Dissertation on

"APRI SCORING AS A PREDICTOR OF HEPATIC FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B AND / OR C INFECTION IN COMPARISON WITH FIBROSCAN"

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CERTIFICATE

This is to certify that the dissertation titled **"APRI SCORING AS A PREDICTOR OF HEPATIC FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B AND / OR C INFECTION IN COMPARISON WITH FIBROSCAN** " is a bonafide work done **by Dr.VIDHYALAKSHMI.C.K.** , 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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DECLARATION

I solemnly declare that the dissertation titled **"APRI SCORING AS A PREDICTOR OF HEPATIC FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B AND / OR C INFECTION IN COMPARISON WITH FIBROSCAN"** is done by me at Madras Medical College, Chennai - 600 003 during the period April 2016 to September 2016 under the guidance and supervision of **Prof**. **Dr. R.PENCHALAIAH** submitted to the Tamilnadu Dr.M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE IN GENERAL MEDICINE (BRANCH-I).

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CONTENTS

INTRODUCTION

INTRODUCTION

Chronic liver disease is considered as a global issue today as it often leads to liver cirrhosis and hepatocellular carcinoma, which is initially characterized by fibrosis in the liver. Liver fibrosis [1] occurs due to a longstanding damage to the liver, that is associated with excess accumulation of extracellular connective tissue protein.

The main etiologies of hepatic fibrosis include longstanding infection of hepatitis B and Hepatitis C , alcohol drinks, and non-alcoholic steatohepatitis of liver (NASH).The accumulation of extracellular connective tissue protein will distort hepatic architectures by forming excessive fibrous tissue and resulting in the development of hepatic nodules. Once the nodules have been developed, the condition is defined as cirrhosis.

Liver biopsy, eventhough being an invasive method, is still regarded as standard criterion for determining the stage of fibrosis. As there are so many obstacles, complication and expensive cost of the invasive method, numerous studies have proposed a diagnostic method for fibrosis staging using non-invasive methods.

Liver fibrosis can be measured by FibroScan significantly, in consistent with or equal to the liver staging made by liver biopsy. The

diagnostic accuracy of FibroScan[2] is higher in comparison to biomarkers to evaluate the stage of liver fibrosis.

FibroScan offers some advantages compared to liver biopsy since it is a rapid and painless test with less interpretation error. Evaluation of liver fibrosis using non-invasive method may also be done by **APRI score**.

By comparing some of simple laboratory markers, the methods can predict those patients with chronic hepatic disease who are progressing to fibrosis, thereby, treatment can be initiated earlier to control further complications.

The primary aim of the study is to compare the predictive value of aspartate aminotransferase to platelet ratio index (APRI) with Fibro Scan as a confirmatory tool for predicting liver fibrosis in patients with chronic hepatitis B and C infection .

AIMS AND OBJECTIVES

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Comparison of the accuracy between aspartate aminotransferase (AST) to platelet count ratio index(APRI) value to Fibroscan to predict fibrosis of liver in patients with chronic Hepatitis B and/or C patients .

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HEPATITIS B INFECTION

About 4000 lakhs people in the world are infected with Hepatitis B virus chronically. Most of these individual won't experience complications, but around 15% to 40% would have sequelae as cirrhosis or hepatocellular carcinoma and die prematurely.

The rate of acute hepatic failure[3] secondary to Hepatitis B virus is declining, so the number of cases for liver transplantation for chronic hepatic failure. This decline is mostly due to wider vaccination programs along with use of antiviral therapy.

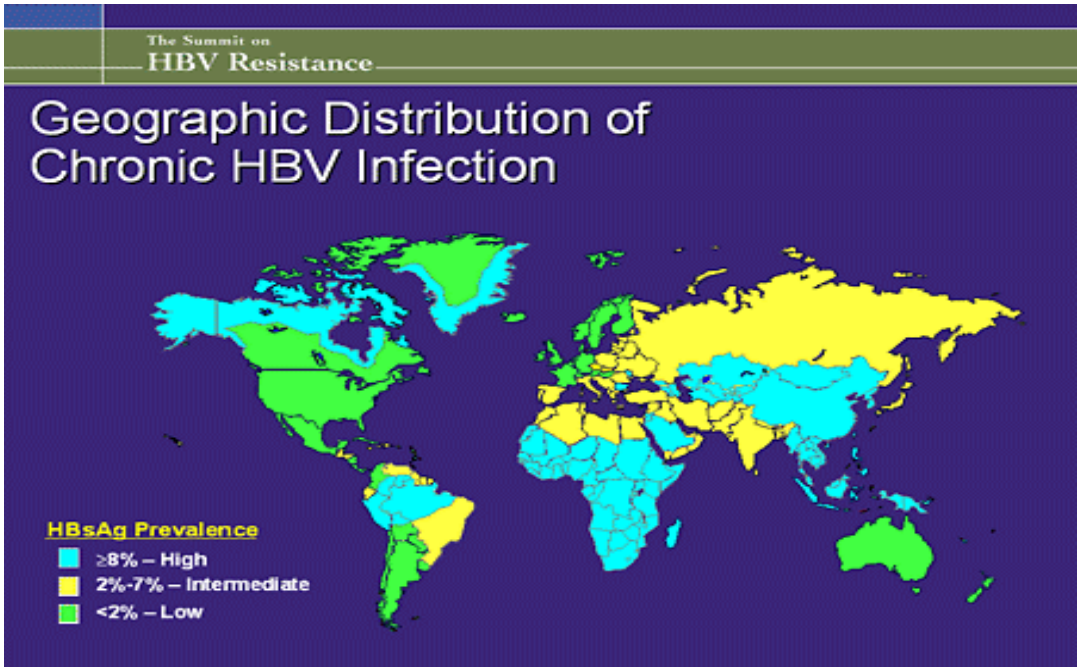
From a global perspective, global implementation of early-life vaccination programs among high- and intermediate-risk countries would ultimately had the greater effect on liver disease–associated mortality among near future generations.

EPIDEMIOLOGY

Geographic Distribution and Source of Infection

The prevalence of HBV infection vary considerably worldwide.

- In regions that are highly endemic, as those of Southeastern Asia, China, and most regions of Africa, 9% of the people were chronic HBV carriers, thus, the lifetime risk of infection varies from 65% to 75%. In the above areas, the mother to child transmission and horizontal spread amongst the adolescents are the prime source of transmission. Approximately,65% of the population globally are residing in areas of highly endemic HBV infection.
- Regions of intermediate risk would include Southern Europe, Japan, India, Soviet Union[1], and north Africa. In these areas, the risk of acquiring the infection is between 30% and 60%. Horizontal transmission involves a broad age range, but neonatal exposure also tends to be common.
- Areas of lower prevalence includes Northern America, West Europe, Australia, where the risk of acquiring Hepatitis B infection is around 20% and the transmission is predominantly horizontal amongst young adults.



INFECTIVITY

HBV is transmitted primarily by percutaneous and through exposure of mucous membrane to infected body fluids. Hepatitis B Virus is 50 to 100 times more infectious as HIV and 15 times more infectious as Hepatitis C. HBeAg seropositivity points toa the fact that there is a higher risk for perinatal transmission, following needle prick exposure and among the household contacts.

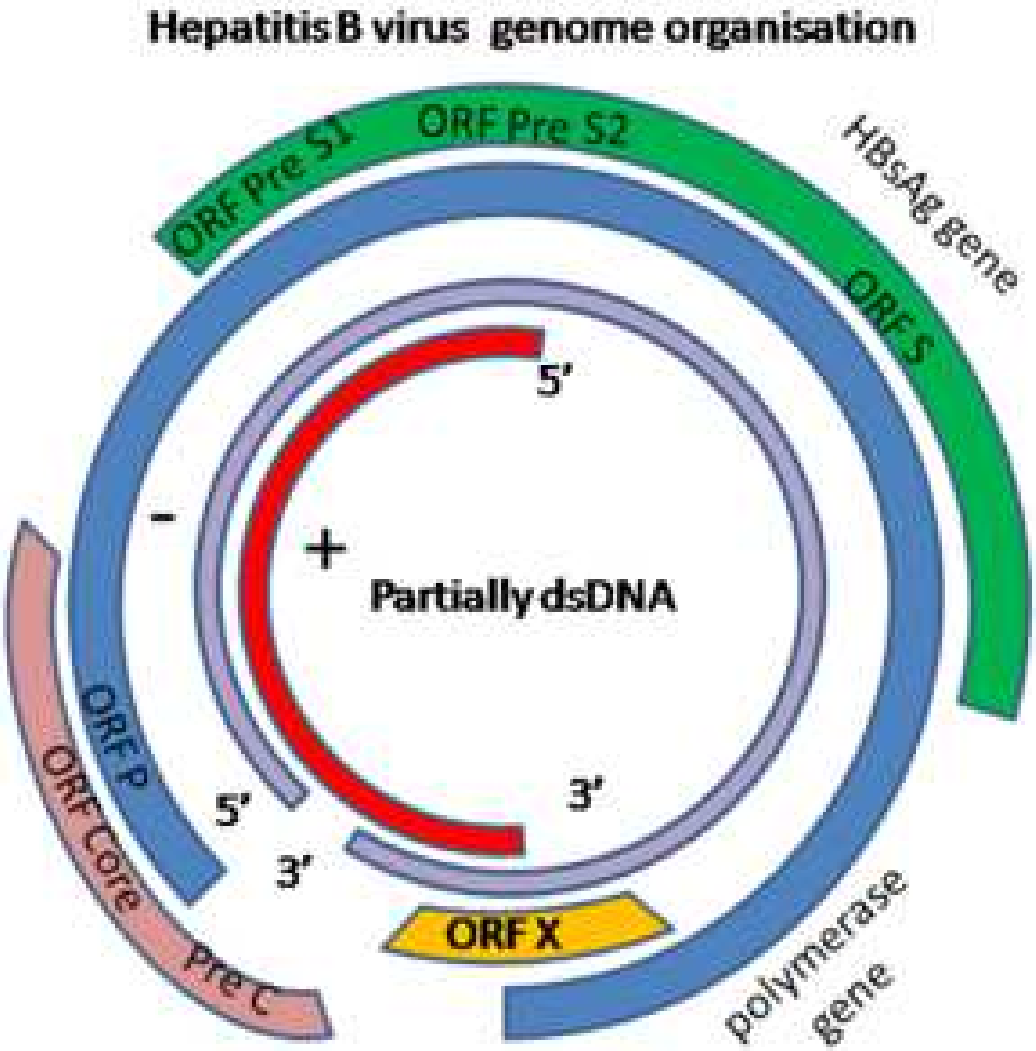
Detection of HBV DNA by newer sensitive techniques like PCR in body fluids, other than stool that is not mixed with blood[1]. Eventhough, HBV replication occur primarily in liver cells, presence of viral intermediates and those of virally proteins in sites, like adrenal gland, colon, skin serves as extrahepatic reservoir for infectious source of virus.

VIROLOGY

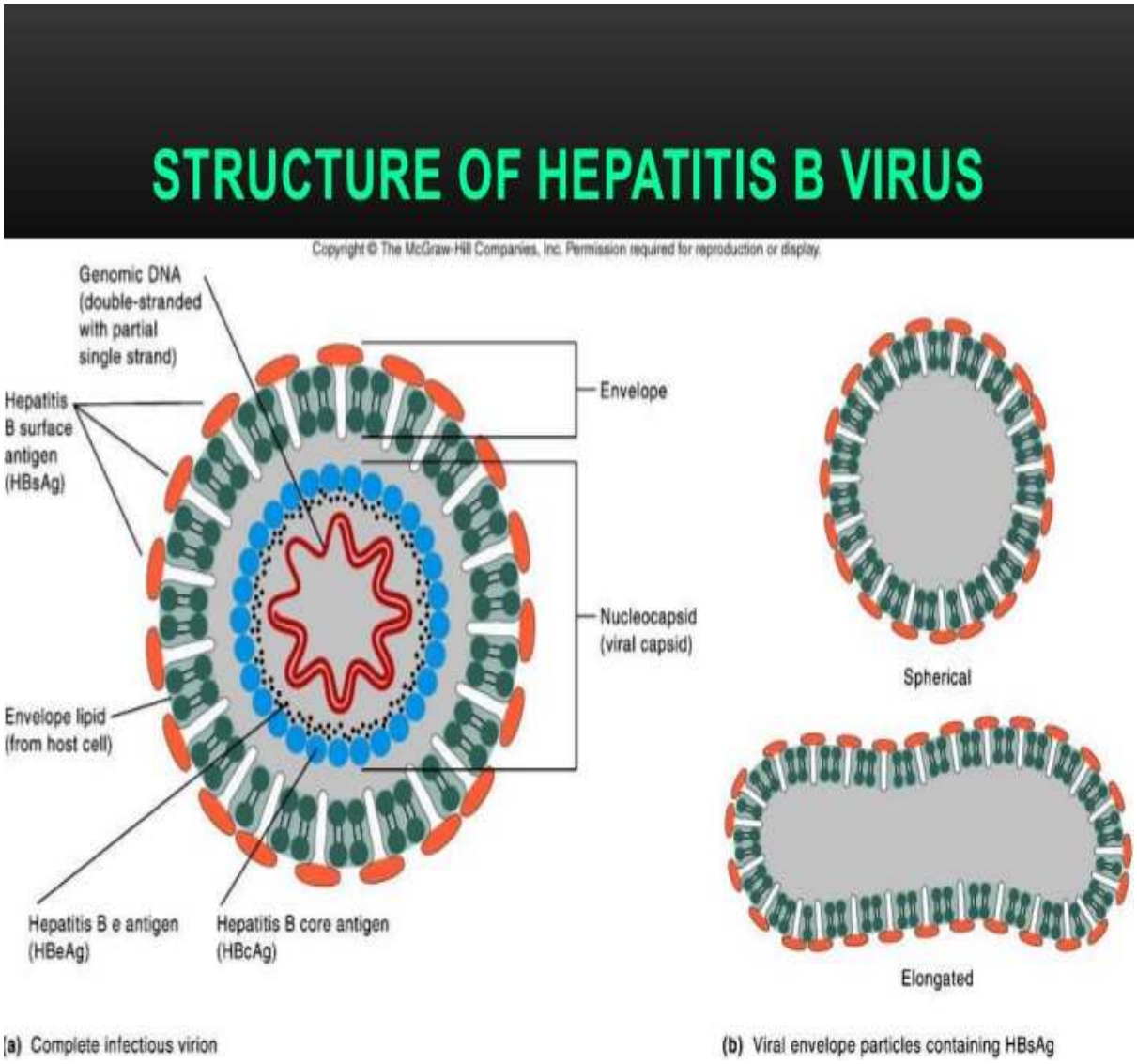
HBV is a small DNA virus belonging to the family Hepadnaviridae. Hepatitis B virus is a small virus which has a DNA genomic structure and a double-stranded structure. The genome consists of around 4 open reading frames, a design where several other genes overlap and also utilises the same DNA for encoding different proteins of virus.

The important 4 viral gene components include the Core gene, Surface gene, X, and the polymerase genes.

- ✓ Core[C] genome[1] helps in encoding the core nucleocapsid component, necessary for packaging of virus and for HBeAg production .
- ✓ Surface [S] gene aids in encoding the pre-S1, pre-S2, and also S protein
- ✓ X gene encode a X protein, with transactivating properties and plays an prime role in hepatocellular carcinoma formation.



- ✓ Polymerase genome has a large open reading frame . It helps in encoding a protein with those functions that are crucial for DNA replication(including priming, RNA- and DNA-dependent DNA polymerase)[1].



VIRAL REPLICATION

HBV being a DNA virus, process of replication occur primarily with the aid of an RNA intermediate and also require an viral reverse transcriptase enzyme. The Mutation rate is much higher for Hepatitis B[1]

virus in comparison to other DNA viruses (around 1010 to 1020 point mutations per day). .

