIONS AND RESULTS

OBSERVATION AND RESULTS

RDW SD & RDW CV were roughly divided into 5 classes to categotize the severity for comparing with other variables. Below tables show the number of patients in each class.

RDWSD		Frequency	Percent
Valid	NORMAL	15	15.0
	46.1-50	18	18.0
	50.1-60	27	27.0
	60.1 - 70	16	16.0
	ABOVE 70	24	24.0
	Total	100	100.0

RDWCV		Frequency	Percent
Valid	NORMAL	15	15.0
	14.5-16.5	22	22.0
	16.5-18.5	28	28.0
	18.5-20.5	14	14.0
	ABOVE 20.5	21	21.0
	Total	100	100.0

AGE OF THE PATIENTS CATEGORISED IN DIFFERENT CLASSES

			AGE_GROUP			Total
			30-40	41-50	51-60	
RDWSD_5GROUPS	NORMAL	Count	5	7	3	15
		% within RDWSD_5GROUPS	33.3%	46.7%	20.0%	100.0%
	46.1-50	Count	3	4	11	18
		% within RDWSD_5GROUPS	16.7%	22.2%	61.1%	100.0%
	50.1-60	Count	8	13	6	27
		% within RDWSD_5GROUPS	29.6%	48.1%	22.2%	100.0%
	60.1 - 70	Count	5	7	4	16
		% within RDWSD GROUPS	31.2%	43.8%	25.0%	100.0%
	ABOVE 70	Count	6	11	7	24
		% within RDWSD_5GROUPS	25.0%	45.8%	29.2%	100.0%
Total		Count	27	42	31	100
		% within RDWSD_5GROUPS	27.0%	42.0%	31.0%	100.0%

.

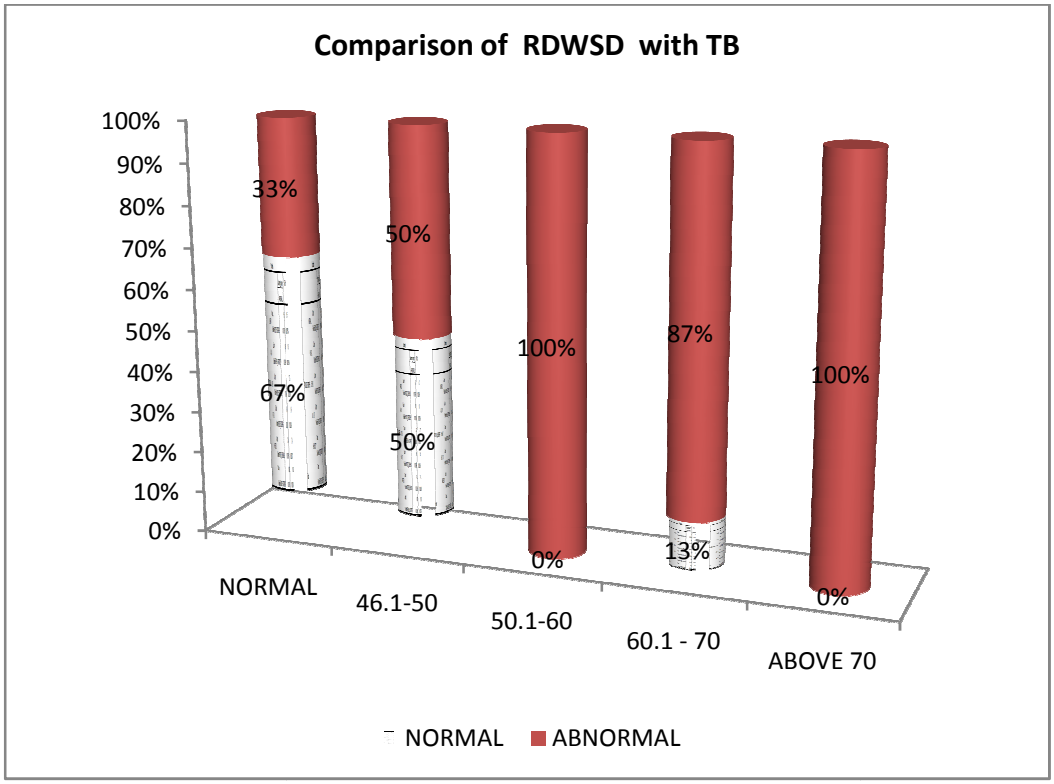
Age independently does not serve to correlate with RDW values

			AGE_GROUP			Total
			30-40	41-50	51-60	
RDWCV	NORMAL	Count	5	7	3	15
		% within RDWCV	33.3%	46.7%	20.0%	100.0%
	14.5-16.5	Count	2	9	11	22
		% within RDWCV	9.1%	40.9%	50.0%	100.0%
	16.5-18.5	Count	10	12	6	28
		% within RDWCV	35.7%	42.9%	21.4%	100.0%
	18.5-20.5	Count	4	6	4	14
		% within RDWCV	28.6%	42.9%	28.6%	100.0%
	ABOVE 20.5	Count	6	8	7	21
		% within RDWCV	28.6%	38.1%	33.3%	100.0%
Total		Count	27	42	31	100
		% within RDWCV	27.0%	42.0%	31.0%	100.0%

RDW CORRELATING WITH TOTAL BILIRUBIN

			TB_GROUP		Total
			NORMAL	ABNORMAL	
RDWSD_5GROUPS	NORMAL	Count	10	5	15
		% within RDWSD_5GROUPS	66.7%	33.3%	100.0%
	46.1-50	Count	9	9	18
		% within RDWSD_5GROUPS	50.0%	50.0%	100.0%
	50.1-60	Count	0	27	27
		% within RDWSD_5GROUPS	0.0%	100.0%	100.0%
	60.1 - 70	Count	2	14	16
		% within RDWSD_5GROUPS	12.5%	87.5%	100.0%
	ABOVE 70	Count	0	24	24
		% within RDWSD_5GROUPS	0.0%	100.0%	100.0%
Total		Count	21	79	100
		% within RDWSD_5GROUPS	21.0%	79.0%	100.0%

P<0.001. Hence it is significant.

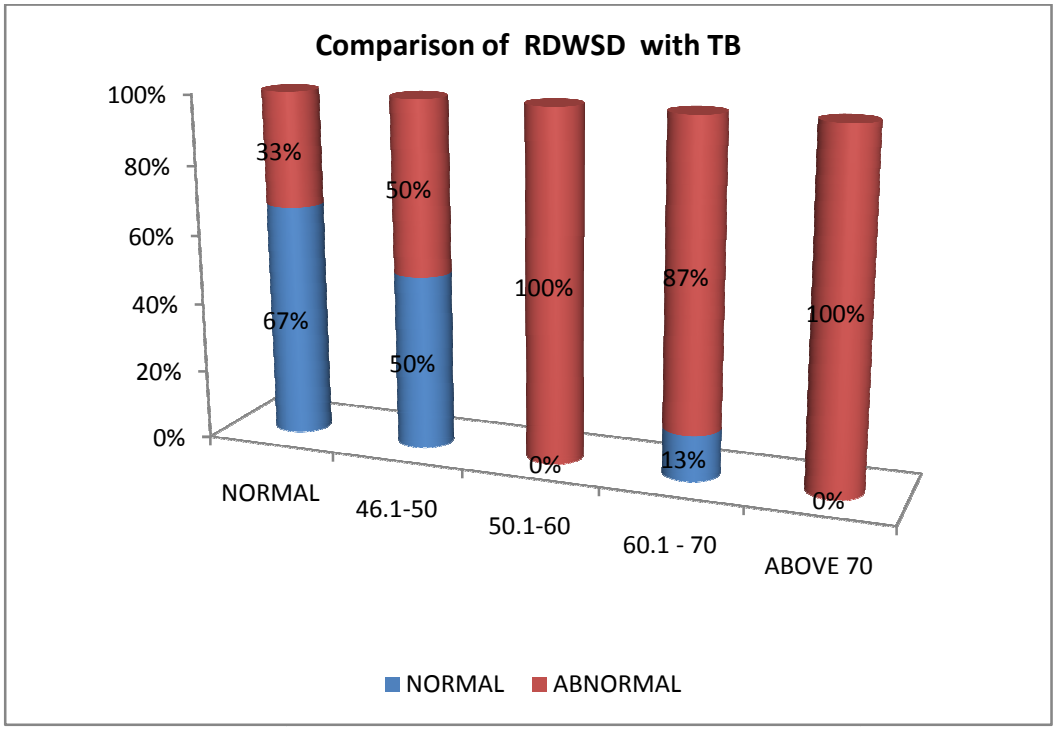

Comparison of RDWSD with TB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
33%
67%
50%
50%
100%
0%
87%
13%
100%
0%
NORMAL
46.1-50
50.1-60
60.1 - 70
ABOVE 70
NORMAL
ABNORMAL