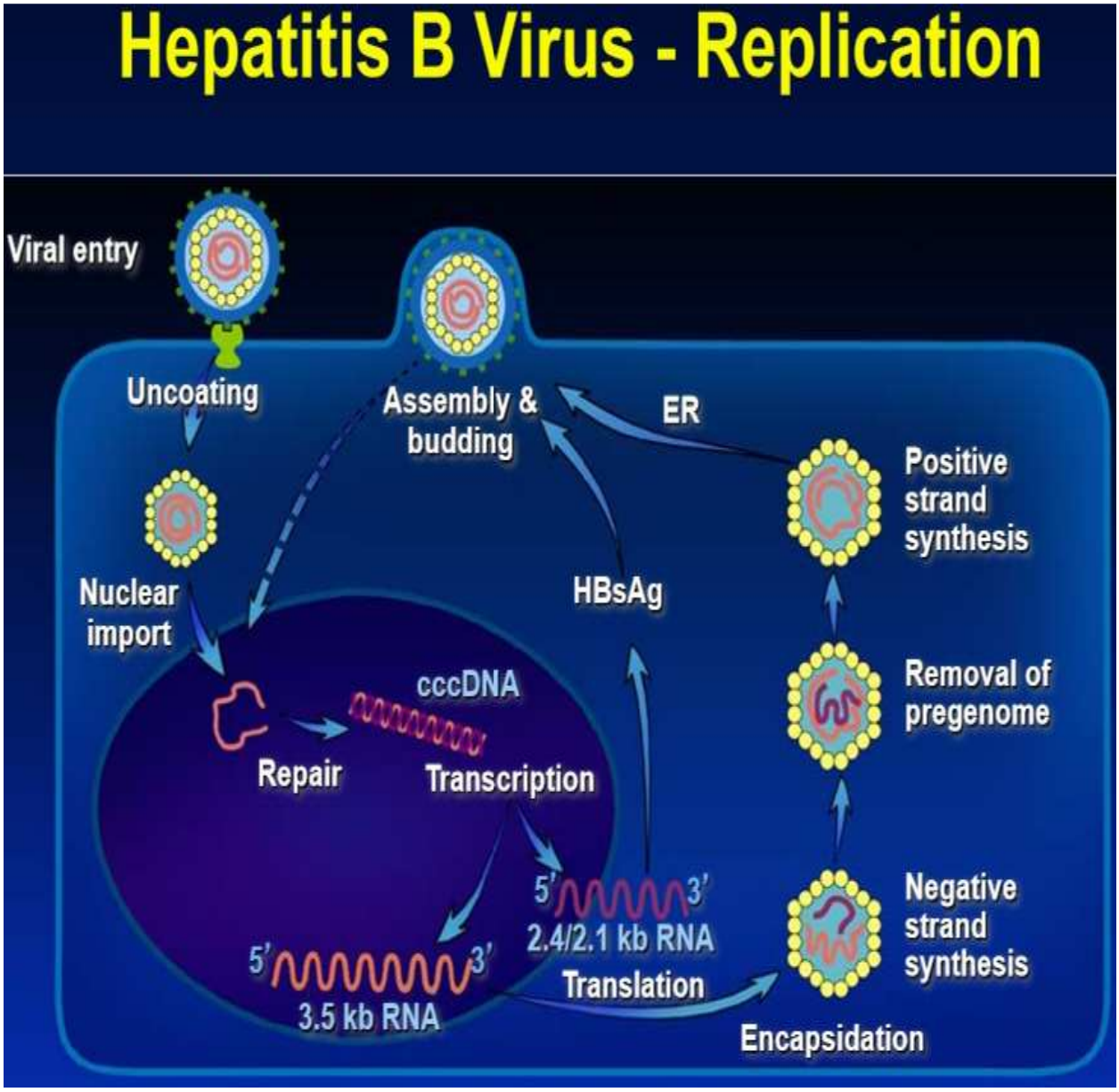
Due to genomic overlap, some of these silent mutations in 1 ORF (e.g., the polymerase gene) might result in substitution of amino acid in overlapping Open reading frame.

Replication of hepatitis B virus usually begin with encapsidation of viral RNA. HBV DNA polymerase tends to reverse transcribe these RNA into a negative-strand HBV DNA, thus in turn serve as templates for positive-strand synthesis resulting in a partially dsDNA

genome.

Concurrent with synthesis of HBV DNA, nucleocapsid also undergoes maturation, however,through a different mechanism, interacting with S protein initiating assembly of virus in the [ER]endoplasmic reticulum. S protein is synthesized in the endoplasmic reticulum, and monomers aggregate excluding the host membranous proteins which ultimately buds into lumen as subviral particles.Once formed, HBsAg tends to undergo glycosylation in the Golgi apparatus and the endoplasmic reticulum.

Noninfectious viral particles (filamentous as well as spherical forms) are secreted in greater number in comparison to matured virions. These subviral particles may exceed virions by a variable factor of 102 to 105[1] in number and will accumulate up to concentrations of several hundred micrograms per ml. of serum.



GENOTYPES

Genomic classification depending on comparisons of genomes had showed 10 genotypes and numerous subtypes of HBV.

- Genotype A ,the prominant genotype seen in United States, North Europe.
- Genotypes B / C are mostly confined to East Asia and also the Far East populations.
- Genotype D were found globally, however with highest prevalence in the Middle East, and Southeast Asia[1] .
- Genotype E is prevalent in West Saharan areas.
- Genotype F noted in Central parts of America.
- Genotype G had been noted in the France.
- Genotype H prevails in parts of Mexico.
- Genotypes I and J were the most recently discovered and had been observed in Ryukyu Islands in Japan and Vietnam respectively.

The strongest clinical association appears to be :

(1) Seroconversion of HBeAg would occur in patients with HBV genotype B prior to genotype C.

(2) The therapy response with interferon (IFN) is better amongst genotypes A and B than with C and D .The viral genotypes might have an effect on the hepatocellular carcinoma[1] .

Clinical Associations

- Seroconversion of HBeAg: hepatitis B < C virus
- Response to Interferon-α treatment: A > B ≥ C > D
- Frequency of Precore or core promoter mutant: genotypes A and F
- Progression of Hepatic disease :B < C
- Evolving chronic hepatic failure: A < non-A
- Risk of Hepatocellular carcinoma: hepatitis B > C.

MUTATIONS

Most of mutations in genomic structure are identified by comparing sequences of nucleotide with that of wild-type HBV that doesn't alter the amino acid sequence in a particular ORF[2.]

Hepatitis B Surface Antigen Gene

HBsAg gene mutants results due to a primary mutation in the HBsAg gene or due to a mutation in DNA polymerase gene during antiviral nucleoside therapy .

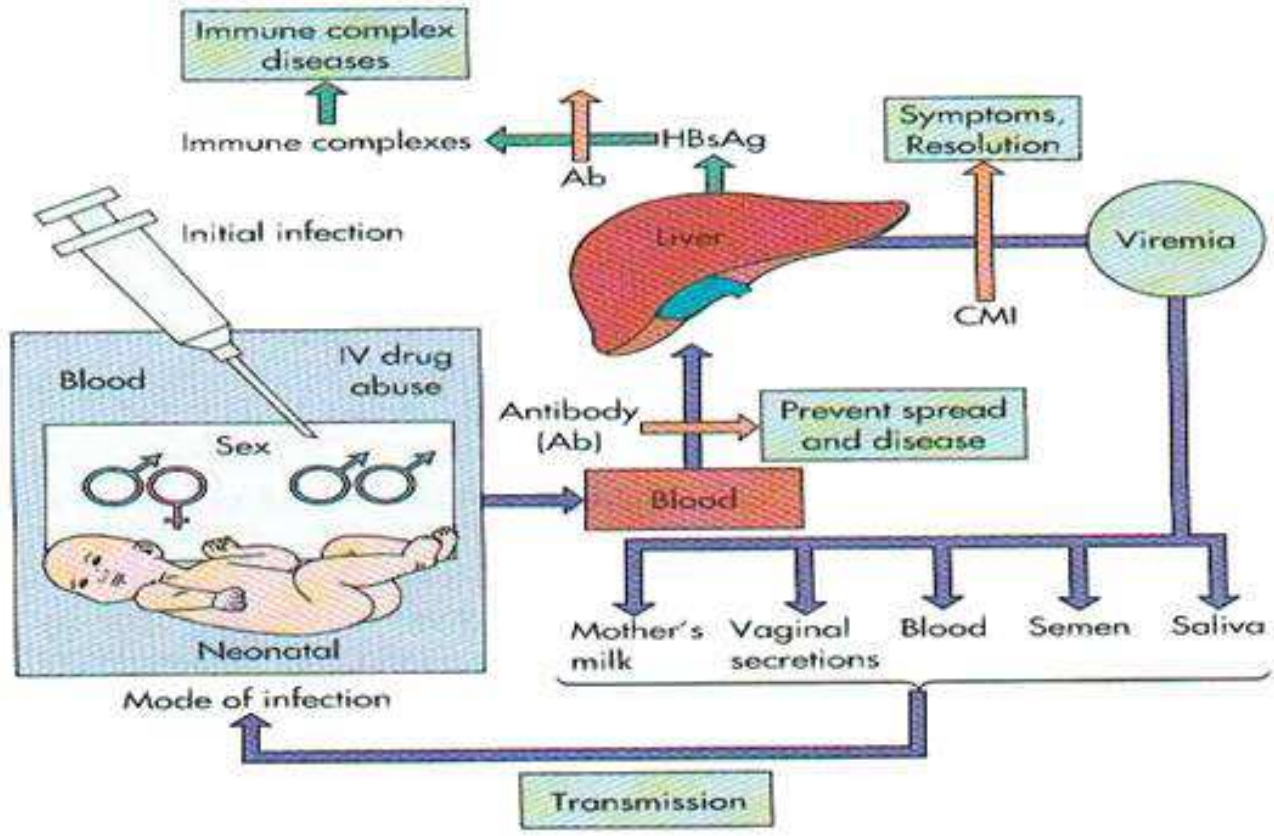
Once mutation appears, mutated virions would usually becomes selected immunologically as dominant form of virus. Mutations in the HBsAg gene between positions of amino acid 124 to 147 are important as this region of HBsAg gene include the major “a” epitope which binds to neutralizing antibody to HBsAg (anti-HBs). The mutation leads to failure for detection of HBsAg by commercial assays, depending on binding to anti-HBs, to failure of neutralization by hepatitis B Immunoglobulin[1] or of vaccination.

HBsAg gene-mutant HBV infection is accompanied by anti-HBc detection. Serum levels of HBV DNA can be varied as they are in HBsAg carriers .Mutants need to be distinguished from “occult” hepatitis B cases, which are linked to cryptogenic cirrhosis and increased HCC risk.

Even in occult HBV infection, HBsAg negative persons may have detectable HBV DNA levels in the serum. Some of them Might not have evidence of serologic markers of infection (e.g., anti-HBc).

Occult infection is primarily due to active suppression of replication of virus with a result, HBV DNA is present in low levels (<200 IU/mL) by the action of host immune system.

PATHOGENESIS



The severity of HBV-associated hepatic involvement is due to severity of immunologic response to the hepatitis B virus by the host. Cellular and humoral responses are necessary for complete clearance with a long-term protection for reinfection. Pathogenesis of disease is mainly due to cellular immune response[1.]

Antigen-specific T-cell response induction would happen in lymphoid organs, where the host T cells will attack viral antigens . The above process tends to result in maturation and expansion of T cells that are specific for viral antigens followed by movement to the liver, for performing their effector function completely.

During an acute Hepatitis B infection, cell of innate immune system and hepatic-infiltrating Hepatitis B-specific CD8+ cells would clear HBV DNA molecules from liver with the help of noncytopathic mechanisms mediated by cytokines.

Cytotoxic T lymphocyte aids in T-cell receptor binding to the peptide-Major histocompatibility complex whose binding on liver surface will help in the infected cell being directly killed and release of the potential antiviral cytokines by already activated Cytotoxic T lymphocyte[1] .

Appropriate presentation of viral peptides is required for MHC class II–restricted CD4+ T cell recognition. Antiviral cytokines is produced by the CD4+ cells which helps in neutralization of antibody production thereby , limiting spread of virus during infection and also aids in prevention of reinfection.

NATURAL HISTORY

Various phases of Hepatitis B infection observed are:

- Immune tolerance,
- immune clearance,
- Inactive carrier state, and
- Reactivation .

These consecutive phases are most likely apparent in patients with acquisition of hepatitis B early in life.

- The *immune tolerance* phase which is the earliest phase to be recognized in patients with infection history at birth or in early years of life, characterized by:

✓ Positivity of HBeAg,

✓ Higher HBV DNA levels ($\geq$107 IU/mL)[3],

- ✓ Lower to normal levels of serum aminotransferases,
- ✓ Minimal necroinflammation or fibrosis in the liver.
- ✓ Rates of HBeAg loss during this phase are low. Perinatal transmission of HBeAg is one of several potential mechanisms in the immunetolerance phase.
- ➢ After several decades only ,the *immune active* phase of HBV infection often begins characterized by:
- ✓ Elevated serum aminotransferase levels,
- ✓ Lower HBV DNA than in the immune tolerance phase,
- ✓ Histologic evidence of chronic hepatitis .

This apparent immunology is triggered by activation against HBV are poorly understood, though CD8+ CTL-involving lysis of infected liver cells has been occurred .

Host immune system continues to put effort against the virus that may result in seroconversion of HBeAg (HBeAg loss with the development of anti-HBe in the serum). HBeAg seroconversion may not always indicate quiescent disease, as much as 30% of those who undergo HBeAg seroconversion enter into a next phase of active disease that is caused by

the selection of HBeAg-negative mutants (precore mutation, core promoter mutantion, or a combination of both).

At least half of these people demonstrate huge fluctuations in HBV DNA and aminotransferase levels every year, and recognition of both active disease and exclusion of the inactive HBsAg carrier state may need serial assessments of serum Hepatitis B DNA and aminotransferase levels.

- Most patients who undergo HBeAg seroconversion, however, enter a third phase (*inactive HBV carrier* stage), which is characterized by

- ✓ Normalization of serum ALT
- ✓ Low (<2000 IU/mL) hepatitis B DNA levels
- ✓ Hepatic necrotic inflammation with fibrosis subside gradually.
    - The inactive HBsAg carrier phase lasting for a lifetime, some patients might develop *reactivation*, which may occur spontaneously due to loss of immunological control over viral replication or can be as a consequence of immunosuppressive drug therapy.
    - Reactivation is defined by the higher levels of Hepatitis B DNA level reappearance in serum, with or without seroreversion of HBeAg, and is often seen with a noticeable

rise in levels of serum ALT. In 20% of cases. if the immune active phase of hepatitis B remains untreated, we can anticipate cirrhosis to develop.

Various factors have been determined which increase the risk of Cirrhosis.

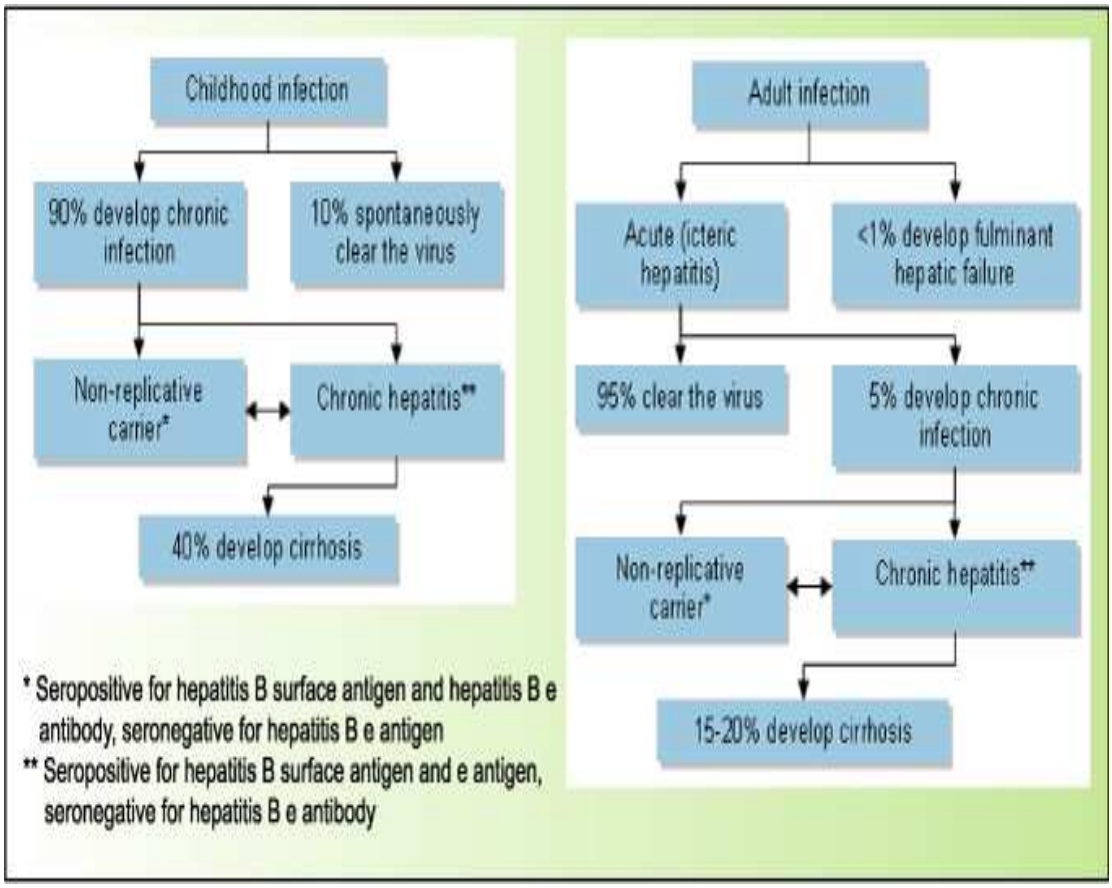
- Elderly,
- Male gender,
- The state of fibrosis at the time of presentation,
- Ongoing Hepatitis B replication.

Combined infection with HDV, Hepatitis C , or HIV, are prone for a higher rate of developing cirrhosis and HCC. With the development of cirrhosis ,major complications may occur: decompensation of liver and hepatocellular carcinoma.

The estimated annual frequency of developing liver decompensation in Hepatitis B-associated cirrhosis is 5% to 8%, whereas that of HCC is 2% to 4%.

Factors associated with an increased risk of HCC include:

- male gender,
- age 45 years or greater,
- having a first degree relative with HCC,
- the presence of cirrhosis,
- HBeAg positivity,
- reversion from anti-HBe to HBeAg positivity,
- increased HBV DNA levels regardless of the HBeAg state.



CHRONIC HEPATITIS B

Acute Infection or symptomatic hepatitis history is usually absent in patients with chronic Hepatitis B infection. Once symptoms appear, fatigue is the most predominant symptom, others being poor appetite and malaise.

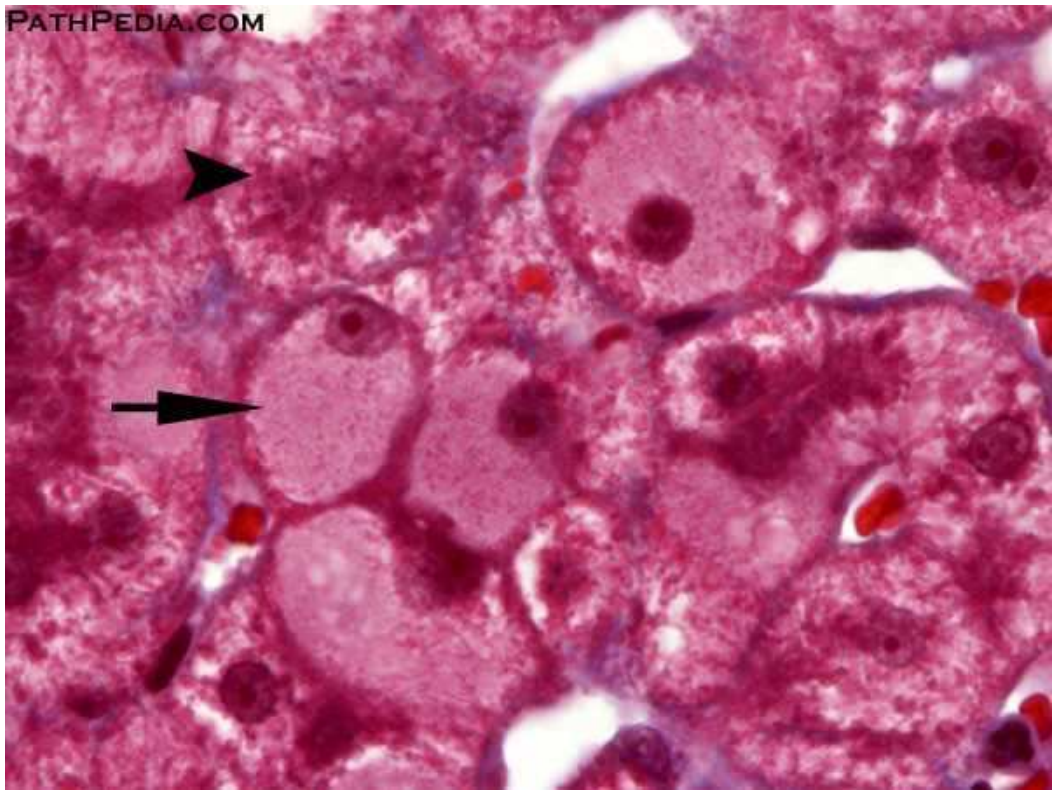
Patients remains asymptomatic at the time of reactivated hepatitis. Overlapping with cirrhosis, reactivation of hepatitis B infection result in overt jaundice with signs of hepatic failure. Physical examination might be normal, or hepatomegaly, splenomegaly can be present. In patient with decompensated cirrhosis, spider angiomas, icterus, ascites, and pedal edema are common.

Cirrhosis progression should always be borne in mind in the presence of hypersplenism, decrease in serum albumin (in the absence of nephropathy), or prolongation of the prothrombin time (PT) is noticed. Patients with advanced cirrhosis tend to have seum aspartate aminotransferase level higher than the alanine aminotransferase levels.

HISTOPATHOLOGIC FEATURES

Chronic Hepatitis B virus infection is usually marked by mononuclear cellular infiltration within the portal triad. Disruption of limiting plate of hepatocytes occurs due to the periportal inflammation (also known as interface hepatitis), and at the interface among collagenous extensions from portal triads to hepatic parenchyma, inflammatory cells often are seen (known as *active septa*).

During the periods of reactivation of hepatitis B, active lobular inflammation is much more severe and remanant of them are present in acute viral hepatitis.



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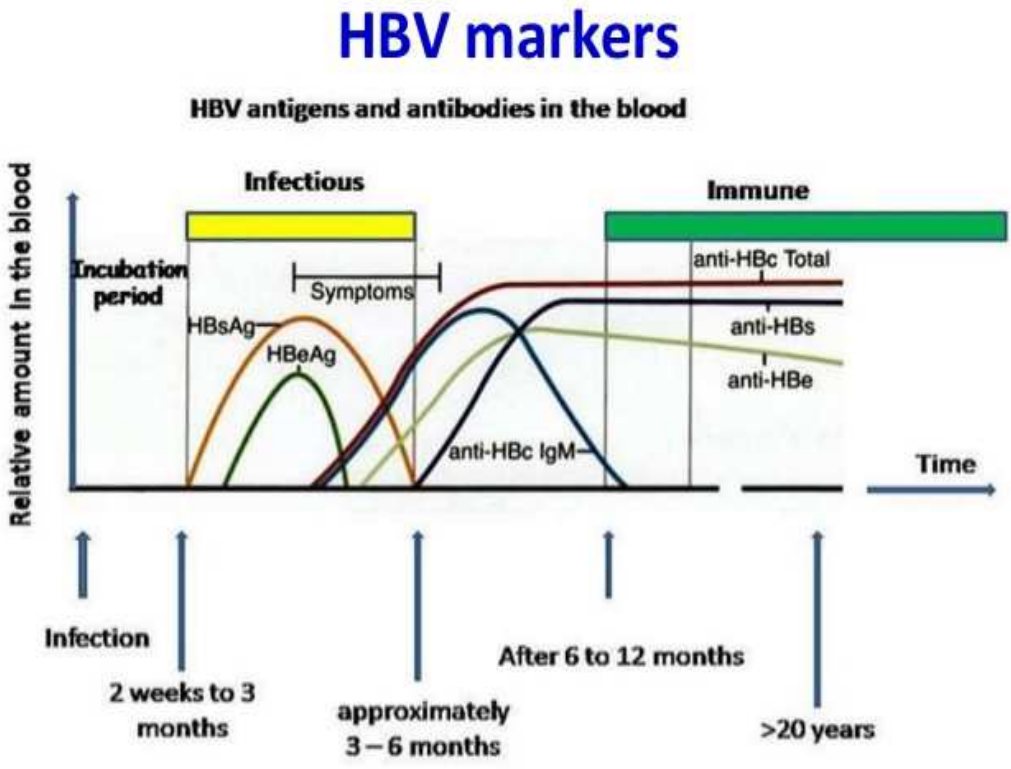
The light microscopy shows a charachteristic histologic feature, which is more specific for chronic hepatitis B infection is the appearance of ground-glass hepatocytes . This structural finding results due to collection of HBsAg particles (25 to 35 nm in diameter) in the dilated endoplasmic reticulum. Due to presence of high levels of cysteine in HBsAg, cells might tend to have a higher affinity for dyes, such as orcein, aldehyde fuchsin and Victorian blue. may also Hepatitis B carriers might have ground glass hepatocytes, seen in around 5% cells. When they are present in excess, indicates active viral replication.

DIAGNOSIS



Following exposure to Hepatitis B viral infection, HBsAg usually appears after 2 to 10 weeks but prior to increment of serum aminotransferase levels. In cases of self-limiting acute hepatitis, HBsAg usually goes to undetectable levels following 4 to 6 months.Evolution to chronic HBV infection is indicted by the persistence of HBsAg for greater than 6 months.

Coexistence of HBsAg and anti-HBs had been reported in approximately 10% to 20% of HBV carriers. The mechanisms most likely are due to antibodies formed against HBsAg protein variants.

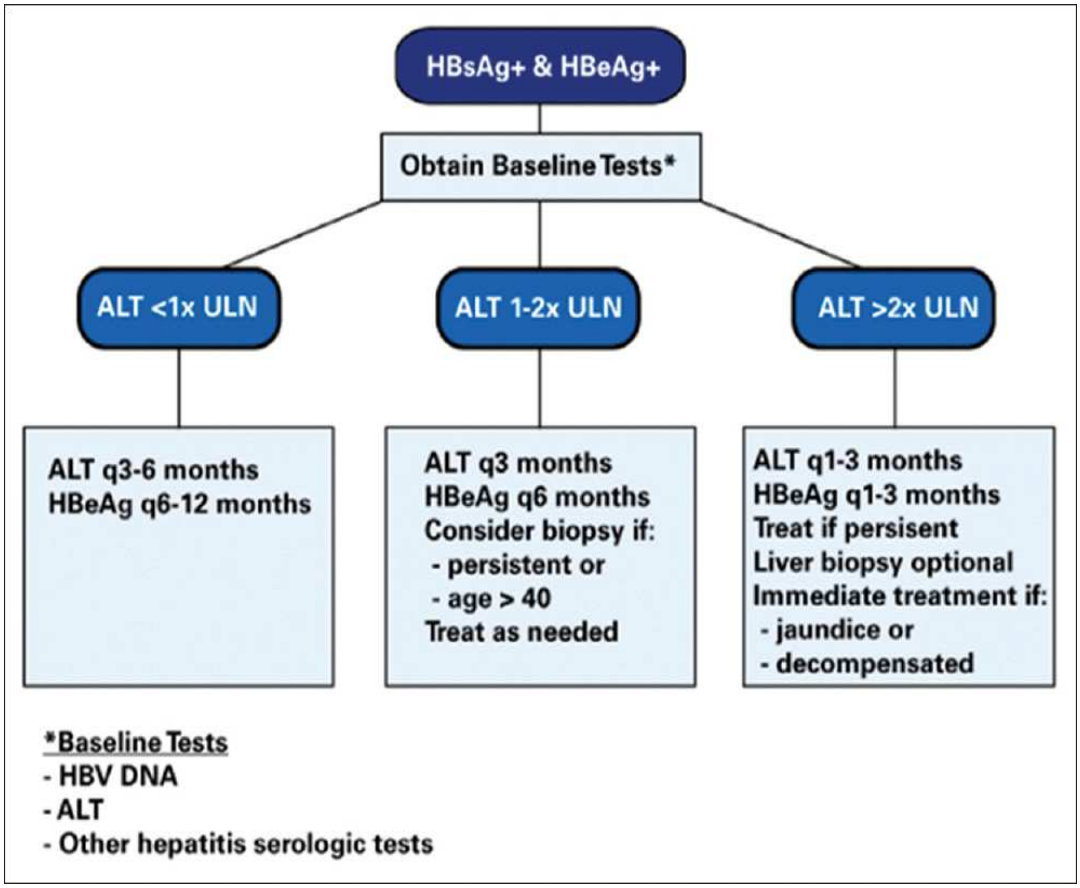
Anti-HBc is usually detectable in chronic HBV infection. IgM class of anti-HBc usually appears following an acute infection and tends to persist for 4- 6 months following the infection and might also persist foryears . During chronic hepatitis B exacerbation, anti-HBc of IgM class becomes detectable and often used as surrogate for active viral replication. Anti-HBc of the IgG class is mostly seen in persons who progress to chronic infection.

In low endemic areas such as the United States, anti-HBc in serum had been detected in 2% to 5% of the given population. Less than 5% of these patients are anticipated to have Hepatitis B DNA levels detectable in serum and therefore resulting in occult viremia. By contrast, isolated

anti-HBc are found in more than 50% of patients in highly endemic regions of the world, and 10% to 40% of patients with this finding might have Hepatitis B DNA detectable in serum.

Anti-HBc isolated reactivity occurs in a clinical situation out of which, the most important to recognize is a false-positive result, which will be usually very weakly reactive and may not be reproducible. Failure to appreciate this, in patients who had no apparent exposure to HBV might result in needless consultation, inappropriate exclusion from vaccination program, and, rejection of the person from blood or organ donation. Such patients often have primary rather than anamnestic response to HBV vaccination[1] .

HBeAg is a viral protein seen at times of acute HBV infection. Once the serum aminotransferase levels peak ,the HBeAg reactivity usually disappears, and presence of persistence of HBeAg 3 months after the illness predictsa higher chance of chronic HBV infection.



The presence of HBeAg in HBsAg-positive carrier indicates active viral replication and maximum infectivity for intimate contacts.

Serum Hepatitis B DNA values might be upto 1012-13 during the immune tolerance phase. Those patients with anti–HBe have a reduced serum hepatitis B DNA levels (105 to 108 copies/mL), with the values being highest found in elevated serum ALT levels.

HBV DNA measurement can be done in serum using different qualitative or quantitative assays. The quantification of serum Hepatitis B DNA is mostly used to assess the need for antiviral treatment and for monitoring response in the treatment course.

TREATMENT

Seven drugs are approved for the treatment of chronic hepatitis B infection. Five of these agents are nucleos(t)ide analogs which suppress HBV replication through an inhibitory effect on viral DNA polymerase. Nucleos(t)ide analogs have superior oral bioavailability and a excellent safety record and are most potential inhibitors of viral replication than IFN-α agents.

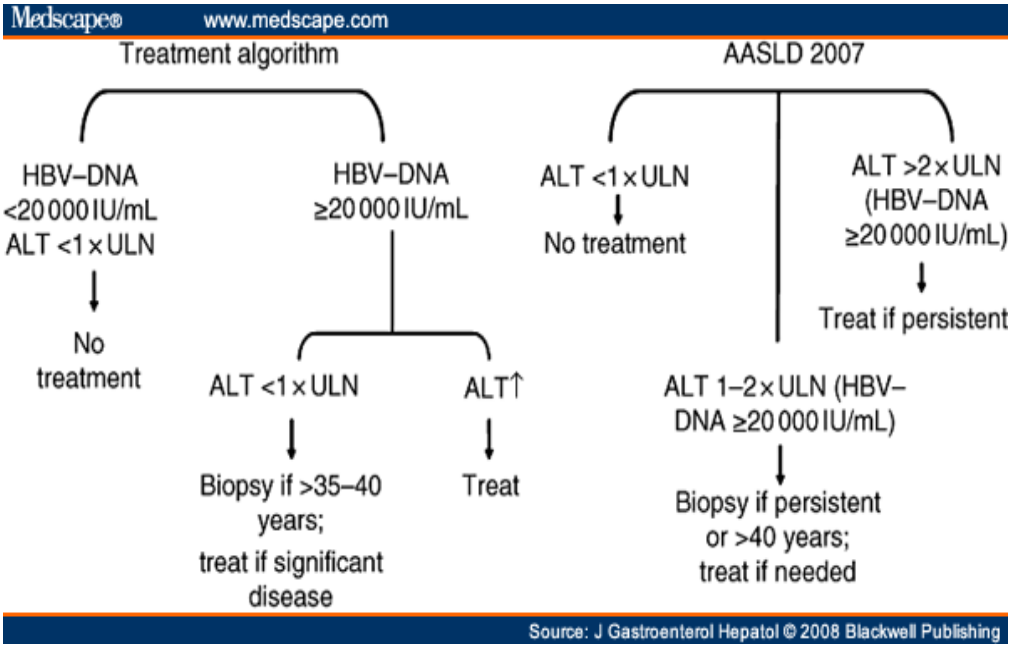
INDICATIONS FOR STARTING ANTIVIRAL THERAPY

Goals

The main treatment goals for chronic hepatitis B patients are:

- to forestall hepatic disease progression,
- prevent late complications (fibrosis, liver failure, and hepatocellular carcinoma),
- increase survival.