RDWCV WITH SERUM TOTAL BILIRUBIN

			TB_GROUP		Total
			NORMAL	ABNORMAL	
RDWCV	NORMAL	Count	10	5	15
		% within RDWCV	66.7%	33.3%	100.0%
	14.5-16.5	Count	8	14	22
		% within RDWCV	36.4%	63.6%	100.0%
	16.5-18.5	Count	0	28	28
		% within RDWCV	0.0%	100.0%	100.0%
	18.5-20.5	Count	1	13	14
		% within RDWCV	7.1%	92.9%	100.0%
	ABOVE 20.5	Count	2	19	21
		% within RDWCV	9.5%	90.5%	100.0%
	Total	Count	21	79	100
		% within RDWCV	21.0%	79.0%	100.0%

P<0.001

Serum total bilirubin levels are 90.5% abnormal in patients with RDWCV above 20.5% . Where as bilirubin is only 33.3% abnormal for patients with normal RDWCV. So it is positively correlating


Comparison of RDWSD with TB
100%
80%
60%
40%
20%
0%
33%
67%
50%
50%
100%
0%
87%
13%
100%
0%
NORMAL
46.1-50
50.1-60
60.1 - 70
ABOVE 70
NORMAL
ABNORMAL

ABNORMAL SERUM ALBUMIN IN RAISED RDW

			albumin_group	Total
			ABNORMAL	
RDWSD_5GROUPS	NORMAL	Count	15	15
		% within RDWSD_5GROUPS	100.0%	100.0%
	46.1-50	Count	18	18
		% within RDWSD_5GROUPS	100.0%	100.0%
	50.1-60	Count	27	27
		% within RDWSD_5GROUPS	100.0%	100.0%
	60.1 - 70	Count	16	16
		% within RDWSD_5GROUPS	100.0%	100.0%
	ABOVE 70	Count	24	24
		% within RDWSD_5GROUPS	100.0%	100.0%
Total		Count	100	100
		% within RDWSD_5GROUPS	100.0%	100.0%

100% Abnormality in serum albumin has observed in patients with RDWSD above 70 FL and 90% abnormality in patients with RDWCV above 20%

SERUM ALBUMIN & RDWCV

			albumin_group	Total
			ABNORMAL	
RDWCV	NORMAL	Count	15	15
		% within RDWCV	100.0%	100.0%
	14.5-16.5	Count	22	22
		% within RDWCV	100.0%	100.0%
	16.5-18.5	Count	28	28
		% within RDWCV	100.0%	100.0%
	18.5-20.5	Count	14	14
		% within RDWCV	100.0%	100.0%
	ABOVE 20.5	Count	21	21
		% within RDWCV	100.0%	100.0%
	Total	Count	100	100
		% within RDWCV	100.0%	100.0%

ASSOCIATION BETWEEN PROTHROMBIN TIME

AND RDW SD

			pt_group		Total
			NORMAL	ABNORMAL	
RDWSD_5 GROUPS	NORMAL	Count	9	6	15
		% within RDWSD_5GROUPS	60.0%	40.0%	100.0%
	46.1-50	Count	14	4	18
		% within RDWSD_5GROUPS	77.8%	22.2%	100.0%
	50.1-60	Count	16	11	27
		% within RDWSD_5GROUPS	59.3%	40.7%	100.0%
	60.1 - 70	Count	4	12	16
		% within RDWSD_5GROUPS	25.0%	75.0%	100.0%
	ABOVE 70	Count	4	20	24
		% within RDWSD_5GROUPS	16.7%	83.3%	100.0%
Total		Count	47	53	100
		% within RDWSD_5GROUPS	47.0%	53.0%	100.0%

Pearson Chi-Square= 21.465* P<0.0001

From the table, it is clear that protrombin time proportionately increase with rise in RDW SD levels, also P value shows significance.

TABLE COMPARING PT & RDW CV

			pt_group		Total
			NORMAL	ABNORMAL	
RDWCV	NORMAL	Count	9	6	15
		% within RDWCV	60.0%	40.0%	100.0%
	14.5-16.5	Count	14	8	22
		% within RDWCV	63.6%	36.4%	100.0%
	16.5-18.5	Count	20	8	28
		% within RDWCV	71.4%	28.6%	100.0%
	18.5-20.5	Count	2	12	14
		% within RDWCV	14.3%	85.7%	100.0%
	ABOVE 20.5	Count	2	19	21
		% within RDWCV	9.5%	90.5%	100.0%
	Total	Count	47	53	100
		% within RDWCV	47.0%	53.0%	100.0%

Pearson Chi-Square= 28.026* P<0.001

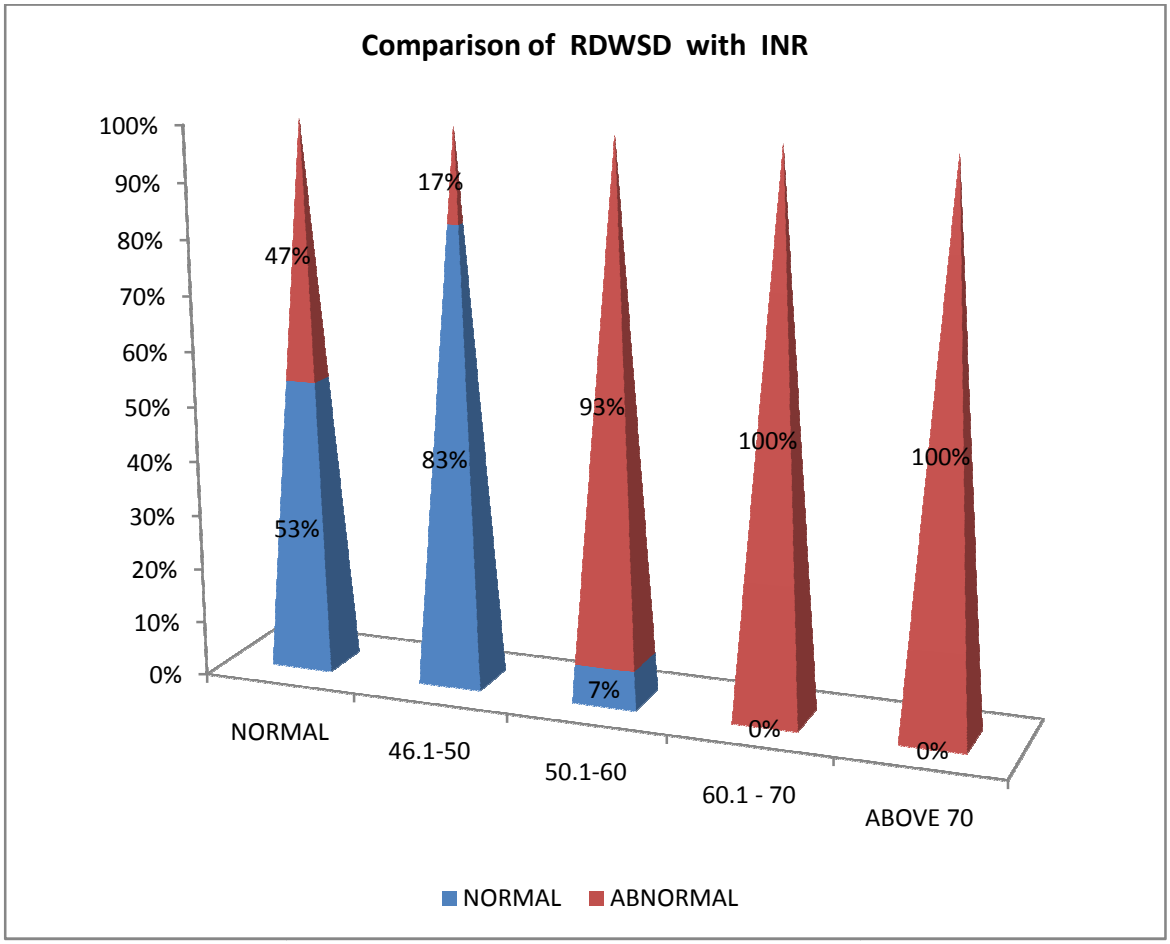
Since the P value <0.001, it is a significant association

TABLE SHOWING CORRELATION BETWEEN INR

AND RDW SD

			INR_GROUP		Total
			NORMAL	ABNORMAL	
RDWSD_5GROUPS	NORMAL	Count	8	7	15
		% within RDWSD_5GROUPS	53.3%	46.7%	100.0%
	46.1-50	Count	15	3	18
		% within RDWSD_5GROUPS	83.3%	16.7%	100.0%
	50.1-60	Count	2	25	27
		% within RDWSD_5GROUPS	7.4%	92.6%	100.0%
	60.1 - 70	Count	0	16	16
		% within RDWSD_5GROUPS	0.0%	100.0%	100.0%
	ABOVE 70	Count	0	24	24
		% within RDWSD_5GROUPS	0.0%	100.0%	100.0%
Total		Count	25	75	100
		% within RDWSD_5GROUPS	25.0%	75.0%	100.0%

Pearson Chi-Square=56.879* P<0.001



This bar diagram highlights abnormal INR values in RDW SD above 50 fl.

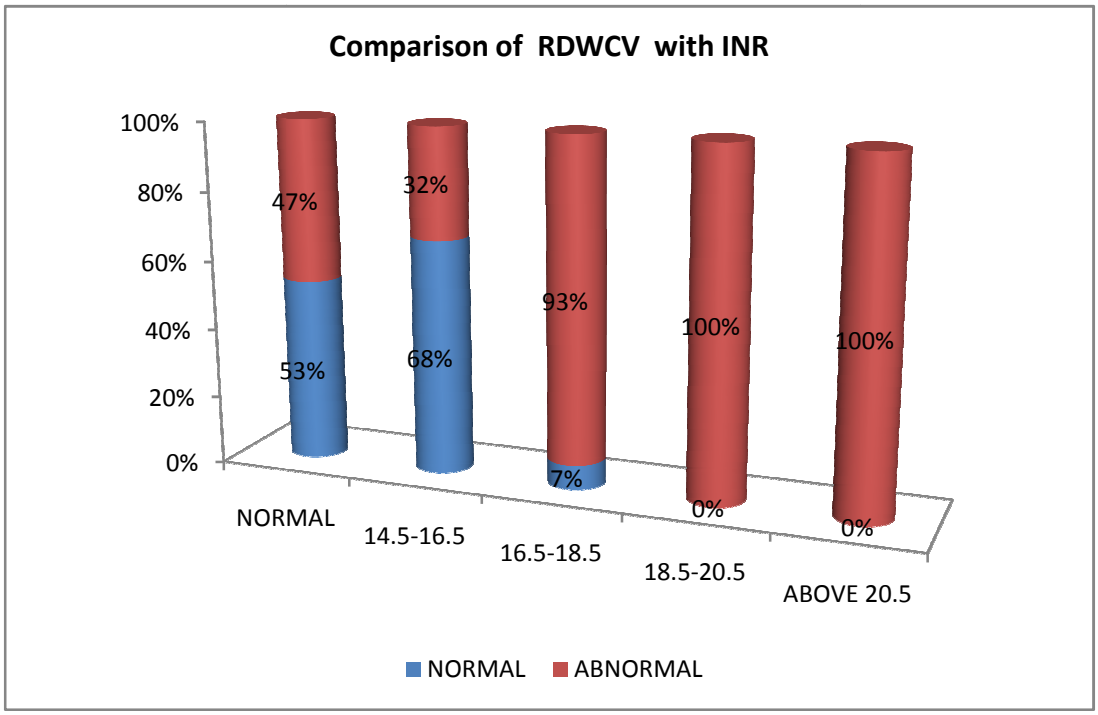
BELOW TABLE AND BAR DIAGRAM SHOWS CORRELATION

BETWEEN INR & RDW CV

			INR_GROUP		Total
			NORMAL	ABNORMAL	
RDWCV	NORMAL	Count	8	7	15
		% within RDWCV	53.3%	46.7%	100.0%
	14.5-16.5	Count	15	7	22
		% within RDWCV	68.2%	31.8%	100.0%
	16.5-18.5	Count	2	26	28
		% within RDWCV	7.1%	92.9%	100.0%
	18.5-20.5	Count	0	14	14
		% within RDWCV	0.0%	100.0%	100.0%
	ABOVE 20.5	Count	0	21	21
		% within RDWCV	0.0%	100.0%	100.0%
Total		Count	25	75	100
		% within RDWCV	25.0%	75.0%	100.0%

Pearson Chi-Square= 44.730* P<0.001

Maximum percent of INR abnormality (92.9%) is seen with RDW CV above 16.5



CORRELATION OF ASCITES SEVERITY WITH RDW SD

			Ascites			Total
			Mild	Moderate	Severe	
RDWSD_5GROUPS	NORMAL	Count	8	7	0	15
		% within RDWSD_5GROUPS	53.3%	46.7%	0.0%	100.0%
	46.1-50	Count	12	6	0	18
		% within RDWSD_5GROUPS	66.7%	33.3%	0.0%	100.0%
	50.1-60	Count	1	24	2	27
		% within RDWSD_5GROUPS	3.7%	88.9%	7.4%	100.0%
	60.1 - 70	Count	1	14	1	16
		% within RDWSD_5GROUPS	6.2%	87.5%	6.2%	100.0%
	ABOVE 70	Count	0	22	2	24
		% within RDWSD_5GROUPS	0.0%	91.7%	8.3%	100.0%
Total		Count	22	73	5	100
		% within RDWSD_5GROUPS	22.0%	73.0%	5.0%	100.0%

Pearson Chi-Square= 44.601* P<0.001

Maximum number of severe ascites (8.3%), moderate ascites (91.7%) are with RDW SD above 70fl

HEPATIC ENCEPHALOPATHY AND RDW SD

			Encephalopathy					Total
			.00	1.00	2.00	3.00	4.00	
RDWSD_5GROUPS	NORMAL	Count	10	3	2	0	0	15
		% within RDWSD_5GROUPS	66.7%	20.0%	13.3%	0.0%	0.0%	100.0%
	46.1-50	Count	15	1	1	0	1	18
		% within RDWSD_5GROUPS	83.3%	5.6%	5.6%	0.0%	5.6%	100.0%
	50.1-60	Count	12	5	8	1	1	27
		% within RDWSD_5GROUPS	44.4%	18.5%	29.6%	3.7%	3.7%	100.0%
	60.1 – 70	Count	3	3	5	3	2	16
		% within RDWSD_5GROUPS	18.8%	18.8%	31.2%	18.8%	12.5%	100.0%
	ABOVE 70	Count	1	0	7	14	2	24
		% within RDWSD_5GROUPS	4.2%	0.0%	29.2%	58.3%	8.3%	100.0%
Total		Count	41	12	23	18	6	100
		% within RDWSD_5GROUPS	41.0%	12.0%	23.0%	18.0%	6.0%	100.0%

Pearson Chi-Square= 63.662* P<0.001

Since the P value is below 0.001,it shows a positive correlation.

			Encephalopathy					Total
			.00	1.00	2.00	3.00	4.00	
RDWCV	NORMAL	Count	10	3	2	0	0	15
		% within RDWCV	66.7%	20.0%	13.3%	0.0%	0.0%	100.0%
	14.5-16.5	Count	16	0	4	0	2	22
		% within RDWCV	72.7%	0.0%	18.2%	0.0%	9.1%	100.0%
	16.5-18.5	Count	11	7	7	2	1	28
		% within RDWCV	39.3%	25.0%	25.0%	7.1%	3.6%	100.0%
	18.5-20.5	Count	2	1	6	5	0	14
		% within RDWCV	14.3%	7.1%	42.9%	35.7%	0.0%	100.0%
	ABOVE 20.5	Count	2	1	4	11	3	21
		% within RDWCV	9.5%	4.8%	19.0%	52.4%	14.3%	100.0%
Total		Count	41	12	23	18	6	100
		% within RDWCV	41.0%	12.0%	23.0%	18.0%	6.0%	100.0%

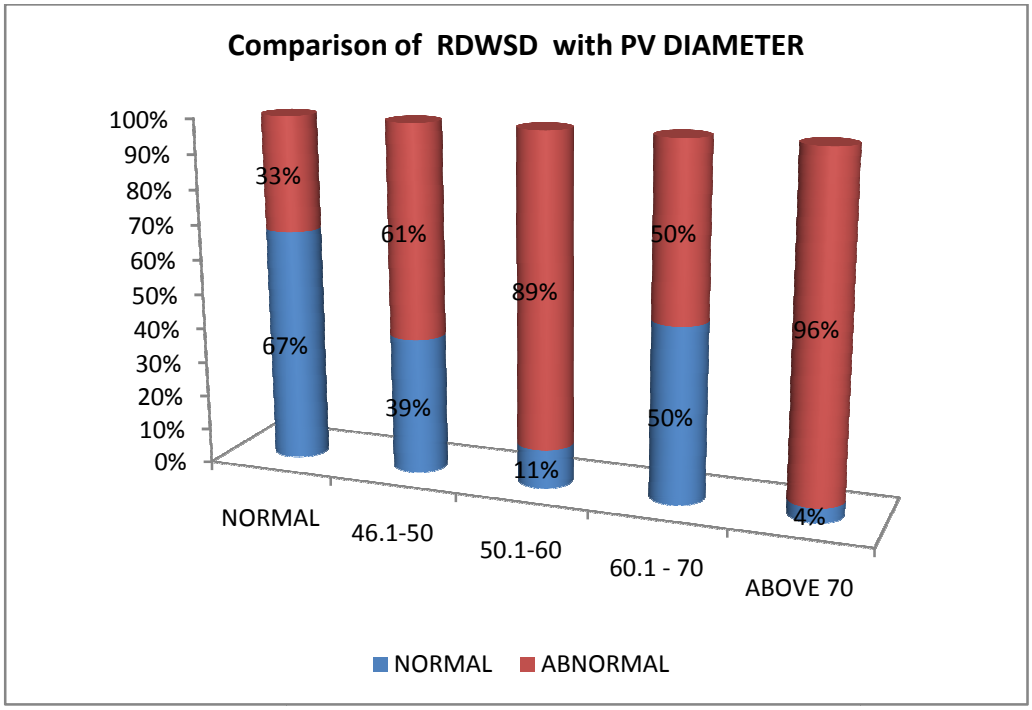
Pearson Chi-Square= 56.836* P<0.001

Maximum of 52.4% of Grade 3 & 14.3% of Grade 4 are RDW CV above 20.5%, whereas 66.7% patients without encephalopathy have normal RDW CV.