All these objectives are obtainable with long-term suppression of viral replication with either an IFN-α or nucleos(t)ide analogs. Our data suggests, among the overall patients with potentially treatable chronic hepatitis B infection ,only 10% are treated adequately.



NUCLEOSIDE AND NUCLEOTIDE ANALOGS

Majority of treatment-naïve" patients are treated with 1 or more nucleos(t)ide analogs rather than IFN. Between 70% and 85% of HBeAg-positive patients would become HBV DNA negative during the first year of treatment. A group of patients might still have HBV DNA levels detectable in serum after several years of therapy with high-genetic-barrier nucleos(t)ide analogs even though, clinical and biochemical response persists. The reason for this persistence of serum HBV DNA is not well understood, but the Hepatitis B DNA levels are almost always below 3000 IU/mL, and drug-resistant mutants had not been demonstrated in this situation.

The lack of adverse effects and good resistance profiles of the orally available antiviral agents are especially important properties as HBeAg seroconversion occurs slowly and requires treatment for an indefinite duration. Eventhough a rapid decline in serum HBV DNA levels on nucleoside therapy occurs, only 20% to 25% of treated patients reach HBeAg seroconversion following 1 year of treatment.

LAMIVUDINE

Due to a high rate of resistant organisms , lamivudine is least considered as a first line therapy, except in persons who require only short-term therapy, such as those undergoing cancer chemotherapy. Prolonged lamivudine resistance had been associated with blunted histological response with much higher hepatitis flares.

Before commencement of antiviral therapy in patients who are born in endemic areas for hepatitis B, care to be taken to inquire if antiviral therapy has ever been consumed previously. In such patients, it is best not to use entecavir due to the high likelihood that prior exposure to lamivudine may predispose the patient to entecavir resistance.

ADEFOVIR DIPIVOXIL

Adefovir is licensed by the FDA after lamivudine became available and is used frequently because it is an efficacious towards lamivudine-resistant HBV[4] . Because of its limited potency, primary treatment failure (<1 log reduction in the serum Hepatitis B DNA level at week 12) was present in 30% of patients.

ENTECAVIR

Entecavir, a nucleoside analog which is more potent than lamivudine or adefovir and a higher genetic barrier to resistance, which requires an additional DNA polymerase mutation superimposing on preexisting lamivudine resistant mutations. This situation appears to be rare in treatment-naïve patients, which explains the fact that resistance had been found in around 2% of treatment-naïve patients continuous treatment for 5 years.

The long-term use of entecavir benefits includes progressive regression of fibrosis, features of cirrhosis reversal, and a reduced incidence of HCC.

TELBIVUDINE

Telbivudine , a nucleoside analog is a more potent drug than lamivudine in all HBeAg-positive and HBeAg-negative patients. Following an year of treatment, around 30% of HBeAg positive patients are predicted to have genetic resistance.

Table 4

Current Treatment Options for Chronic Hepatitis B

	Interferon	Lamivudine*	Adefovir*	Entecavir*
Route	Subcutaneous or intramuscular	Oral	Oral	Oral
Doses	15–35 MU weekly or 180 mcg weekly	100 mg daily	10 mg daily	0.5 mg or 1 mg daily
Side effects	Many	Negligible	Potential nephrotoxicity	Negligible
Resistance	None	14%–32% year 1 >70% year 5	None year 1 3% year 2 6% year 3	None in treatment-naïve patients,10% at year 2
Cost	High	Low	Intermediate	High
Advantages	Finite treatment duration, no resistance	Low cost, low side-effect profile	Effective against lamivudine resistance	No reported resistance in nucleoside-naïve patients, low side-effect profile, effective against lamivudine resistance
Disadvantages	High side-effect profile; injection	High rate of resistance	Renal toxicity	Limited long-term data, highest cost of oral agents
Efficacy† (%)	30	16–18	12	21
Durability† (%)	80–90	50–80	NA	NA

** Flare-up of the disease upon discontinuation of the drug is associated with this agent.*
† Seroconversion at one year for hepatitis B e antigen–positive patients.
MU: million units. Source: Reference 5.

TENOFOVIR DISOPROXIL FUMARATE[22]

Tenofovir is chemically almost similar to adefovir, but had significantly higher rate of antiviral potency. High genetic barrier is responsible for making it more resistant and a strong antiviral potency. Tenofovir is being used more frequently as a first-line therapy, in cases

where heavy exposure to lamivudine is present, known cases with lamivudine resistance, or following its suboptimal response to adefovir[5] .

EMTRICITABINE

Emtricitabine is morphologically similar to lamivudine and tends to inhibit Hepatitis B DNA polymerase. FDA has not approved its for use in hepatitis B, neither alone nor in a combined tablet with tenofovir which is commonly used for HIV Infected patients. As it is structural similar to lamivudine, it's resistance profile is also the same.

HBV-HEPATITIS C COINFECTION

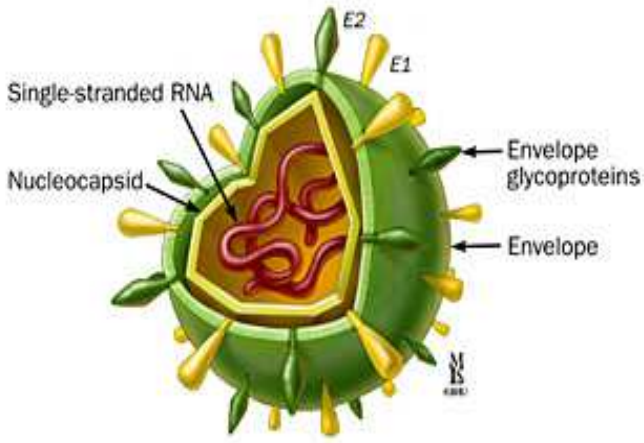
HBV-Hepatitis C –coinfected patients as compared to monoinfected patients usually have a higher degree of cirrhosis and grave prognosis. Before and after treatment is initiated close monitoring is recommended. Authors in such instances, had higher success in treating patients and simultaneously in combintion of a nucleos(t)ide analog, pegylated IFN-α, and ribavirin.

HEPATITIS C INFECTION

Chronic Hepatitis C , has the importance that it is the only type of chronic viral infection which can be completely cured by antiviral therapy. More importantly, successful antiviral treatment helps in

preventing complications of many Hepatitis C infected patients. As much as up to 80% of Hepatitis C genotype 1 infected patients who can tolerate treatment with pegylated interferon-α , ribavirin, and also a first generation Hepatitis C protease inhibitor achieves a higher sustained virologic response (SVR). The Chronic Hepatitis C infection leads to decompensated cirrhosis and hepatic carcinoma (HCC).

VIROLOGY



STRUCTURE:

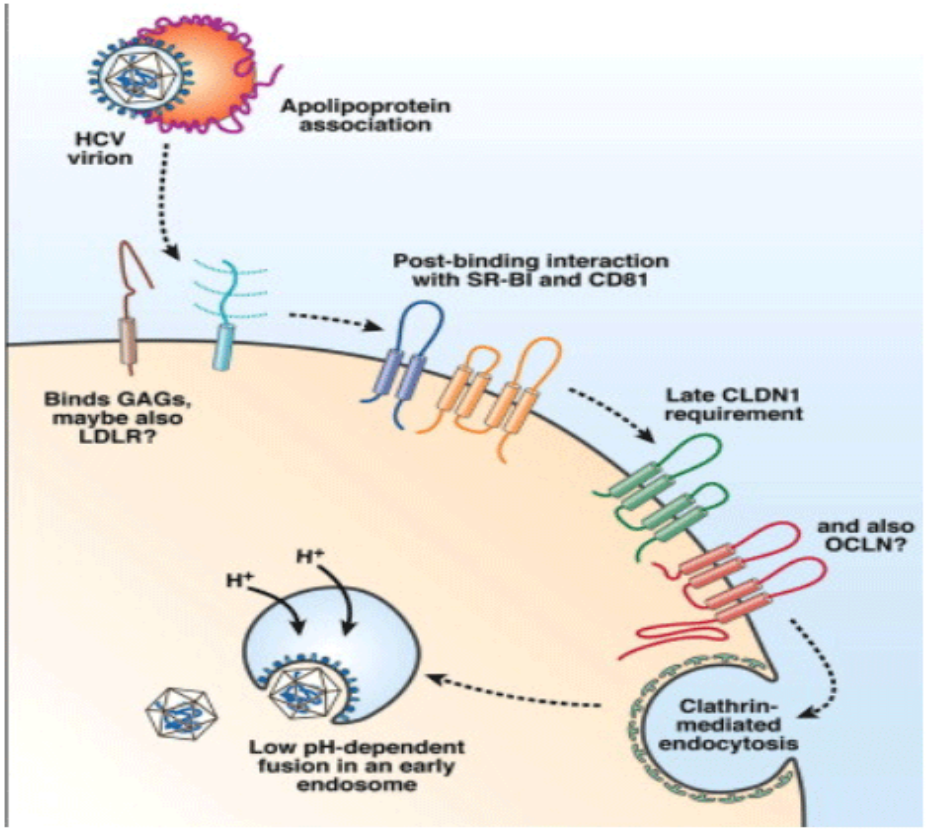
The Hepatitis C virion that is an enveloped virus is 50 nm in diameter has been visualized by an electron microscopy. There are two envelope proteins, and a smoother outer layer. This layer has a "fishbone" configuration with a icosahedral symmetry.

These enveloped proteins anchor to host cell–derived lipid bilayer envelope membrane which surrounds the nucleocapsid. The nucleocapsid consists of multicopies of core protein forming an icosahedral coat to encapsulate the genomic RNA.

VIRAL REPLICATION AND LIFE CYCLE

Although T and B cells, a peripheral blood mononuclear cells, and also dendritic cells have reported to have supported Hepatitis C replication, liver which is the prime site of viral replication. Hepatitis C entry into the cell also involves the attachment of namely the envelope protein to cellular surface molecules[21].

Apart from this, human scavenger receptor class B type 1 (SR-B1) is also essential for the Hepatitis C entry.



EPIDEMIOLOGY:

Different epidemiologic patterns of Hepatitis C infection has been present around the world. They are :

(1) previous health care exposure with a prevalence that peaks mostly in elderly;

(2) another is exposure through IV drug usage , where middle age group has a peak prevalence.

TRANSMISSION

Mode of transmission of Hepatitis C is by two routes

- Percutaneous (blood transfusion and needleprick inoculation) and
- Nonpercutaneous (sexual contact and through perinatal exposure)[6].

PATHOGENESIS

Persistence of Hepatitis C can be determined by:

(1)inadequate induction of innate immune response,

(2) evasion of the immune responses through various viral mechanisms,

(3)sufficiency of induction or maintenance of any adaptive immune response,

(4) viral quasispecies production

(5) induction of immunologic tolerance[20].

50% to 90% of persons with acute Hepatitis C infection develop chronic hepatitis. In the group of patients where acute Hepatitis C resolves, an early T-cell response has occured. Up to 20 years after resolution of infection this response may be detected and can contribute

to protection in subsequent exposures to Hepatitis C .Though immune response plays an important role in prevention of viral persistence, in cases without the viral clearance, immune response mediates the liver cell destruction and also cirrhosis.

CHRONIC HEPATITIS C

Serum ALT levels tends to remain elevated in chronic Hepatitis C infected patients. Because of levels that commonly fluctuate, nearly 50% of patients may have normal alt level at any given point of time.

The Alanine transaminase level [19] might remain normal for 20% of cases for prolonged periods of time, though transiently elevations occur even in such cases. Persistently normal levels of alanine aminotransferase are very common among females , and they tend to be associated with lower levels of serum Hepatitis C RNA and a lower inflammation with fibrosis on hepatic biopsy specimens.

Other symptoms that can be present are arthralgias, nausea, anorexia, myalgias, mucosal dryness, and difficulty in concentration. The severity of the symptoms would be directly proportional to the severity of underlying hepatic disease.

DIAGNOSIS

There are many molecular assays and immunologic that can be used to detect or infact monitor Hepatitis C infection. In addition, any presence of anti-Hepatitis C in the high titer in serum, that indicates exposure to this virus but can not differentiate in acute or chronic or resolved infection. Anti-Hepatitis C usually is persistant for several years in patients even after resolution of this infection or Sustined Virologicl Response following the antiviral therapy.

Anti-Hepatitis C titers can decline over time and can however become undetectable for 5 to 20 years even after Hepatitis C clearance. Initially serologic assays can used for diagnosis. but for confirming infection the virologic assays is required and monitoring the response to treatment or evaluating the immunocompromised patients.

INDIRECT ASSAYS

EIAs[18] can detect antibodies which are against various Hepatitis C antigens. Three generations of the EIAs are developed so far. The third-generation EIAs are used to detect the antibodies against Hepatitis C core, NS3, NS4, and also NS5 antigens even within the 7th to 8th week after infection, with sensitivity and also specificity rates of 99% and with sensitivity.

DIRECT ASSAYS

Quantitative, highly sensitive, and “real-time” Hepatitis C RNA tests generally represent the state of art for determining the Hepatitis C viremia in anti-Hepatitis C –positive persons. The lower limit for detection of many assays varies between 10 and 15 international units (IU)/ ml. Such assays can have the linear dynamic range between 1 to 7 log10 IU/mL and these are preferable testing methods in practice.

Transcription-mediated amplification (TMA)[17] are extremely sensitive, though the available assays aren’t usually quantitative in the test range of lower dynamic range. Advantages of this kind of high sensitive tests are positivity within the 1 to 3 weeks of acute infection and also detection of even low-level residual infection in the antiviral therapy.

NATURAL HISTORY

Once the chronic Hepatitis C infection is established, spontaneous Hepatitis C clearance seldom occurs. The Chronic Hepatitis C might lead to continuous liver damage which results in liver cirrhosis or also HCC . Individual course of such liver disease is hugely variable. Patients may report symptoms like right abdominal discomfort or nausea with fatigue.Other symptoms include weight loss, myalgia, arthralgias.

All these clinical features are usually uncharacteristic and may not be associated with the severity of liver injury and are restricted to patients in advanced cirrhosis. More feared complication in chronic Hepatitis C infection is when liver-related mortality because of decompensated liver cirrhosis or even development of HCC.

FACTORS ASSOCIATED WITH PROGRESSION

For fibrosis progression, age is the very important factor of risk in chronic Hepatitis C infection. A long duration of infection is generally associated with higher stage of liver fibrosis. However, Hepatitis C infection during early childhood seems to follow a comparitively milder course..

TREATMENT

Before Hepatitis C was identified, IFN-α monotherapy has been approved for chronic Hepatitis C treatment, then known as the *non-A, non-B hepatitis*. Substantial advances are made since the introduction of longer-acting pegylated formulations of IFN, prolonged treatment periods, and oral guanosine analog ribavirin. In 2011, first DAAs, telaprevir and boceprevir, which are being approved for treating chronic Hepatitis C genotype 1 infection, and during 2013, simeprevir yet

another protease inhibitor, sofosbuvir, a nucleotide polymerase were also approved.

Drugs

INTERFERONS

IFN-based regimens were the cornerstone of antiviral therapy for Hepatitis C infection since 1980s. IFNs are in general naturally occurring glycoproteins which exert a wide array of antiviral, antiproliferative, and also immunomodulatory effects.

Pegylated IFNs consists of IFN which is bound to a molecule of polyethyleneglycol (PEG) of various length. A large size of themolecule increases to a larger extent half-life of the IFN, hence allowing once a week dosage.

In the United States there are two pegylated IFNs which are licensed to use. The 40-kd peginterferon alfa-2a, is used for a fixed dosage of 180 μg per week. Next is the 12-kd peginterferon alfa-2b [16], that is prescribed in accordance with the patient's body weight. The a dosage is 1.5 μg/kg per week. Instead of the standard IFN which were used prior, the Pegylated IFNs are used resulting in a significant increase in SVR.

RIBAVIRIN

Ribavirin, a oral guanosine analog which acts against DNA and RNA viruses. The ETR improves whenever ribavirin is used with IFN as a combination, the rate of relapse is lesser.