PORTAL VEIN DIAMETER WITH RDW SD

CROSSTAB			pv_diameter_group		Total
			NORMAL	ABNORMAL	
RDWSD_5GROUPS	NORMAL	Count	10	5	15
		% within RDWSD_5GROUPS	66.7%	33.3%	100.0%
	46.1-50	Count	7	11	18
		% within RDWSD_5GROUPS	38.9%	61.1%	100.0%
	50.1-60	Count	3	24	27
		% within RDWSD_5GROUPS	11.1%	88.9%	100.0%
	60.1 - 70	Count	8	8	16
		% within RDWSD_5GROUPS	50.0%	50.0%	100.0%
	ABOVE 70	Count	1	23	24
		% within RDWSD_5GROUPS	4.2%	95.8%	100.0%
Total		Count	29	71	100
		% within RDWSD_5GROUPS	29.0%	71.0%	100.0%

Pearson Chi-Square= 26.003* P<0.001



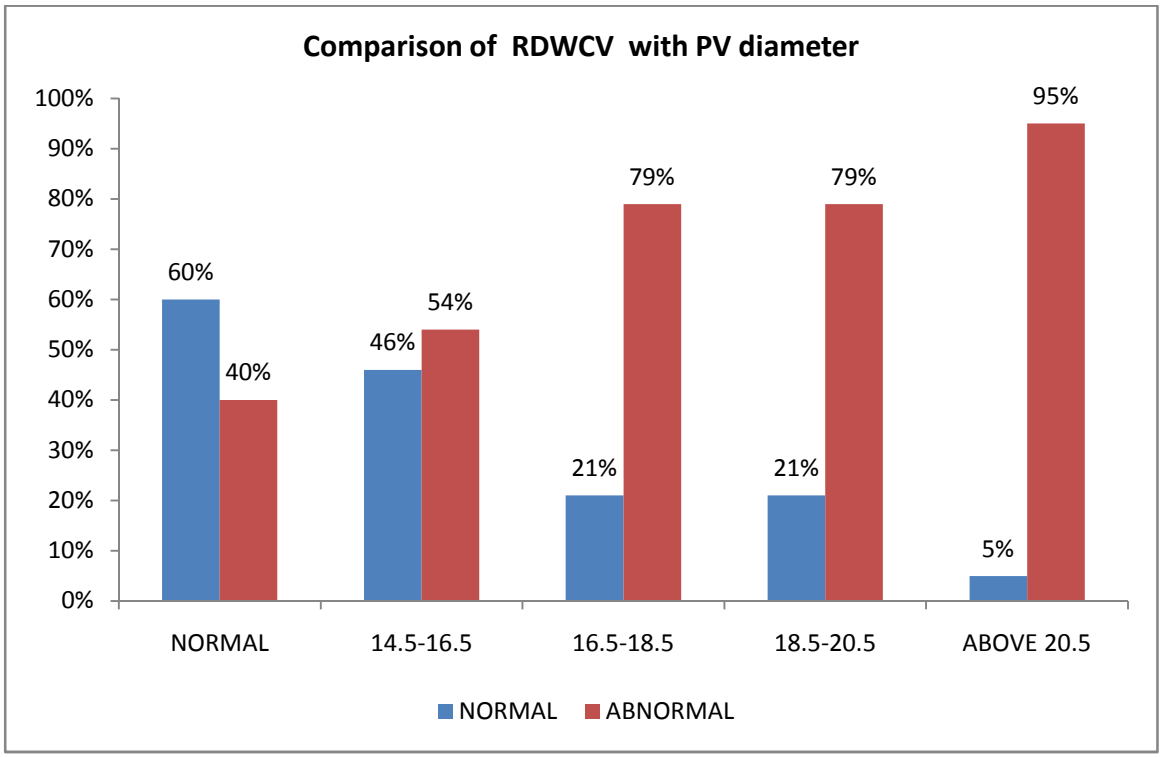
Most important variable in doppler to determine portal hypertension: portal vein diameter shows a positive correlation.

RDW CV AND PORTAL VEIN DIAMETER

			pv_diameter_group		Total
			NORMAL	ABNORMAL	
RDWCV	NORMAL	Count	9	6	15
		% within RDWCV	60.0%	40.0%	100.0%
	14.5-16.5	Count	10	12	22
		% within RDWCV	45.5%	54.5%	100.0%
	16.5-18.5	Count	6	22	28
		% within RDWCV	21.4%	78.6%	100.0%
	18.5-20.5	Count	3	11	14
		% within RDWCV	21.4%	78.6%	100.0%
	ABOVE 20.5	Count	1	20	21
		% within RDWCV	4.8%	95.2%	100.0%
	Total	Count	29	71	100
		% within RDWCV	29.0%	71.0%	100.0%

Pearson Chi-Square= 17.055* P=0.002

Since 95.2% of increased portal vein diameter is seen in patients with RDW CV above 20.5%, it clearly signifies the positive association



PORTOSYSTEMIC COLLATERALS WITH RDW SD

			Portosystemic_collaterals		Total
			N	Y	
RDWSD_5GROUPS	NORMAL	Count	14	1	15
		% within RDWSD_5GROUPS	93.3%	6.7%	100.0%
	46.1-50	Count	18	0	18
		% within RDWSD_5GROUPS	100.0%	0.0%	100.0%
	50.1-60	Count	27	0	27
		% within RDWSD_5GROUPS	100.0%	0.0%	100.0%
	60.1 - 70	Count	11	5	16
		% within RDWSD_5GROUPS	68.8%	31.2%	100.0%
	ABOVE 70	Count	5	19	24
		% within RDWSD_5GROUPS	20.8%	79.2%	100.0%
Total		Count	75	25	100
		% within RDWSD_5GROUPS	75.0%	25.0%	100.0%

Pearson Chi-Square= 55.578* P<0.001

Maximum collaterals (79.2)% is seen with rdw sd values above 70fl. Also P value below 0.001 signifies the positive correlation

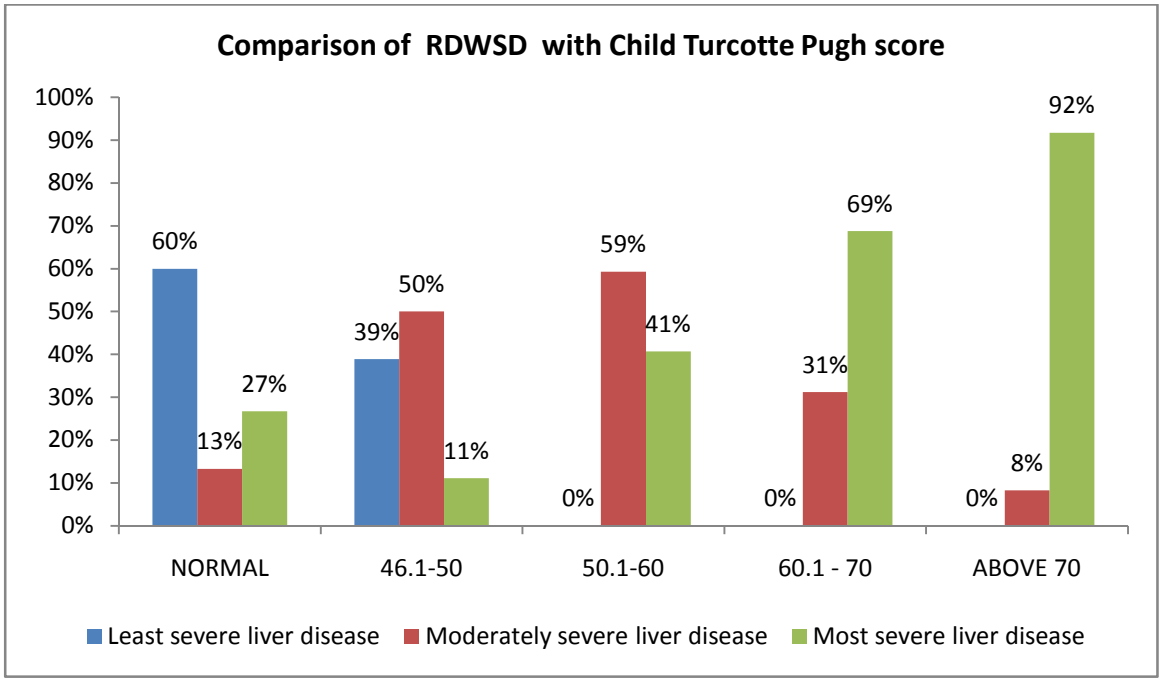
CH CHILD TURCOTTE PUGH SCORE WITH RDW SD

		Child_Turcotte_Pugh_score			Total
		least severe liver disease	moderately severe liver disease	most severe liver disease	
NORMAL	Count	9	2	4	15
	% within RDWSD_5GROUPS	60.0%	13.3%	26.7%	100.0%
46.1-50	Count	7	9	2	18
	% within RDWSD_5GROUPS	38.9%	50.0%	11.1%	100.0%
50.1-60	Count	0	16	11	27
	% within RDWSD_5GROUPS	0.0%	59.3%	40.7%	100.0%
60.1 - 70	Count	0	5	11	16
	% within RDWSD_5GROUPS	0.0%	31.2%	68.8%	100.0%
ABOVE 70	Count	0	2	22	24
	% within RDWSD_5GROUPS	0.0%	8.3%	91.7%	100.0%
	Count	16	34	50	100
	% within RDWSD_5GROUPS	16.0%	34.0%	50.0%	100.0%

Pearson Chi-Square= 64.755* P<0.001

Similar to the individual components, the entire scorimg system significantly correlating with RDW SD , consequently showing the P value below 0.001

BAR DIAGRAM SHOWING THE CTP SCORE CORRELATION WITH RDW SD

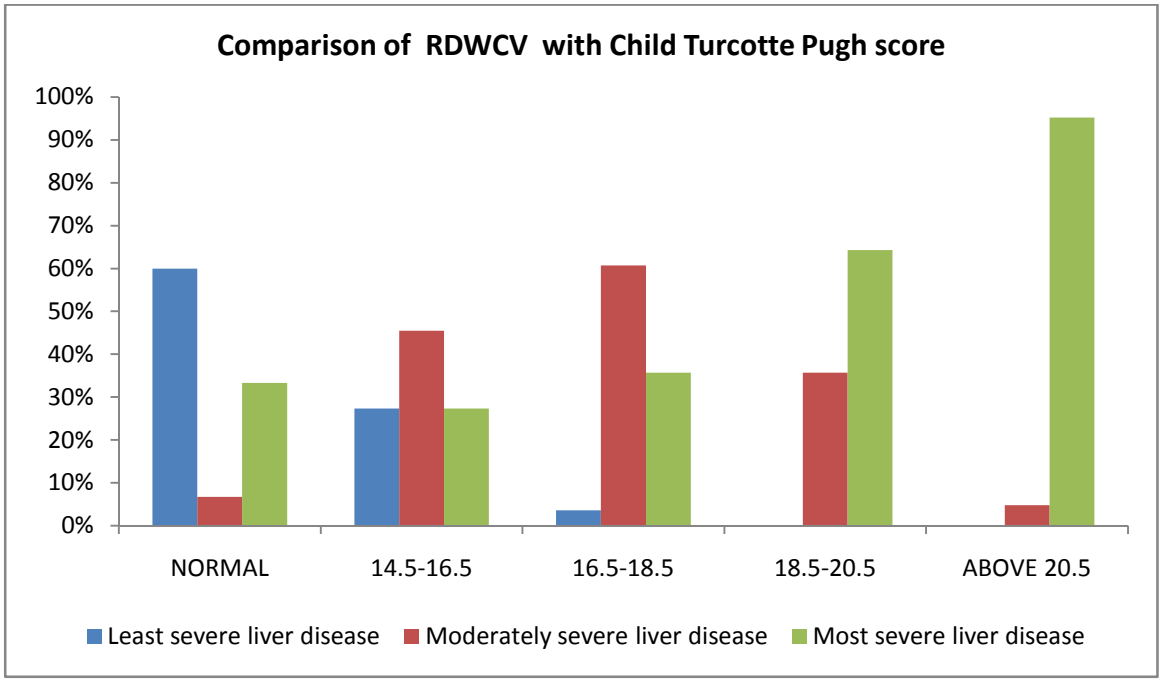


RDW CV CORRELATION WITH CTP SCORE

Crosstab

			Child_Turcotte_Pugh_score			Total
			least severe liver disease	moderately severe liver disease	most severe liver disease	
RDWCV	NORMAL	Count	9	1	5	15
		% within RDWCV	60.0%	6.7%	33.3%	100.0%
	14.5-16.5	Count	6	10	6	22
		% within RDWCV	27.3%	45.5%	27.3%	100.0%
	16.5-18.5	Count	1	17	10	28
		% within RDWCV	3.6%	60.7%	35.7%	100.0%
	18.5-20.5	Count	0	5	9	14
		% within RDWCV	0.0%	35.7%	64.3%	100.0%
	ABOVE 20.5	Count	0	1	20	21
		% within RDWCV	0.0%	4.8%	95.2%	100.0%
Total		Count	16	34	50	100
		% within RDWCV	16.0%	34.0%	50.0%	100.0%

Pearson Chi-Square= 56.930* P<0.001


Comparison of RDWCV with Child Turcotte Pugh score
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
NORMAL
14.5-16.5
16.5-18.5
18.5-20.5
ABOVE 20.5
Least severe liver disease
Moderately severe liver disease
Most severe liver disease

DISCUSSION

DISCUSSION

This study is a type of prospective observational study conducted in the male medical wards of Institute of Internal Medicine at Rajiv Gandhi Government General Hospital. A Sample population of 100 subjects were enrolled in the study. based upon the designed inclusion and exclusion criteria. The study was approved by institute ethics committee and the informed consent were obtained from the patients involved in the study. They were subjected to history taking, physical examination and the appropriate investigations.

The main objective behind this study to observe and highlight the importance of RDW in patients with chronic liver disease and to correlate the same with mortality. Hence many variables were used and so compared.

Of the 100 patients included in the study, 27% (maximum) had the RDW SD range of 50-60fl & RDW CV range of 16.5-18.5%. Age, as a variable does not appear to be significant independently as P value being 0.267.

Serum levels of total bilirubin shows better correlation with both RDW SD & RDW CV. With the P value of <0.001, table clearly depicts that patients with RDW SD above 70fl have 100% abnormal bilirubin

levels & those with RDW CV >16.5% have abnormal values of 90 & above. Being the excretory component, bilirubin levels are increased in liver injury, thereby emphasizing its sensitivity.

Prothrombin time and INR values also indicates the liver function as they are altered in coagulopathy. In our study, they are well comparable with RDW as they show significant P value of <0.001.

One of the synthetic function of liver, serum albumin levels was taken into account. Then correlated with RDW values. Inverse relation was observed as patients with RDW SD above 50fl & RDW CV above 16.5 had high levels of serum albumin.

The first two variables of CTP score- Encephaloathy and Ascites shows a significant correlation with P value <0.001.Patients with RDW SD above50 & RDW CV above 20.5% had moderate to sever ascites. Similarly Grade 3 & Grade 4 encephalopathy were seen in patients with RDW levels.

The potal vein diameter in doppler is a predictor of portal hypertension. This variable is compared with RDW values and it is directly proportional as increased portal diameter shows elevated RDW. This study further highlighted the presence of portosystemic collaterals in high RDW values.The CTP score as determined by individual variables

was proportionately increased & comparable with RDW values. In the study by Attia et al, this score is comparable and equal efficious with MELD scoring as a predictor of mortality.

CONCLUSION

CONCLUSION

Although there are several evidences in favour of the non-invasive biomarkers in the diagnosis of CLD & Portal hypertension, the reliability of the procedure is under study. However, RDW may be one of the economically advantageous diagnostic tool.

In the purview of prognostic significance of the patients with portal hypertension, RDW in this study showed a remarkable association in regard to the severity of CTP score. Moreover, as a non-invasive diagnostic marker, RDW may become a promising investigatory tool in treating as well as predicting the outcome of the patient suffering from liver pathology.

Eventhough assessment of RDW in relation with severity of portal hypertension may be a newer approach, the characteristic standard prognostic scoring modality like CTP score have been included in the study to overcome the possible misinterpretation of the results.In future, other standard scoring modalities in addition to series of required non-invasive diagnostic tests integrated with RDW may find its prospects in the medical arena.

LIMITATIONS

LIMITATIONS

Sample size of the study may not be adequate in determining the prognostic prospects of the chronic liver disease.

Data collected from the population may not suffice in predicting the outcome of portal vein velocity in relation to RDW.

RDW being studied as an important diagnostic tool in several diseases such as coronary artery disease, ischemic stroke & others, but the data is lacking in pertinent to correlation of RDW in patients with portal hypertension as a sequel of CLD.