Ribavirin exhibits an synergistic effect once administered as a combination with IFN have been proposed, including:

(1) alterations of the cytokine environment from type 2 T-helper cell (Th2) to a T helper 1immune response[15];

(2) intracellular guanosine triphosphate depletion through the mechanism of inhibition of the enzyme inosine monophosphate dehydrogenase (IMPDH);

(3) HCV RNA-dependent RNA polymerase inhibition;

(4)induces mutagenesis during Hepatitis C RNA replication,

(5) increasing responsiveness to the type I IFNs.

Ribavirin usually is tolerated, though it causes hemolytic anemia. The dose which is administered depending on patient's weight, and also the Hb level has to be followed up during treatment.

Hepatitis C Virus (HCV) Summary of Treatment

HCV Genotype	*Treatment Protocol*	*Treatment lasts*	*Cure Rates (Sustained virological response)*
Genotype-1	Telaprevir plus Interferon and Ribavirin or Boceprevir plus Interferon and Ribavirin	24 to 48 weeks 28 to 48 weeks	70-75%
Genotypes -2 and 3	Interferon plus Ribavirin	24 weeks	80%
Other HCV genotypes	Interferon plus Ribavirin	48 weeks	40-70%

Side effects of Drug Treatment for HCV

Drug	*Common Side Effects*
Interferon injections	Influenza like symptoms, fatigue, sleep problems, mood disorders, depression and psychosis. Bone marrow suppression (anemia, low white blood cells and low platelets)
Ribavirin	Anemia, nausea, skin problems
Telaprevir	Bone marrow suppression, skin problems (which can be fatal), nausea, indigestion, burning and itching of the anus, headaches
Boceprevir	Distorted taste, bone marrow suppression (anemia, low white blood cells, low platelets), nausea

DIRECT-ACTING ANTIVIRAL AGENTS

Novel DAAs against Hepatitis C includes compounds which target HCV protease, HCV NS5A protein and HCV polymerase. These drugs inhibits HCV replication by interfering with respective step in these HCV life cycle[14].

HCV protease inhibitors ("…previrs") usually have high antiviral potency but may differ with respect to the development of its resistance. Most compounds show better responsive rates in HCV genotype 1b rather than in genotype 1a infection.

Boceprevir and telaprevir are 2 protease inhibitors approved by the FDA in 2011. Simeprevir which became available in 2014 and the protease inhibitor faldaprevir have higher advantages as compared to

boceprevir and telaprevir in terms of dosage schedule and side effect profile.

NS5A inhibitors ("…asvirs") are characterized by high antiviral potency at picomolar doses. The cross-genotype efficiecy of these agents vary. Limited data on the efficiency of these drugs are only available in patients with these non-genotype 1 HCV. In 2014, Ledipasvir was the first NS5A inhibitor approved by FDA.

HCV polymerase inhibitors ("…buvirs") [13]can be categorized as nucleoside or nucleotide analog and non-nucleoside polymerase inhibitors. Non-nucleoside polymerase inhibitors are the weakest class of the compounds against HCV due to low barrier to resistance. Most drugs in this class are active mostly against HCV genotype 1b but to a lesser extent only against HCV genotype 1a. They are developed to be used only as a combination with other DAAs, largely with protease inhibitors and NS5A inhibitors.

Nucleoside analogs are active with all Hepatitis C genotypes. Nucleoside analog resistant variants might emerge but they have very low fitness and do not rapidly expand. They cause a chain termination, thereby blocking HCV replication.

The first approved nucleotide NS5B polymerase inhibitor was sofosbuvir.

HCV Genotype	Therapy	Duration	SVR Rate[5]
Genotype 1	Interferon Ribavirin Protease Inhibitor	24-48 weeks	67-75%
Genotype 2	Interferon Ribavirin	24 weeks	74%
Genotype 3	Interferon Ribavirin	24 weeks	69%
Genotype 4	Interferon Ribavirin	48 weeks	60%
Genotype 5	No guidelines	Not applicable	N/A
Genotype 6	No guidelines	Not applicable	N/A

LIVER BIOPSY

There is a wider range of risk of progressive liver injury from the acquisition of HCV infection, as a score of patients may show less degree of progression after decades of infection and others may progress rapidly. Percutaneous liver biopsy could be used effectively to assess the patients . Other noninvasive methods to assess liver fibrosis[7] are used instead of liver biopsy. Liver biopsies are performed mainly to exclude other causes of liver disease.

Several scoring systems are used so as to quantify liver injury to grade inflammation and also stages of fibrosis.

- Knodell and colleagues described a system called as Histology Activity Index (HAI).

The different criteria used to classify include both periportal tract inflammation and necrosis(grading from 0 to 10), inflammation of lobules and necrosis (grades0 to 4), portal tract inflammation (0 to 4), and cirrhosis (0 to 4). This scoring system combines both inflammation and fibrosis in 1score.

- Scheuer created a scoring system which separates grades from stages: Portal inflammation and interface hepatitis (0 to 4), lobular activity (0 to 4)[8], and fibrosis stage (0 to 4).

The Ishak system remains a modification of the Knodell's system. Histologic gradeis separated from staging of cirrhosis.

- Ishak's fibrosis scores range between 0 to 6 (1 or 2, portal fibrotic expansion; 3 or 4, bridging fibrosis; 5 or 6, cirrhosis).
- The METAVIR scoring system is a popular scoring system in practice which is simpler than any other system. Inflammation being graded between 0 to 4 (none, mild, moderate, and severe),

and fibrosis is staged between 0 to 4 (1, portal fibroticexpansion; 2, portal fibrosis with septa formation; 3, bridging fibrosis; 4, cirrhosis)[9].

Ziol: Determination of Liver Stiffness Cutoff Values with Transient Elastography

METAVIR Score	Optimal Cutoff*	Sensitivity	Specificity	PPV	NPV
F ≥ 2 (F0-1 vs. F2-3-4)	**8.8 kPa**	0.56	0.91	0.88	0.56
F ≥ 3 (F0-1-2 vs. F3-4)	**9.6 kPa**	0.86	0.85	0.71	0.93
F ≥ 4 (F0-1-2-3 vs. F4)	**14.6 kPa**	0.86	0.96	0.78	0.97

*Optimal Cutoff = value that provided higher total sensitivity and specificity
PPV = Positive Predictive Value
NPV = Negative Predictive Value

Though liver biopsy remains the diagnostic tool to grade inflammation and stage of fibrosis, disadvantages of liver biopsy includes:

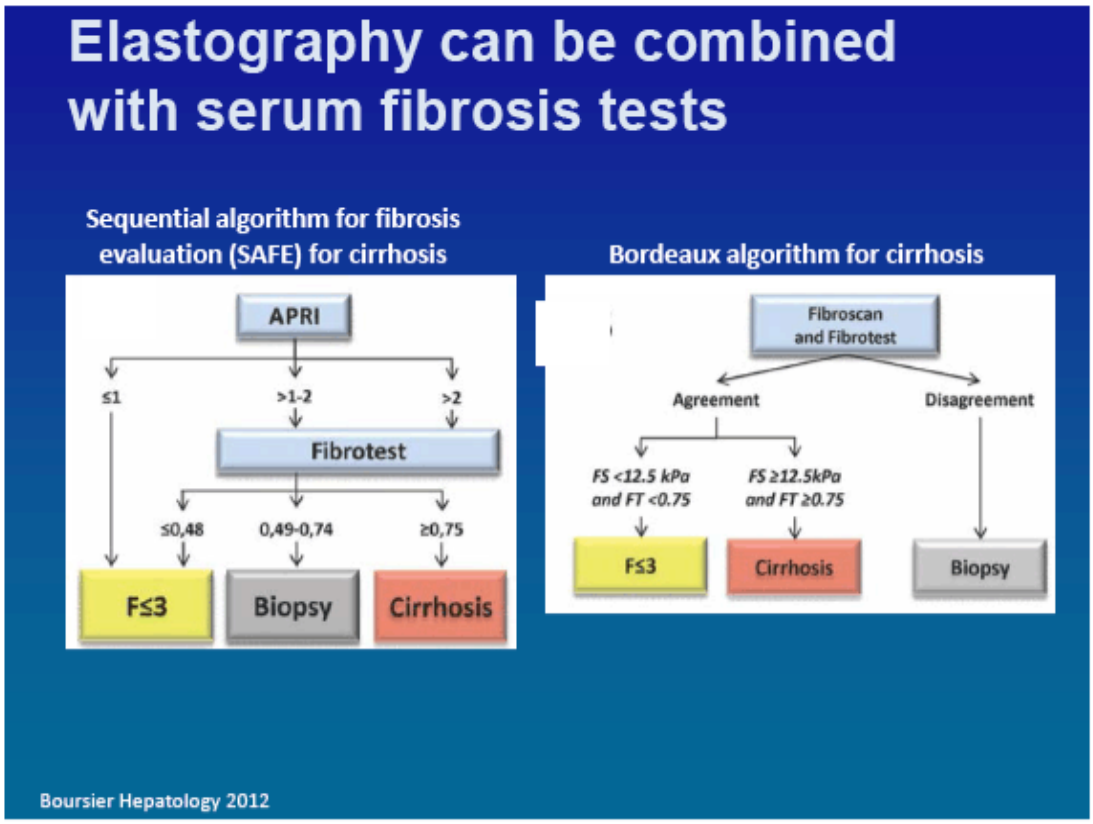
(1) associated pain in some series, hemorrhage or bile leak;

(2) expensive;

(3) poor acceptance by the patient;

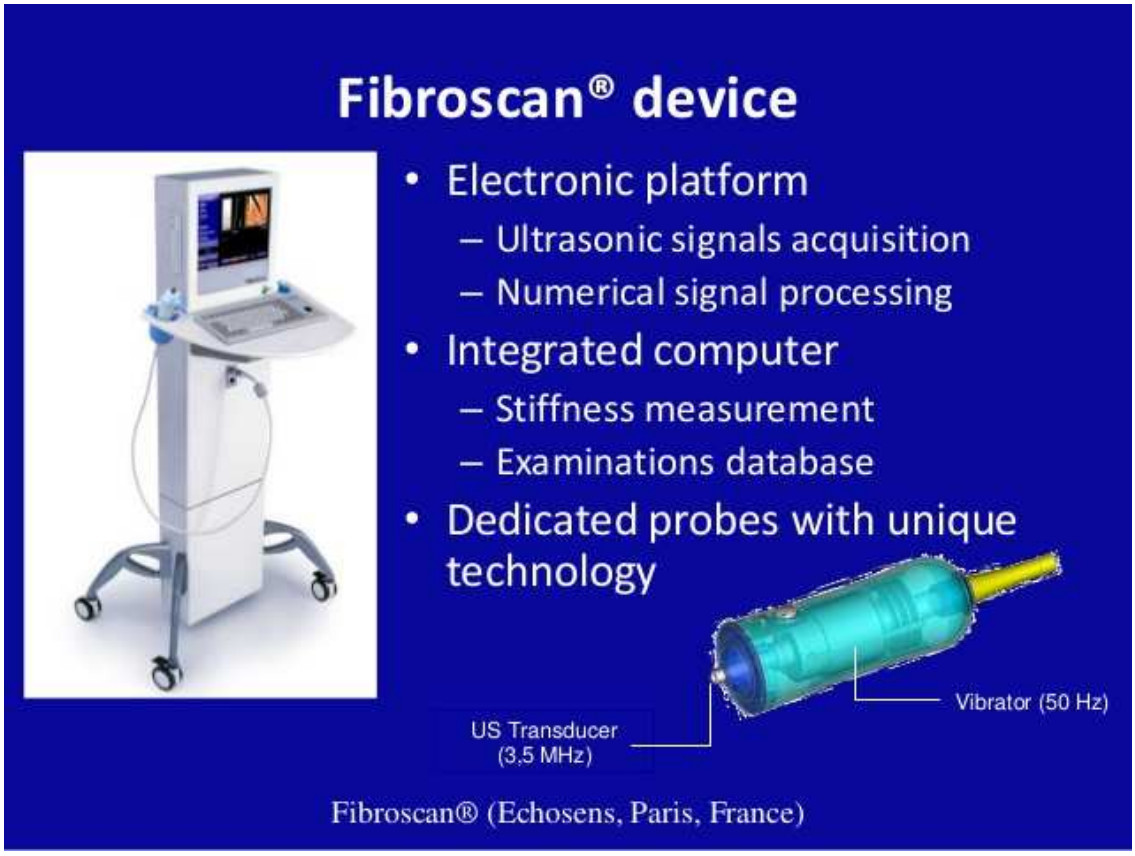
(4) interobserver difference during interpretation of findings

(5) inaccuracy in interpreting the results [10]



Due to the disadvantages seen with liver biopsy, many noninvasive tests had been in research. FibroSure , a noninvasive method to measure fibrosis, that has sex and age adjustments, obtained from serum levels of α2-macroglobulin, haptoglobin, apolipoprotein A-1, GGTP, and total bilirubin.

Different techniques and instruments (e.g., transient elastography, acoustic radiation force impulse imaging, magnetic resonance elastography) are being available to determine liver stiffness.



The most frequently used system is transient elastography (Fibroscan) for the assessment of liver elasticity, which is correlating inversely with degree of liver fibrosis. In a meta-analysis, the AUC of Fibroscan to predict fibrosis was 0.94.

Table 1 Recommended values for different stage of fibrosis

Disease	F0–F1 (Kpa)	F2 (Kpa)	F3 (kpa)	F4 (kpa)
Hepatitis B	≤6.0	≥6.0	≥9.0	≥12.0
Hepatitis C	≤7.0	≥7.0	≥9.5	≥12.0
HCV–HIV coinfection	≤7.0	≤10	≥11.0	≥14.0
Cholestatic liver disease	≤7.0	≥7.5	≥10.0	≥17.0
NAFLD/NASH	≤7.0	≥7.5	≤10	≥14.0

The AST-to-platelet ratio index (APRI) is used primarily in order to diagnose or exclude cirrhosis. During an initial evaluation, 81% of cirrhotic patients were precisely identified with a score of 0.5 or less; however, the index may not help in discriminating among fibrosis of lower level.

There is an inverse relationship between platelet count and Aspartate aminotransferase level with progression of liver fibrosis. During progression of cirrhosis and accompanying portal hypertension, results in increased sequestration of cells with lysis in spleen.

Thus, Hypersplenism being the most commonest cause of platelet reduction related with cirrhosis and portal hypertension. Another cause is decreased production of thrombopoietin by the liver . The increased Aspartate aminotransferase level is due to mitochondrial injury that is associated with the HCV infection.

Combining transient elastography along with serum markers will increase the accuracy of predicting fibrosis and cirrhosis and will avoid liver biopsy in many patients. It is, however, not indicated following a antiviral therapy, although histology usually improve significantly over a period of time following eradication of HCV [11.]

MATERIALS AND METHODS

MATERIALS AND METHODS

Study Centre

Department of HEPATOLOGY, Madras medical college and Rajiv gandhi government general hospital, Chennai

Duration of Study

6 months

Study Design

Observational Study (prospective and retrospective)

Sample Size

100 patients

Inclusion Criteria

Patients with chronic hepatitis B or/and C virus infection without treatment aged 18 years or over.

Exclusion Criteria

Patient with

1.Coinfection with HIV

2.Alcohol drink >30g/day within past 6 months

3.Other etiologies of chronic liver disease

4.Chronic renal failure

5.Platelet count of 75,000/cu.mm. or less

6.Bedridden patients.

Data Collection and Methods

Chronic hepatitis B and/or C patients attending Hepatology OP of RGGGH are subjected to detailed history taking , clinical examination and required investigations.