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BIBLIOGRAPHY

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ANNEXURES

PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

OP/ NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

COMPLAINTS :

Duration of illness

Abdominal Distension

Haemetemesis/malena/

other bleeding manifestations

PAST HISTORY :

Similar illness

Co-morbidities

PERSONAL HISTORY :

Alcohol Duration Quantity

OTHERS

GENERAL EXAMINATION :

Pallor: Icterus: Clubbing: Lymphadenopathy: Odema:

VITALS :

Pulse Rate: BP: Respiratory rate: Temperature:

SYSTEMIC EXAMINATION :

CARDIOVASCULAR SYSTEM :

RESPIRATORY SYSTEM :

ABDOMEN :

Ascites Splenomegaly

CENTRAL NERVOUS SYSTEM

COMPLETE HEMOGRAM

HB: RDW: MCH: MCV:

MCHC: Platelet: PS:

LIVER FUNCTION TEST

TB: DB: Albumin: Liver enzymes:

PT:aPTT: INR:

RENAL FUNCTION TEST

ULTRA SOUND ABDOMEN

Ascites

Splenomegaly

PORTAL VEIN DOPPLER

Diameter of main portal vein

Direction of flow

Mean velocity

Cavernous transformation

Porto systemic collaterals

CHILD TURCOTTE PUGH SCORE

Total bilirubin (mg/dl)

Serum albumin (g/dl)

Prothrombin time (secs)

Ascites

Hepatic encephalopathy

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

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

CERTIFICATE OF APPROVAL

To
Dr.Jayasudha.D.
Post Graduate in M.D. (General Medicine)
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.Jayasudha.D,

The Institutional Ethics Committee has considered your request and approved your study titled **"ASSESSMENT OF RED CELL DISTRIBUTION WIDTH IN PORTAL HYPERTENSION AND ITS CORRELATION WITH CHILD TURCOTTE PUGH SCORE AMONG PATIENTS WITH CHRONIC LIVER DISEASE" - NO. (II) 08032016.**

The following members of Ethics Committee were present in the meeting hold on **22.03.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
5.Dr.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
6.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
7.Prof.Srinivasagalu,Director,Inst.of Int.Med.,MMC,Ch-3	: Member
8.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

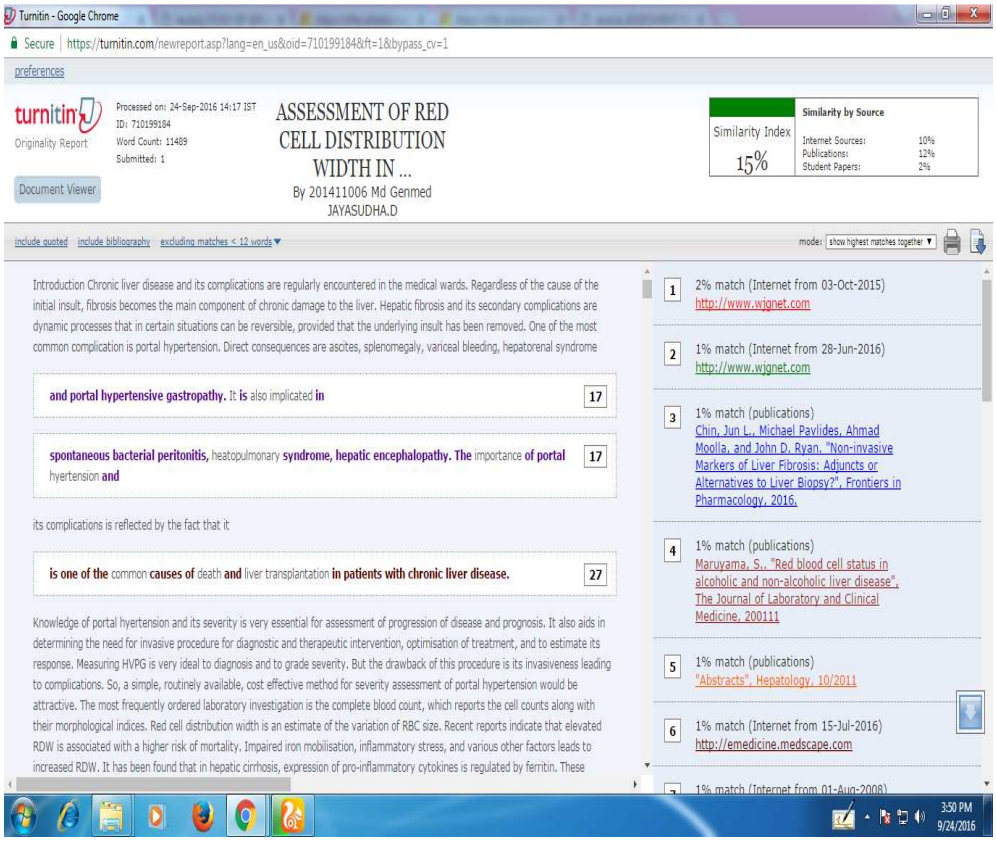
We approve the proposal to be conducted in its presented form.

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

MADRAS MEDICAL COLLEGE
31 MAR 2016
CHENNAI-600 003

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003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Introduction Chronic liver disease and its complications are regularly encountered in the medical wards. Regardless of the cause of the initial insult, fibrosis becomes the main component of chronic damage to the liver. Hepatic fibrosis and its secondary complications are dynamic processes that in certain situations can be reversible, provided that the underlying insult has been removed. One of the most common complication is portal hypertension. Direct consequences are ascites, splenomegaly, variceal bleeding, hepatorenal syndrome
and portal hypertensive gastropathy. It is also implicated in 17
spontaneous bacterial peritonitis, heatopulmonary syndrome, hepatic encephalopathy. The importance of portal hyertension and 17
its complications is reflected by the fact that it
is one of the common causes of death and liver transplantation in patients with chronic liver disease. 27
Knowledge of portal hyertension and its severity is very essential for assessment of progression of disease and prognosis. It also aids in determining the need for invasive procedure for diagnostic and therapeutic intervention, optimisation of treatment, and to estimate its response. Measuring HVPG is very ideal to diagnosis and to grade severity. But the drawback of this procedure is its invasiveness leading to complications. So, a simple, routinely available, cost effective method for severity assessment of portal hypertension would be attractive. The most frequently ordered laboratory investigation is the complete blood count, which reports the cell counts along with their morphological indices. Red cell distribution width is an estimate of the variation of RBC size. Recent reports indicate that elevated RDW is associated with a higher risk of mortality. Impaired iron mobilisation, inflammatory stress, and various other factors leads to increased RDW. It has been found that in hepatic cirrhosis, expression of pro-inflammatory cytokines is regulated by ferritin. These
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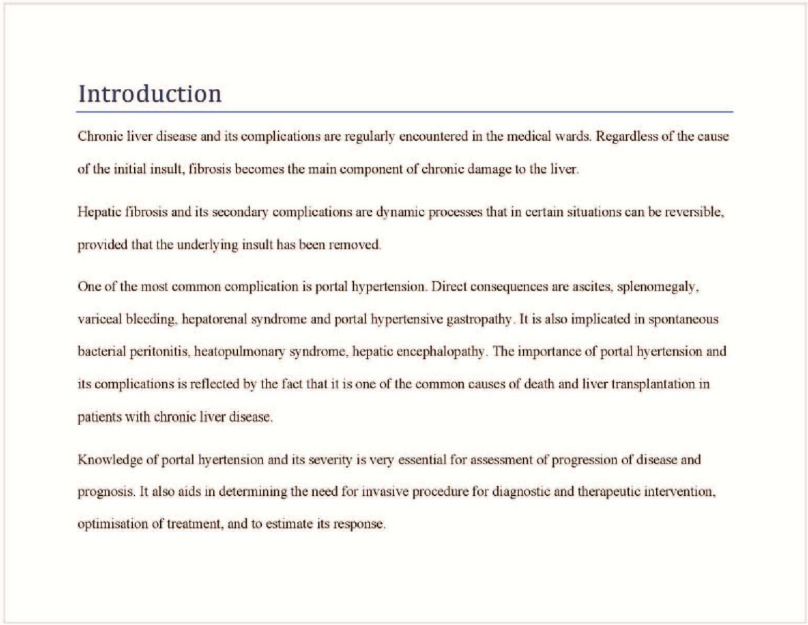

Introduction

Chronic liver disease and its complications are regularly encountered in the medical wards. Regardless of the cause of the initial insult, fibrosis becomes the main component of chronic damage to the liver.

Hepatic fibrosis and its secondary complications are dynamic processes that in certain situations can be reversible, provided that the underlying insult has been removed.

One of the most common complication is portal hypertension. Direct consequences are ascites, splenomegaly, variceal bleeding, hepatorenal syndrome and portal hypertensive gastropathy. It is also implicated in spontaneous bacterial peritonitis, heatopulmonary syndrome, hepatic encephalopathy. The importance of portal hyertension and its complications is reflected by the fact that it is one of the common causes of death and liver transplantation in patients with chronic liver disease.