Materials and Methods

From Chronic hepatitis B and/or C patients attending the Hepatology department OPD, selected for clinical study as per inclusion/exclusion criteria the following data are collected:

-Demographic data

-Medical history

Patients are subjected to:

-Platelet count

-Liver function tests(Aspartate aminotransferase)

-Fibroscan

Product / procedure / investigation detail

Platelet count

Liver function tests(Aspartate aminotransferase)

Fibroscan

Analysis Plan

SPSS, Epi INFO softwares

Sponsorship

No

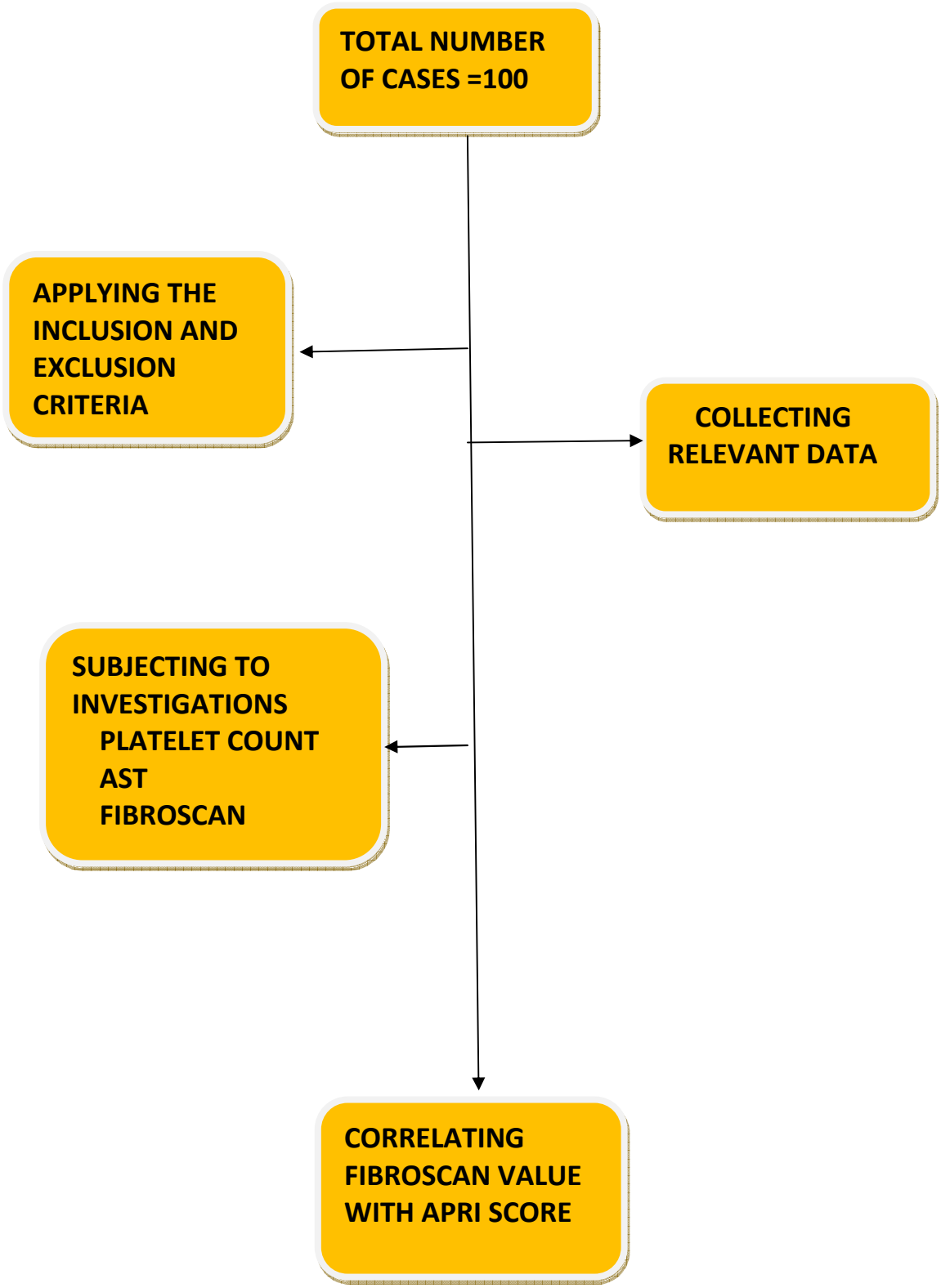
Conflict of interest

None

OBSERVATIONS AND RESULTS

OBSERVATION AND RESULTS

FLOW CHART OF THE METHODOLOGY

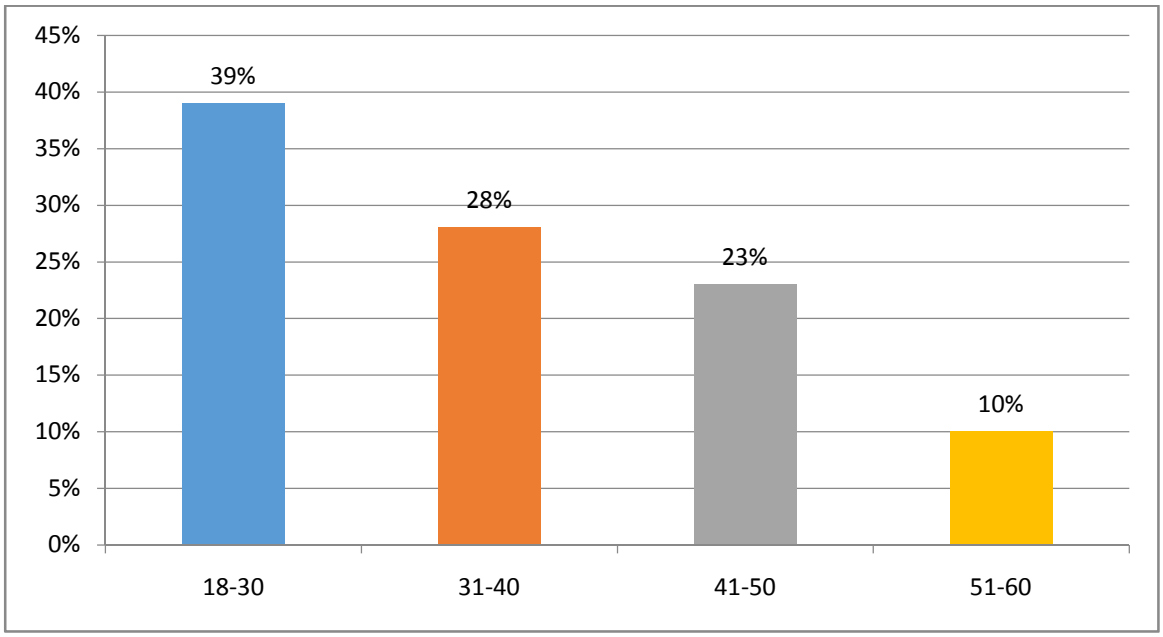


FREQUENCY OF AGE GROUP AMONG PATIENTS COLLECTED FOR OUR STUDY

AGE_SCORE	FREQUENCY	PERCENT
18-30	39	39.0
31-40	28	28.0
41-50	23	23.0
51-60	10	10.0
Total	100	100.0

In our study, patients are collected among a wider range of age group from 18 years to 60 years who were diagnosed to have acquired Hepatitis B virus /and C infection .From our study, nearly 40% of patients are in their twenties.

BAR DIAGRAM DEPICTING THE AGE DISTRIBUTION IN OUR STUDY POPULATION



FREQUENCY OF SEX DISTRIBUTION IN OUR STUDY SCORE

SEX	FREQUENCY	PERCENT
MALE	56	56.0
FEMALE	44	44.0
Total	100	100.0

Sex distribution appears to be almost equally distributed among males and females.

BAR DIAGRAM SHOWING THE SEX DISTRIBUTION IN OUR STUDY SCORE

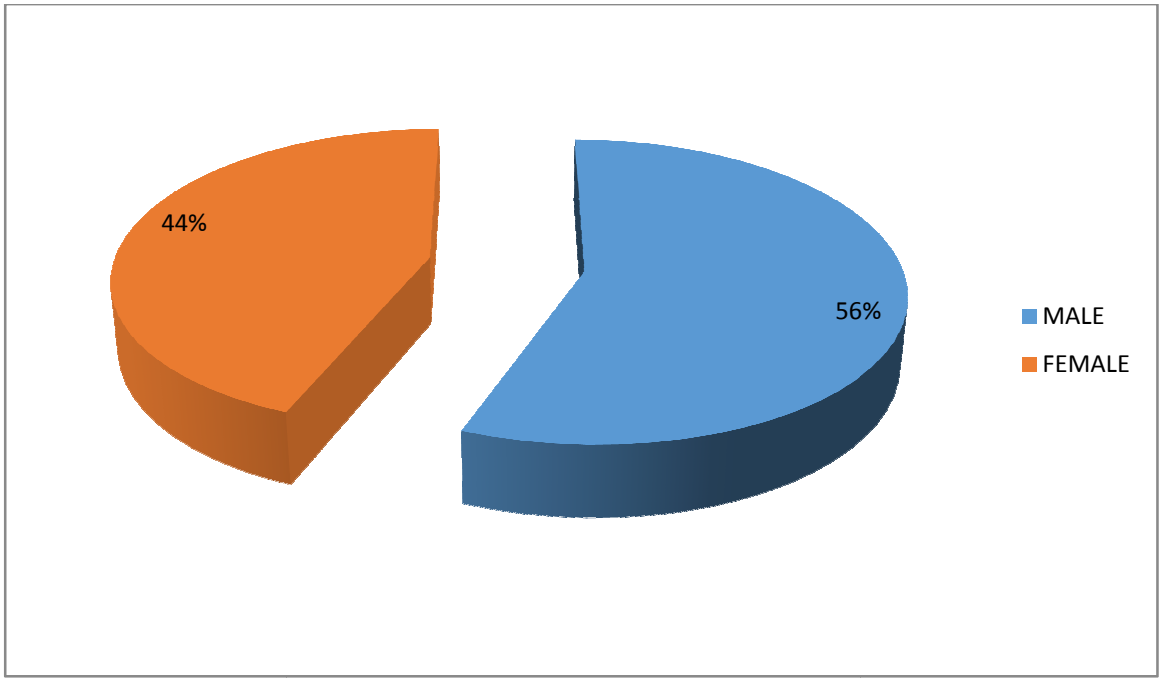


TABLE SHOWING THE DISTRIBUTION OF HISTORY FOR WHICH PATIENTS WERE SUBJECTED TO BLOOD INVESTIGATIONS AND DETECTED AS HEPATITIS B / C INFECTION

HISTORY	FREQUENCY	PERCENT
ANTENATAL SCREENING	6	6.0
EASY FATIGUE	7	7.0
FEVER OF UN KNOWN ORIGIN	10	10.0
INCIDENTALLY DETECTED	65	65.0
LOSS OF APPETITE	12	12.0
Total	100	100.0

From the above table, we could identify that around 65% of patients were detected incidentally during routine health check ups or during blood donation. about 10% has history of loss of appetite, another 12% had history of fever.

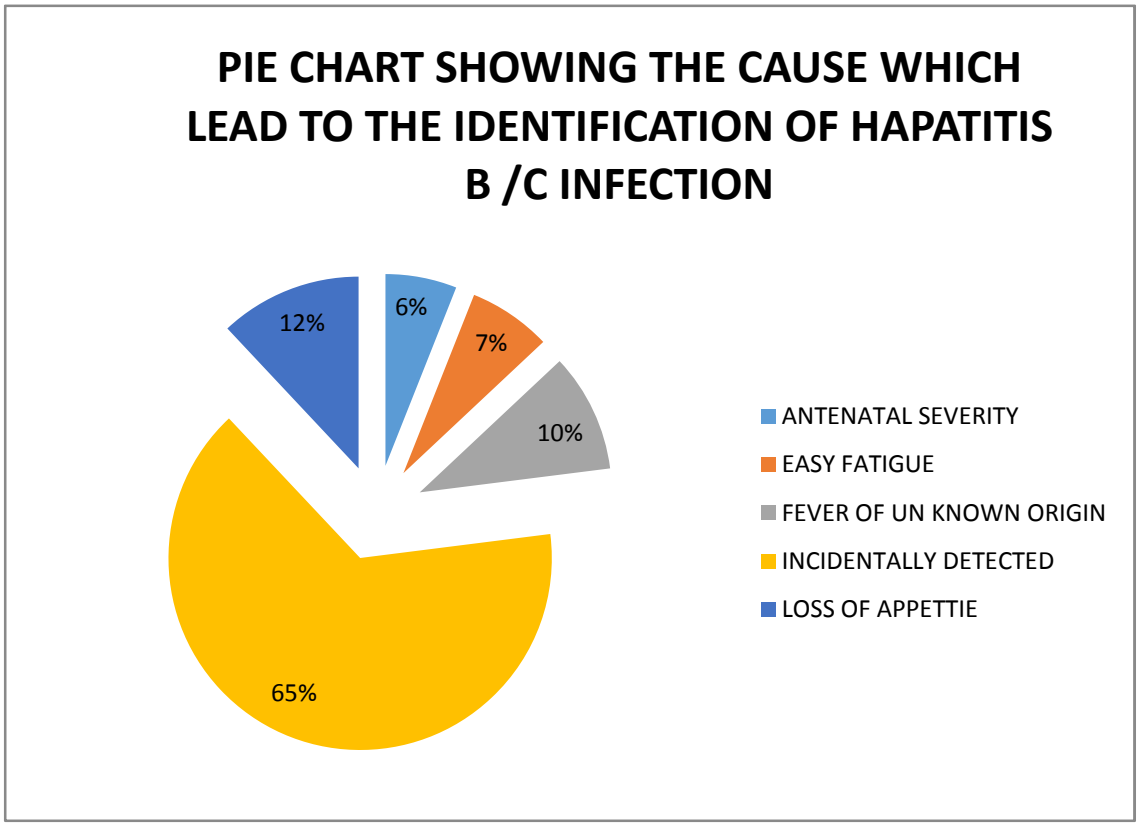

PIE CHART SHOWING THE CAUSE WHICH LEAD TO THE IDENTIFICATION OF HAPATITIS B /C INFECTION
6%
7%
10%
65%
12%
ANTENATAL SEVERITY
EASY FATIGUE
FEVER OF UN KNOWN ORIGIN
INCIDENTALLY DETECTED
LOSS OF APPETTIE

TABLE SHOWS THE PERCENTAGE OF PATIENTS WHO ACQUIRED THEIR INFECTION THROUGH BLOOD TRANSFUSION

BLOOD TRANSFUSION	FREQUENCY	PERCENT
NO	91	91.0
YES	9	9.0
Total	100	100.0

Table provides the data that around 9% of our patients with hepatitis B/C in the study score acquired their infection through blood transfusion.

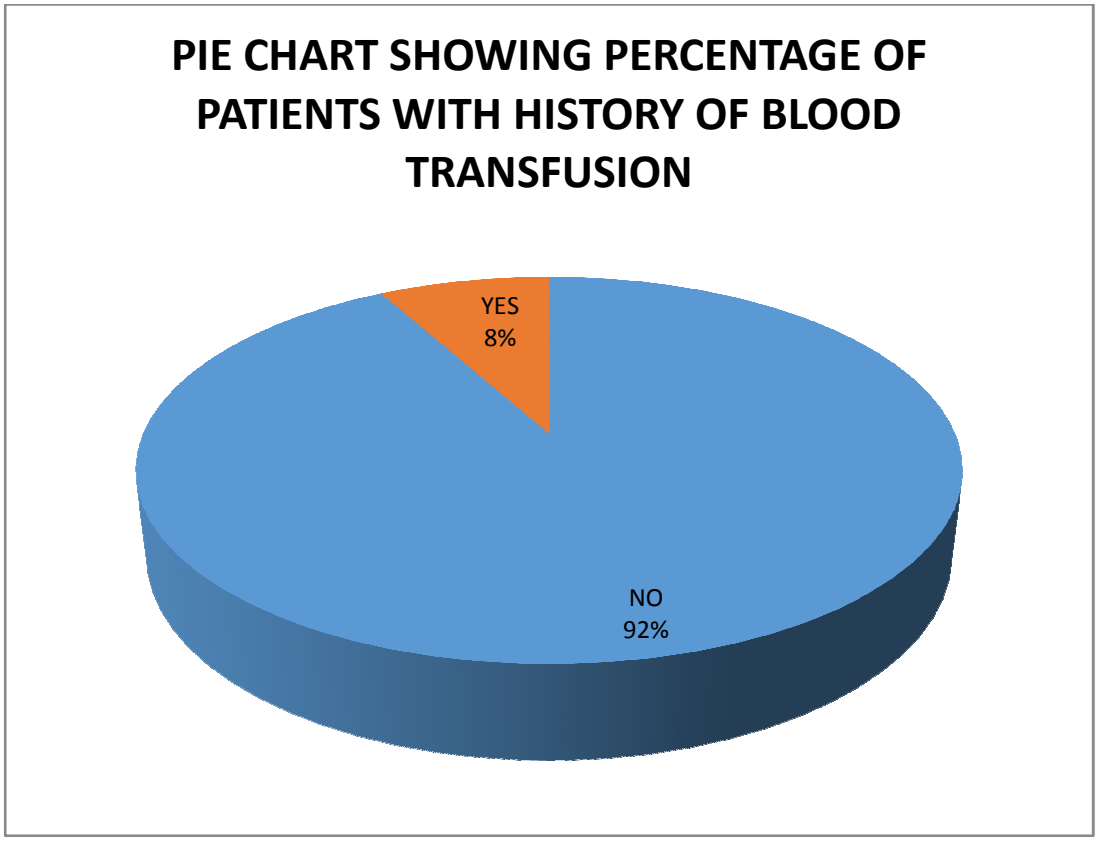
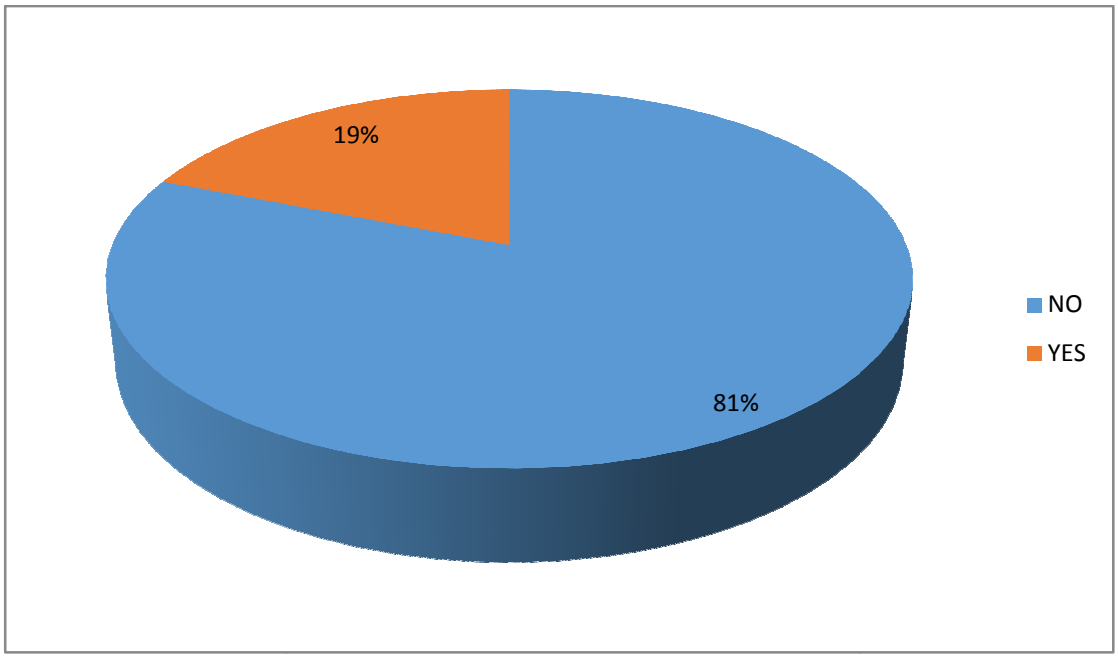


TABLE SHOWS THE PERCENTAGE OF PATIENTS WHO HAD HISTORY OF PREVIOUS SURGERY

PREVIOUS SURGERY	FREQUENCY	PERCENT
NO	81	81.0
YES	19	19.0
Total	100	100.0

From above table, we could identify that around 20% of patients had history of previous surgery ,which might be the cause of acquiring Hepatitis B/C infection

PIE CHART SHOWING PERCENTILE OF PATIENTS WITH PREVIOUS SURGERY HISTORY

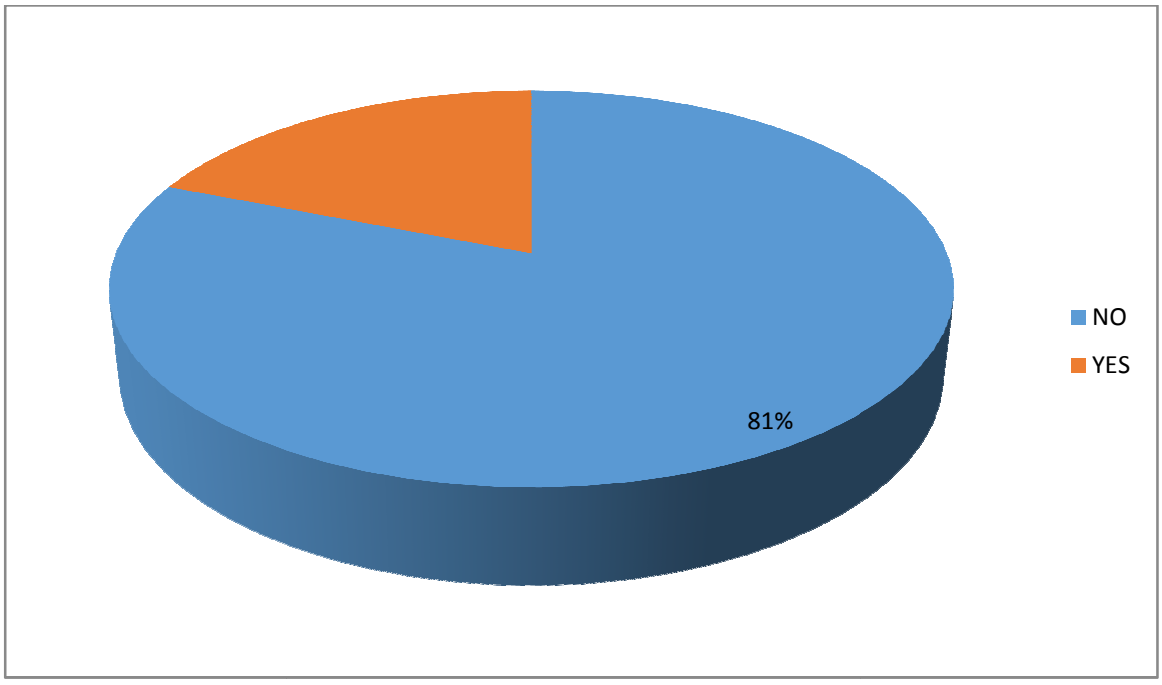


FREQUENCY OF PATIENTS WITH HISTORY OF TATTOOING

TATTOOING	FREQUENCY	PERCENT
NO	81	81.0
YES	19	19.0
Total	100	100.0

In our study score, around 20% of patients had history of tattooing, which could have been the source of Hepatitis B/C infection.

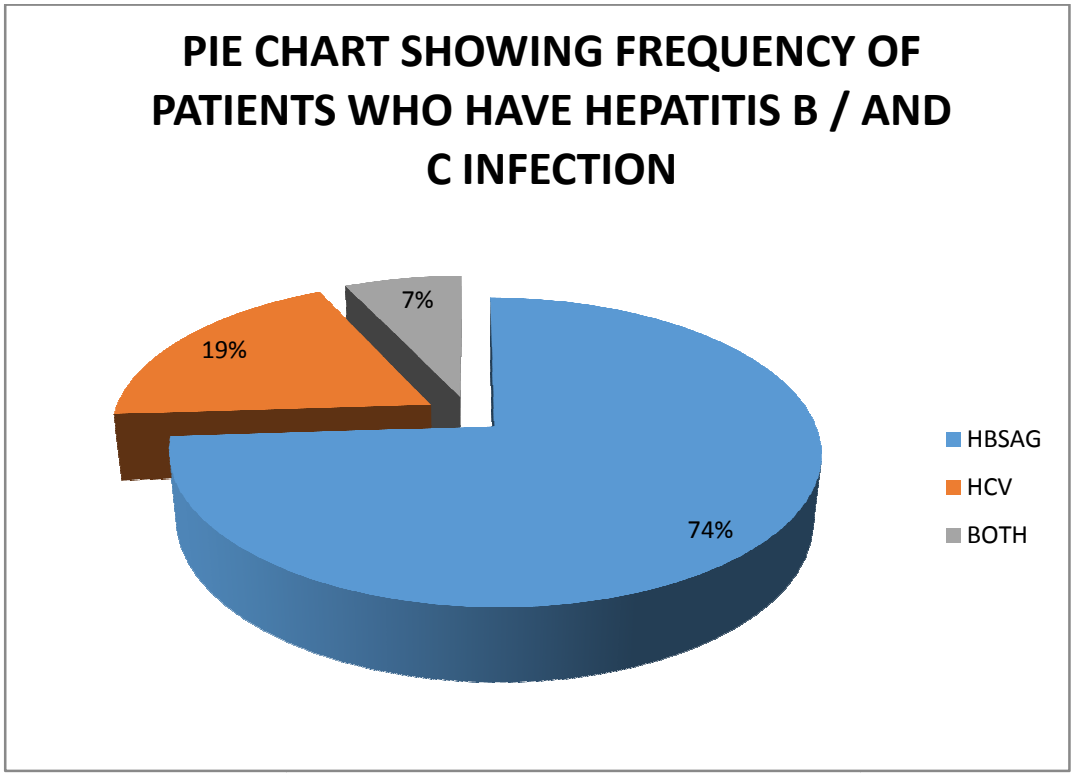
PIE CHART SHOWING PERCENTILE OF PATIENTS WITH PREVIOUS TATTOOING HISTORY



FREQUENCY OF PATIENTS WHO HAVE HEPATITIS B / AND HEPATITIS C INFECTION

HBSAG	FREQUENCY	PERCENT
HBSAG	74	74.0
HCV	19	19.0
BOTH	7	7.0
Total	100	100.0

Data collected from the above table shows about 74% patients had Hepatitis B infection, about 19% patients had Hepatitis C infection with coinfection present among 7% of patients.

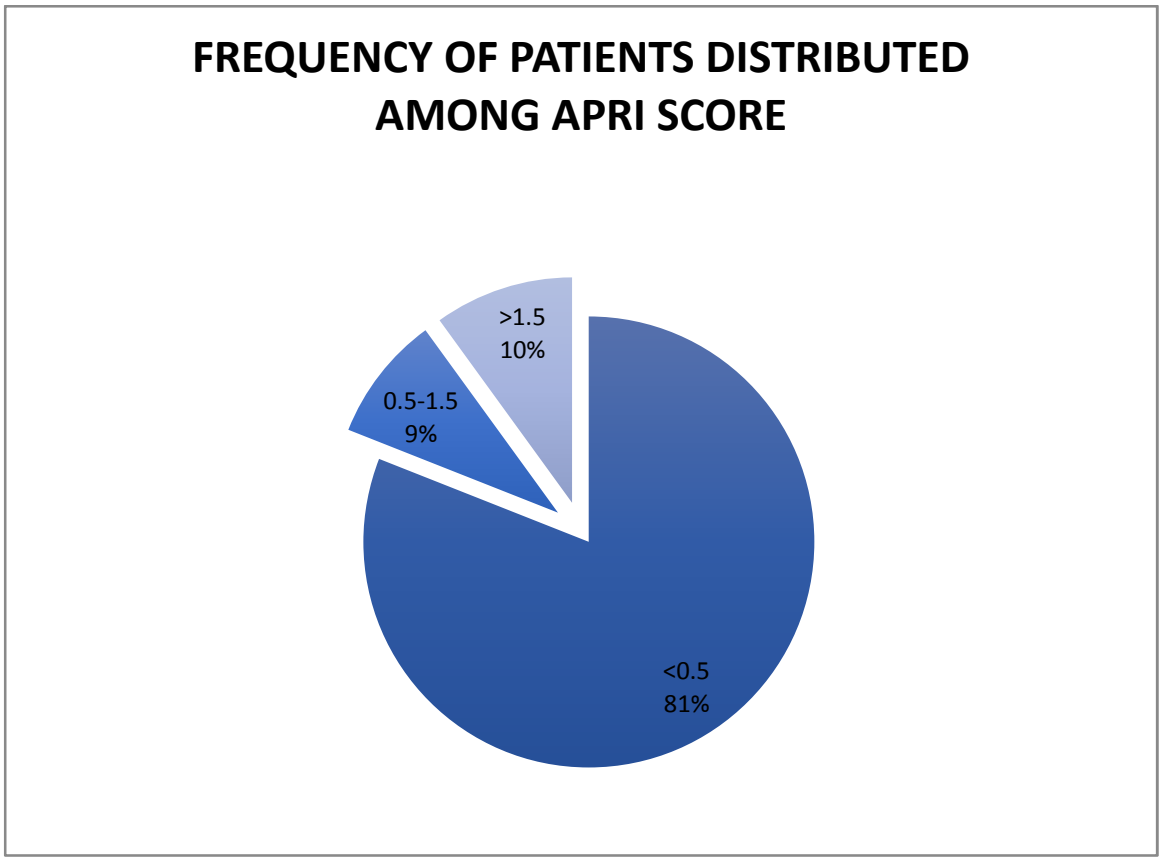


FREQUENCY OF PATIENTS DISTRIBUTED AMONG

APRI SCORE

APRI_SCORE	FREQUENCY	PERCENT
<0.5	81	81.0
0.5-1.5	9	9.0
>1.5	10	10.0
Total	100	100.0

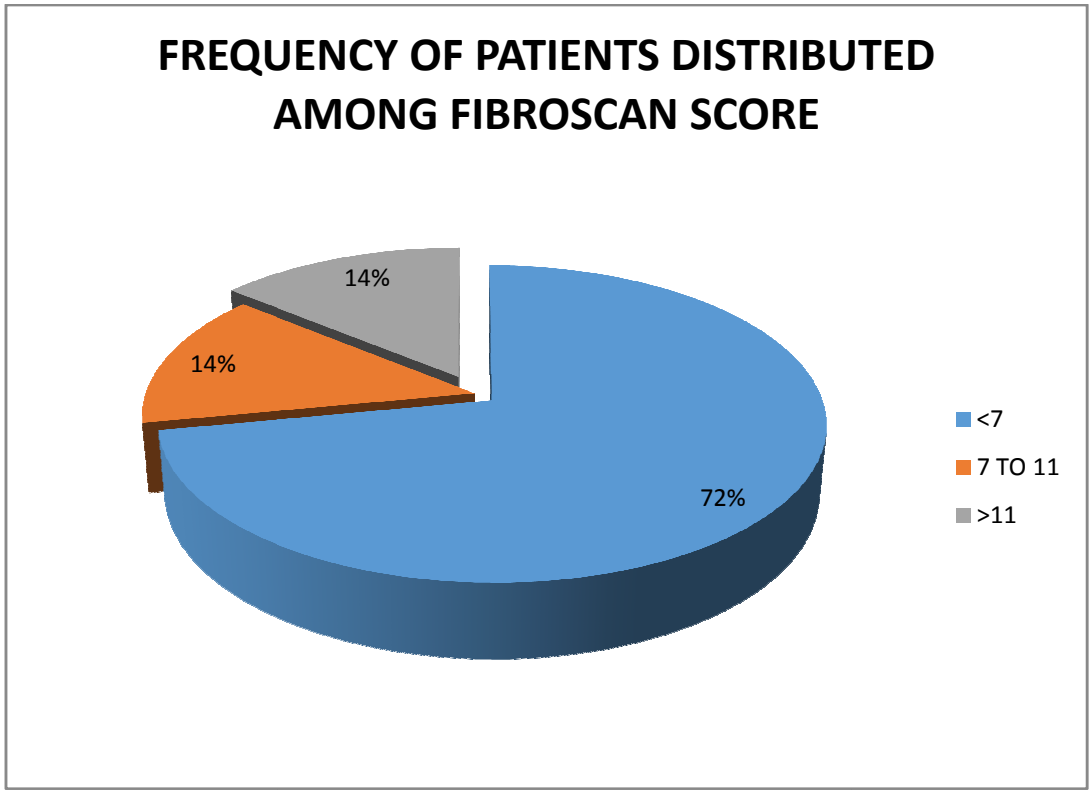
Among our study population, 81% patients fall within the APRI SCORE <0.5 denoting normal liver architecture, 9% patients comes under 0.5 -1.5 indicating ongoing or developing fibrosis, about 10% patients have their APRI SCORE >1.5 suggesting developed fibrosis /cirrhosis.


FREQUENCY OF PATIENTS DISTRIBUTED AMONG APRI SCORE
>1.5
10%
0.5-1.5
9%
<0.5
81%

FREQUENCY OF PATIENTS DISTRIBUTED AMONG FIBROSCAN SCORE

FIBROSCAN_SCORE	FREQUENCY	PERCENT
<7	72	72.0
7-11	14	14.0
>11	14	14.0
Total	100	100.0

Among 100 patients in our study score, 72% has Fibroscan value < 7 implying normal liver architecture, with 14% having value >11 indicating well developed fibrosis or cirrhosis with another 14% in the score in between with ongoing fibrosis.