Knowledge of portal hyertension and its severity is very essential for assessment of progression of disease and prognosis. It also aids in determining the need for invasive procedure for diagnostic and therapeutic intervention, optimisation of treatment, and to estimate its response.

INFORMATION SHEET

We are conducting a study on "ASSESSMENT OF RED CELL DISTRIBUTION WIDTH IN PORTAL HYPERTENSION AND ITS CORRELATION WITH CHILD TURCOTTE PUGH SCORE AMONG PATIENTS WITH CHRONIC LIVER DISEASE" among patients who are admitted in male medical wards, Rajiv Gandhi Government General Hospital, Chennai and for that your co- operation to undergo ultrasound, portal doppler and your blood sample may be valuable to us.

The purpose of this study is to predict the severity of portal hypertension in patients with chronic liver disease and to correlate this parameter with Child Turcotte Pugh score.

We are selecting certain cases and if you are found eligible, we would perform extra tests and special studies which in any way do not affect your final report or management.

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

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

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

Signature of Investigator

Signature/left thumb impression of Participant

Date:
Place:

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ் காந்தி அரசு பொது மருத்துவமனையில் நீண்ட கால கல்லீரல் பாதிப்பினால் ஏற்பட்ட போர்டல் நாள இரத்த அழுத்தம் உள்ள நோயாளிகளுக்கு சிவப்பு அணு விநியோக அகலத்தை மதிப்பீடு செய்து அதனை சைல்ட் டர்கோடீ புக் கணக்கீடுடன் சம்மந்தப்படுத்தும் ஆய்வு நடைபெற்று வருகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களை இரத்த பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக்கொள்கிறோம். முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின்வாங்கலாம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்/

இடது கட்டைவிரல் ரேகை

தேதி : பெயர் :

PATIENT CONSENT FORM

Study Detail	:	"ASSESSMENT OF RED CELL DISTRIBUTION WIDTH IN PORTAL HYPERTENSION AND ITS CORRELATION WITH CHILD TURCOTTE PUGH SCORE AMONG PATIENTS WITH CHRONIC LIVER DISEASE"
Study Centre	:	Institute of Internal Medicine, Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

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

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

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

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination and necessary investigations. ❑

Signature of Investigator

Signature/thumb impression

Study Investigator's Name:

Patient's Name and Address:

DR.JAYASUDHA.D

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு

நீண்ட கால கல்லீரல் பாதிப்பினால் ஏற்பட்ட போர்டல் நாள இரத்த அழுத்தம் உள்ள நோயாளிகளுக்கு சிவப்பு அணு விநியோக அகலத்தை மதிப்பீடு செய்து அதனை சைல்ட் டர்கோடீ புக் கணக்கீடுடன் சம்மந்தப்படுத்தும் ஆய்வு.

பெயர் :
வயது :
பால் :
எண்:

தேதி:
வெளிநோயாளி எண்:
ஆராய்ச்சி சேர்க்கை

இந்த ஆராய்ச்சியின் மூலம் சிவப்பு அணு விநியோக அகலத்தை மதிப்பீடு செய்து அதனை கல்லீரல் பாதிப்பினால் ஏற்பட்ட போர்டல் நாள இரத்த அழுத்தத்துடனும்இ சைல்ட் டர்கோடீ புக் கணக்கீடுடனும் சம்மந்தப்படுத்தப்படும் என்பதை ஆராய்ச்சியாளர் கூற அறிந்துக்கொண்டேன்.

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விவரங்களை நான் புரிந்துக்கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் பங்குபெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம்

பங்கேற்பாளர் கையொப்பம்/
இடது கட்டைவிரல் ரேகை

MASTER CHART

S. No.	Age	Sex	Hb (g/dL)	Platelet (x1000/µL)	RDW-SD (fL)	RDW-CV (%)	TB (mg/dL)	Serum albumin (g/dL)	PT (sec)	INR	Ascites	Encephalopathy
1	53	M	14	304	44.7	15.1	0.3	2.3	12.9	1.17	Moderate	2
2	41	M	13.5	95	49.1	14.7	4	3.5	17.8	1.56	Moderate	4
3	46	M	6.9	95	66.8	17.9	12.5	2.6	23.5	2.03	Moderate	3
4	39	M	5.4	250	69.3	22.1	20.5	2.2	18.9	1.72	Moderate	3
5	40	M	7.4	176	52.8	17.4	7.4	2.2	16.1	1.36	Moderate	4
6	40	M	9.3	132	57.3	17.7	28.9	2.2	19.8	1.82	Severe	3
7	42	M	5.4	43	58.9	15.2	2.9	2.9	17	2.4	Mild	2
8	45	M	12.5	52	67.6	19.2	0.2	3.7	22.8	1.93	Moderate	3
9	43	M	11.2	37	60.3	16	27.5	2.2	26	2.4	Moderate	4
10	45	M	14.9	141	41.5	14	3.3	2.9	14.9	1.32	Mild	0
11	40	M	9.3	132	57.3	17.7	28.3	2.4	19.8	1.82	Moderate	2
12	51	M	14.5	191	52.4	17	2.1	3.5	17.9	1.52	Moderate	1
13	39	M	8.3	160	50.5	17.8	1	3.2	16.5	1.46	Moderate	1
14	34	M	5.7	116	63.9	22.8	0.4	2.7	19.3	1.63	Moderate	4
15	57	M	9.6	99	62	16	4.8	2.1	18.5	1.57	Moderate	0
16	32	M	2.7	95	48.6	21.4	0.5	3.3	14.5	1.22	Moderate	1
17	45	M	16.5	284	52.6	18.3	2	3.9	21.3	1.88	Moderate	2
18	40	M	10.3	30	63.1	19.4	3.9	3	16.7	1.48	Moderate	2
19	58	M	6	14	84.2	22	2	2.6	16.1	1.42	Severe	3
20	57	M	5.6	99	47	13.7	0.2	2.5	10.1	1.12	Moderate	2
21	47	M	3.1	72	66.4	21.1	7.3	3.2	20.3	1.72	Moderate	2
22	40	M	9.7	38	61.5	20.4	10.1	2.5	14.8	1.25	Moderate	0
23	58	M	8.4	42	65.6	18.9	4	2.4	13.7	1.23	Moderate	2
24	50	M	13	41	53.9	17.6	1.9	2.5	19	2.4	Severe	2
25	30	M	13.6	396	44.4	13.8	0.8	3	18.8	1.59	Mild	0
26	45	M	8.8	260	62.3	22.7	5.1	2.4	22	2.3	Severe	0
27	58	M	7.1	229	43.9	12.5	0.6	3.9	14.8	1.32	Moderate	0
28	45	M	11.4	280	72.1	20.9	5.5	2.9	26	4	Moderate	0
29	57	M	5	91	80.1	23.1	3.8	2	12.7	1.23	Moderate	3
30	47	M	11.6	165	57.5	16.2	2.1	1.9	18	1.12	Moderate	0
31	53	M	10.4	120	49.4	17.5	2.5	3.2	12.8	1.3	Moderate	0
32	34	M	7.2	91	80.3	22.4	4.8	2.1	21	1.9	Moderate	3
33	46	M	9	102	61.5	17.3	2.5	3.1	14	2	Moderate	2
34	57	M	12	232	48	15.5	0.4	3.4	16	1.03	Moderate	0
35	37	M	15	340	41	12.5	0.8	3.9	10	1.14	Moderate	0
36	43	M	10	88	72	19	1.2	3	13	2	Moderate	2
37	58	M	9.4	74	81	22	2.8	2.3	18	3.2	Moderate	2
38	52	M	14	242	48	15	2.5	3.7	9	1.1	Mild	0
39	36	M	12	120	54	17	2.8	3.1	12	1.3	Moderate	0
40	47	M	10	120	77	20	12.1	1.7	16.5	5.6	Moderate	3

Spleen size	Liver size	Liver echoes	PV diameter (mm)	PV velocity (cm/s)	Portosystemic collaterals	Child Turcotte Pugh score	Child Turcotte Pugh score
11	13	N	12	12	N	9	B
9	11	C	11	10	N	11	C
14	8	C	18	8	N	12	C
17	7	C	16	9	Y	12	C
11	12	C	12	12	N	12	C
12.9	11	C	11	13	N	13	C
12	13	C	13	11	N	12	C
12.5	8.5	C	16	8	N	8	B
13.4	9	C	12	9	N	14	C
11	10	C	12	10	N	9	B
12.9	11	C	11	13	N	11	C
10	14	C	13	17	N	9	B
14.8	10	C	17	8	N	8	B
15	10	C	20	8	Y	10	C
9.8	9.6	A	9	14	N	10	C
18.3	9	C	21	9	N	8	B
13	10	A	18	12	N	9	B
15	10	C	8	14	N	10	C
15.3	9	C	18	8	Y	12	C
9.1	11	C	32	10	N	10	C
13	12	C	13	20	N	11	C
13.6	9	C	25	9	Y	10	C
14.2	10	C	13	10	Y	11	C
11	9.5	C	16	11	N	13	C
9	12	C	9	26	N	7	A
16	8	C	12	9	Y	13	C
11	12	A	12	14	N	6	A
9.5	9	C	13	10	N	12	C
14	7	C	17	9	N	12	C
12	10	C	15	14	N	11	C
13.6	9.1	C	14	9	N	8	B
16	7	C	24	6	Y	13	C
11	10	C	17	9	N	10	C
12	11	A	16	18	N	7	B
9	11	A	12	20	N	6	A
11	11	A	13	16	N	9	B
16	7	C	28	7	Y	12	C
10	10	A	12	14	N	6	A
13.5	10	C	18	9	N	8	B
16	8	C	22	6	Y	14	C

41	55	M	9	90	81	22	7.1	1.3	18	3.4	Moderate	3
42	43	M	14	113	55	15	2.9	3.4	13	1.5	Moderate	0
43	36	M	15	220	43	13.5	4.8	3.3	16	2.2	Moderate	1
44	44	M	9.5	130	51.5	18	2.6	3.3	10	1.3	Moderate	0
45	51	M	10.5	240	49	16.5	0.8	3.2	11	1.1	Mild	0
46	53	M	8.8	78	60.3	19.5	1.4	3.3	20.5	2	Moderate	1
47	36	M	15	200	48	16.5	1.8	3.9	12	1.2	Mild	0
48	37	M	6.8	66	80	21.5	4.4	2	18.5	1.9	Moderate	3
49	42	M	16	280	41	13	0.7	3.8	11	1.14	Mild	0
50	47	M	9	110	52	16.5	2.6	3.3	12	1.6	Moderate	2
51	36	M	9.4	76	78	21.5	2.7	2.6	16	2.2	Moderate	2
52	45	M	10	101	52.5	18.5	2.1	3.2	14	2.1	Moderate	1
53	55	M	11	150	43.5	12.5	4.1	3.1	17	1.8	Moderate	1
54	46	M	14	120	55.5	18	2.4	3	12	1.5	Moderate	1
55	48	M	7.1	88	76	20.5	5.1	2.2	20	1.9	Moderate	3
56	41	M	13	220	45	13	0.7	3.7	6	1.2	Mild	0
57	51	M	12	170	48	15.5	1.8	3.6	7	1.1	Mild	0
58	42	M	6.1	56	74.5	22.5	12.1	1.8	12	3.1	Moderate	3
59	47	M	13.5	124	52.5	18.5	2.5	3.2	12	1.3	Moderate	0
60	52	M	15.5	248	47.5	16	0.4	3.4	6	1.03	Moderate	0
61	57	M	5.4	14	79	21	4.3	1.4	18	3	Moderate	3
62	37	M	13	200	47.5	15.5	2.4	3.6	8	1	Mild	0
63	48	M	11	145	51.5	17.5	2.3	3.1	10	1.04	Moderate	0
64	52	M	9.5	98	68.3	19	1.4	3	15	1.9	Moderate	2
65	39	M	14	280	44	12	0.6	3.7	5	1.15	Mild	0
66	47	M	13.5	133	55	18.5	2.3	3	10	2.1	Moderate	1
67	51	M	12.5	121	53.5	18	2.6	3.2	14	1.3	Moderate	0
68	41	M	6.5	32	80.3	21.8	3.8	1.8	16	1.8	Moderate	3
69	44	M	14.5	220	42	12.5	3.8	3.3	14	2.2	Moderate	2
70	47	M	11	200	47.5	16	0.8	3.4	12	1.04	Mild	0
71	53	M	10.5	98	53.5	18.8	2.2	3.1	16	1.3	Moderate	0
72	40	M	9.5	102	54.5	18	2.6	3.2	14	2.1	Moderate	2
73	41	M	15.5	270	44.5	13.5	0.6	3.6	6	1.14	Mild	0
74	46	M	8.5	74	81.5	20	2.9	2.4	18	4.5	Moderate	2
75	51	M	12.5	110	56.5	18.5	2.7	3.1	14	1.3	Moderate	0
76	50	M	7.5	68	79.5	21	4.2	2.2	20	1.8	Moderate	4
77	47	M	14	250	48	16	0.6	3.4	8	1.01	Mild	0
78	49	M	12	48	64.5	18.5	1.6	3	12	2.1	Moderate	1

14	9	C	25	7	Y	14	C
12	11	C	16	10	N	8	B
11.5	10	A	15	11	N	11	C
13.5	9	C	15	9	N	8	B
10	13	N	13	16	N	7	B
11	12	A	12	18	N	9	B
10	10	A	14	10	N	6	A
15	8	C	21	8	Y	13	C
10	13	A	14	16	N	6	A
13.5	10	C	15	10	N	9	B
15	8	C	22	7	Y	12	C
13	10	C	16	9	N	10	C
12.5	11	C	14	10	N	11	C
14	10	C	17	8	N	8	B
16	7	C	23	8	Y	13	C
10	14	N	11	20	N	6	A
11	13	C	15	10	N	6	A
14	8	C	21	8	Y	14	C
12	10	C	19	10	N	8	B
10	13	A	10	16	N	7	B
13	8	C	21	7	Y	14	C
9	12	A	15	10	N	6	A
12	9	C	17.5	8	N	8	B
9	13	A	12	14	N	9	B
10	12	N	11	20	N	6	A
13	10	C	17	8	N	10	C
12	10	C	18	8	N	8	B
15	7	C	21	6	Y	13	C
12	11	C	16	9	Y	11	C
10	13	N	12	18	N	7	B
13	10	C	18	8	N	8	B
11	9	C	19	8	N	10	C
10	13	N	12	16	N	6	A
14	7	C	21	7	Y	12	C
12.5	11	C	16	9	N	8	B
14	7	C	20	6	Y	13	C
9	13	N	11	15	N	7	B
10	13	N	12	14	N	9	B

79	52	M	13.5	210	48	15.5	2.5	3.7	15	1.1	Mild	0
80	48	M	6.5	84	80.5	22	2.8	1.7	21	4.2	Severe	4
81	32	M	14	212	45	14	4.8	3.3	16	2.2	Moderate	1
82	46	M	8.5	66	79	20.5	9.5	1.7	19	5.5	Moderate	3
83	37	M	11.5	130	53.5	18	2.6	3.1	14	1.4	Moderate	0
84	49	M	16	280	48.5	16.5	2.3	3.8	8	1.08	Mild	0
85	58	M	4.5	33	81	21	2.9	2.2	21	4.5	Moderate	2
86	38	M	9.5	120	65.5	18.5	1.3	3.1	10	2	Mild	1
87	44	M	14	350	42	12.5	0.8	3.8	5	1.15	Mild	0
88	55	M	12	180	48	16	0.4	3.4	8	1.05	Mild	0
89	38	M	10.5	115	54	17.5	2.7	3.1	11	2.1	Moderate	2
90	53	M	6	54	81	22.5	5.2	2.2	15	1.8	Moderate	3
91	52	M	12.5	180	53.5	17	2.5	3.2	10	1.3	Moderate	0
92	38	M	6.8	89	78.5	19	4.8	2.1	20	1.9	Moderate	3
93	49	M	5.8	73	81	22.5	10.1	1.7	19	5.6	Moderate	3
94	47	M	10.4	124	57	17.5	2.8	3.1	13	1.3	Moderate	0
95	55	M	10.5	220	54	16	2.5	3.1	17	2	Moderate	2
96	59	M	13	180	49.5	16	0.4	3.4	8	1.03	Mild	0
97	51	M	12.5	130	48	17	2.5	3.8	6	1.1	Mild	0
98	37	M	7.4	72	78	20	2.8	2.3	18	3.2	Moderate	2
99	39	M	8.5	98	75	18.5	1.2	3	14	2	Moderate	2
100	43	M	14.5	250	40.5	12	0.8	3.9	5	1.14	Mild	0

12	11	A	15	10	N	6	A
14	6	C	22	6	Y	14	C
12.5	11	A	15	9	N	11	C
14	7	C	20	7	N	14	C
13	10	C	16	8	N	8	B
12	11	A	14	9	N	6	A
13.5	7	C	19	6	Y	12	C
11	13	N	12	15	N	9	B
9	13	N	11	21	N	6	A
10	12	A	12	18	N	7	B
13	9	C	16	9	N	10	C
14	7	C	19	7	Y	13	C
13	11	C	18	10	N	8	B
13	8	C	21	6	Y	13	C
14	6	C	19	7	Y	14	C
12.5	11	C	17	9	N	8	B
12	10.5	C	18	9	N	10	C
9	13	A	12	16	N	7	B
12.5	11	A	17	14	N	6	A
13.5	9	C	22	8	Y	12	C
10	13	N	11	17	N	9	B
9	13	N	10	19	N	6	A