CROSSTABULATION CORRELATING APRI SCORE WITH FIBROSCAN VALUES

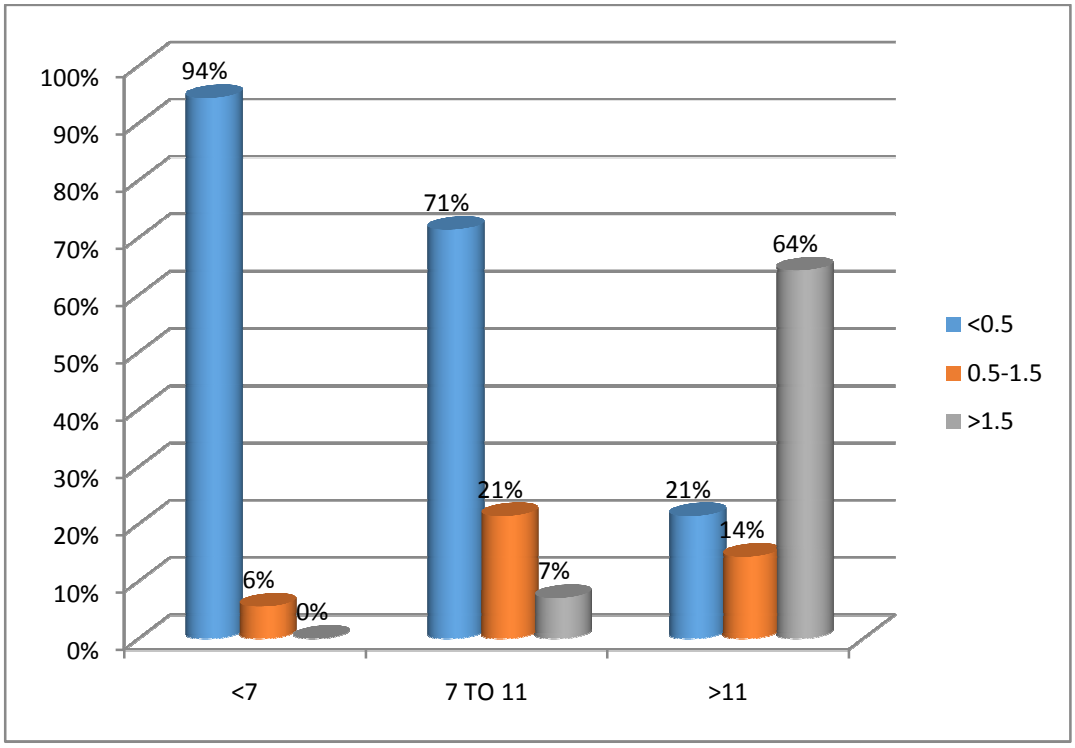
APRI_SCORE * FIBROSCAN_SCORE Crosstabulation			FIBROSCAN_SCORE			Total
			<7	7-11	>11	
Apri_Score	<0.5	Count	68	10	3	81
		% within FIBROSCAN_SCORE	94.4%	71.4%	21.4%	81.0%
	0.5-1.5	Count	4	3	2	9
		% within FIBROSCAN_SCORE	5.6%	21.4%	14.3%	9.0%
	>1.5	Count	0	1	9	10
		% within FIBROSCAN_SCORE	0.0%	7.1%	64.3%	10.0%
Total		Count	72	14	14	100
		% within FIBROSCAN_score	100.0%	100.0%	100.0%	100.0%

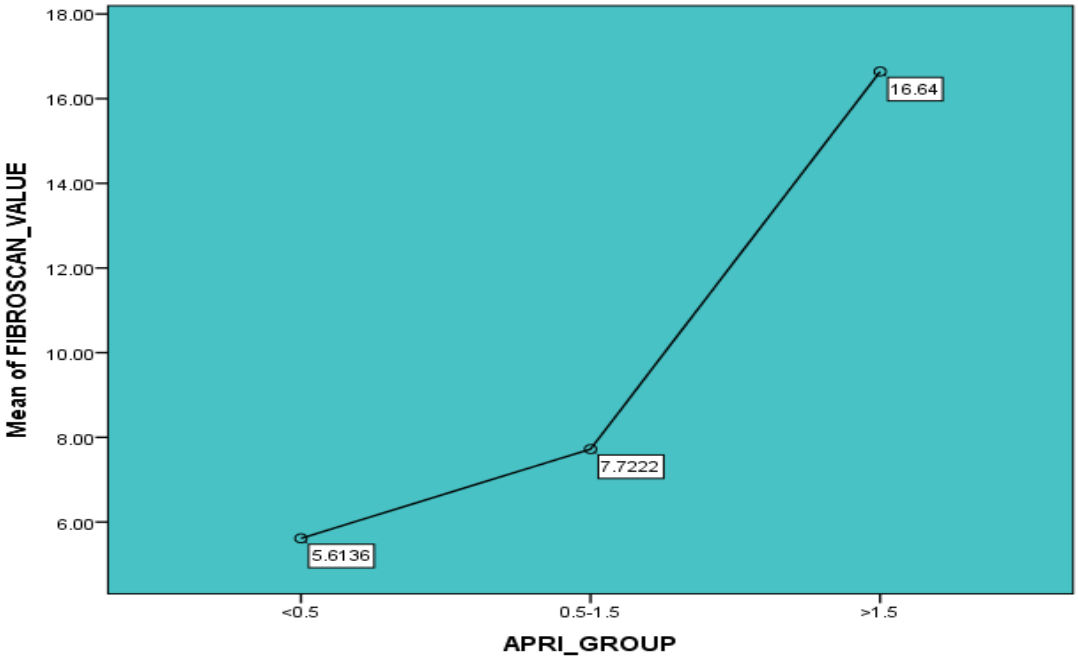
Chi-Square = 60.257 ** P<0.001

It is evident from the above table that out of 72 patients with normal liver architecture identified on Fibroscan , 68 patients are found to correlate well with APRI score. Similarly, out of 14 ptients detected as having developed fibrosis or cirrhosis on Fibroscan , 9 patients correlate well with APRI score.

It is clearly depicted that APRI score and Fibroscan values correlate well significantly, as the p value is < 0.001.

BAR DIAGRAM CORRELATING APRI SCORE WITH FIBROSCAN VALUES



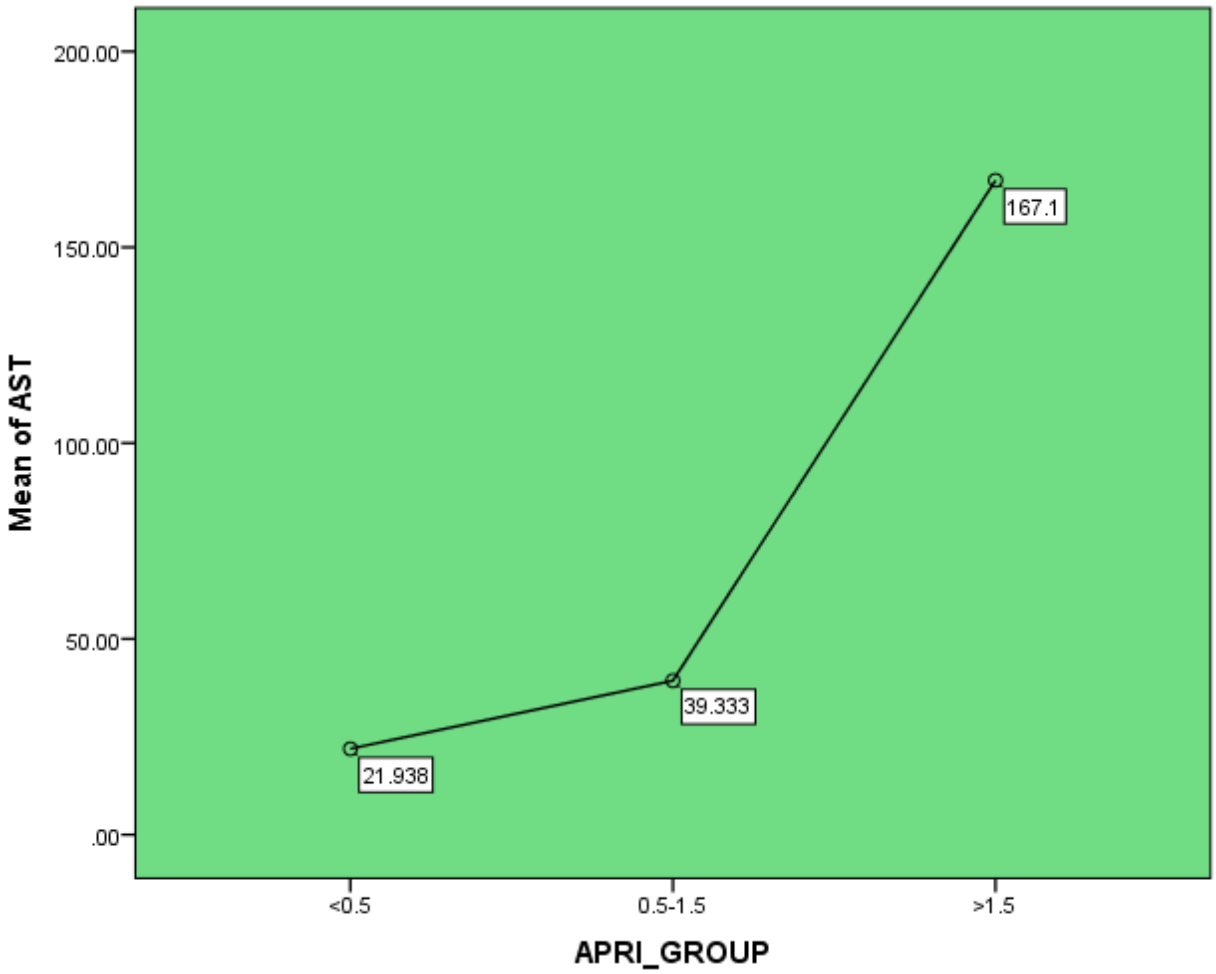


CROSSTBULATION CORRELATING ASPARTATE MINOTRANSFERASE VALUES AND FIBROSCAN SCORE WITH APRI SCORE

CORRELATION		AST	APRI	FIBROSCAN − VALUE
AST	Pearson Correlation	1	.628**	.519**
	Sig. (2-tailed)		.000	.000
	N	100	100	100
APRI	Pearson Correlation	.628**	1	.543**
	Sig. (2-tailed)	.000		.000
	N	100	100	100
FIBROSCAN_VALUE	Pearson Correlation	.519**	.543**	1
	Sig. (2-tailed)	.000	.000	
	N	100	100	100
**. Correlation is significant at the 0.01 level (2-tailed).				

It is evident from the above table that as the AST value increases, APRI value also tends to rise. Correlation is considered significant at the 0.01 level.

DIAGRAM CORRELATING AST VALUES WITH APRI SCORE



CROSSTBULATION CORRELATING ASPARTATE MINOTRANSFERASE VALUES AND FIBROSCAN VALUES WITH APRI SCORE

APRI SCORE		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	F VALUE
						Lower Bound	Upper Bound			
AST	<0.5	81	21.94	8.00	0.89	20.17	23.71	10.00	46.00	51.774**
	0.5-1.5	9	39.33	17.94	5.98	25.54	53.13	20.00	64.00	
	>1.5	10	167.10	136.63	43.21	69.36	264.84	52.00	508.00	
	Total	100	38.02	60.58	6.06	26.00	50.04	10.00	508.00	
FIBROSCAN_VALUE	<0.5	81	5.61	1.93	0.21	5.19	6.04	3.20	11.70	72.805**
	0.5-1.5	9	7.72	2.60	0.87	5.72	9.72	4.10	11.80	
	>1.5	10	16.64	6.45	2.04	12.03	21.25	7.30	27.30	
	Total	100	6.91	4.28	0.43	6.06	7.76	3.20	27.30	

**P<0.001

It is evident from the above table that as the AST value increases, APRI value also tends to rise. Correlation is considered significant at the 0.001 level.

Values in the APRI score correlate well significantly with Fibroscan values.

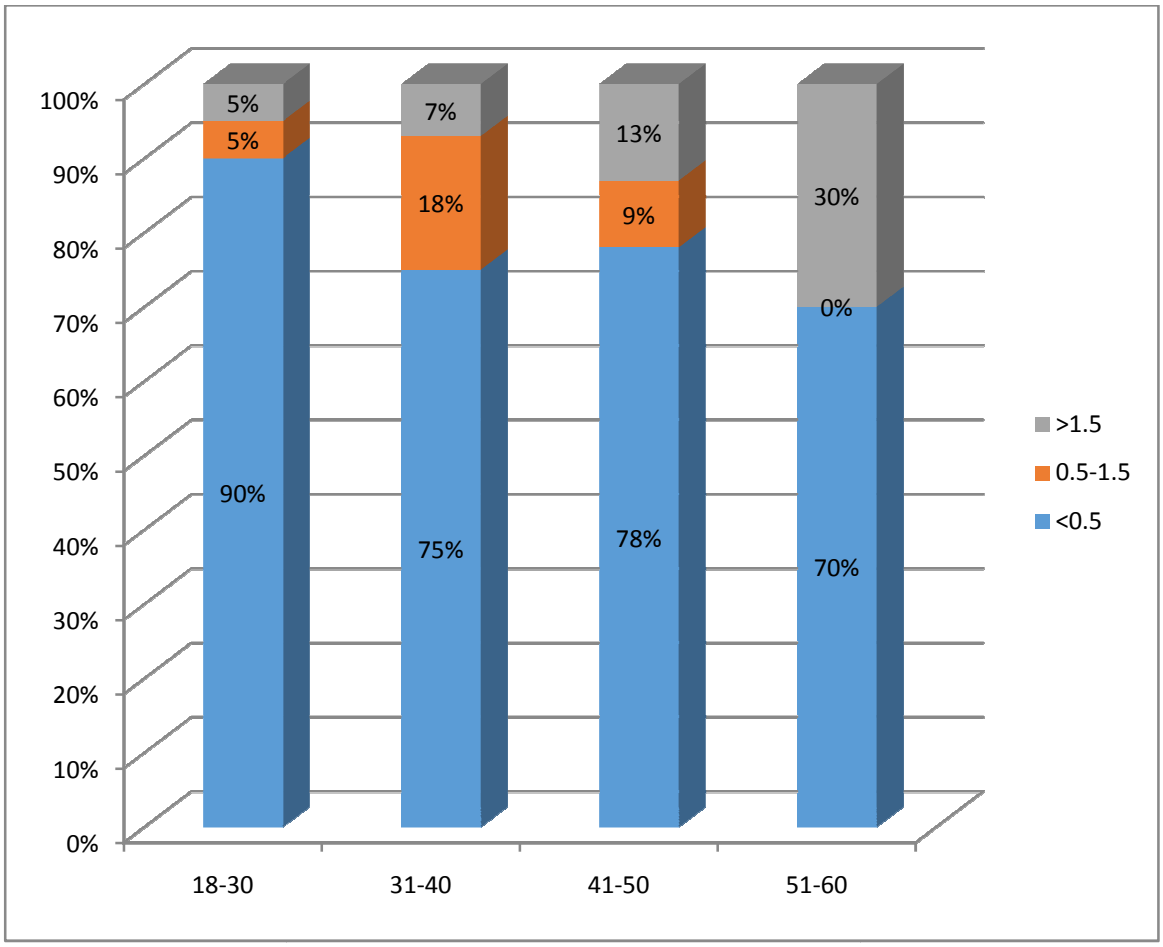
CROSSTABULATION DEPICTING AGE WISE DISTRIBUTION OF APRI SCORE

CROSSTAB			AGE_SCORE				Total
			18-30	31-40	41-50	51-60	
APRI SCORE	<0.5	Count	35	21	18	7	81
		% within AGE_SCORE	89.7%	75.0%	78.3%	70.0%	81.0%
	0.5-1.5	Count	2	5	2	0	9
		% within AGE_SCORE	5.1%	17.9%	8.7%	0.0%	9.0%
	>1.5	Count	2	2	3	3	10
		% within AGE_SCORE	5.1%	7.1%	13.0%	30.0%	10.0%
Total		Count	39	28	23	10	100
		% within AGE_SCORE	100.0%	100.0%	100.0%	100.0%	100.0%

Pearson Chi-Square = 10.023 P= 0.124

The above table points out that there is no specific correlation between increasing age and APRI score. Thus, this cross tabulation has a p value of 0.124 which is considered as insignificant.

BAR DIAGRAM DEPICTING AGE WISE DISTRIBUTION OF APRI SCORE



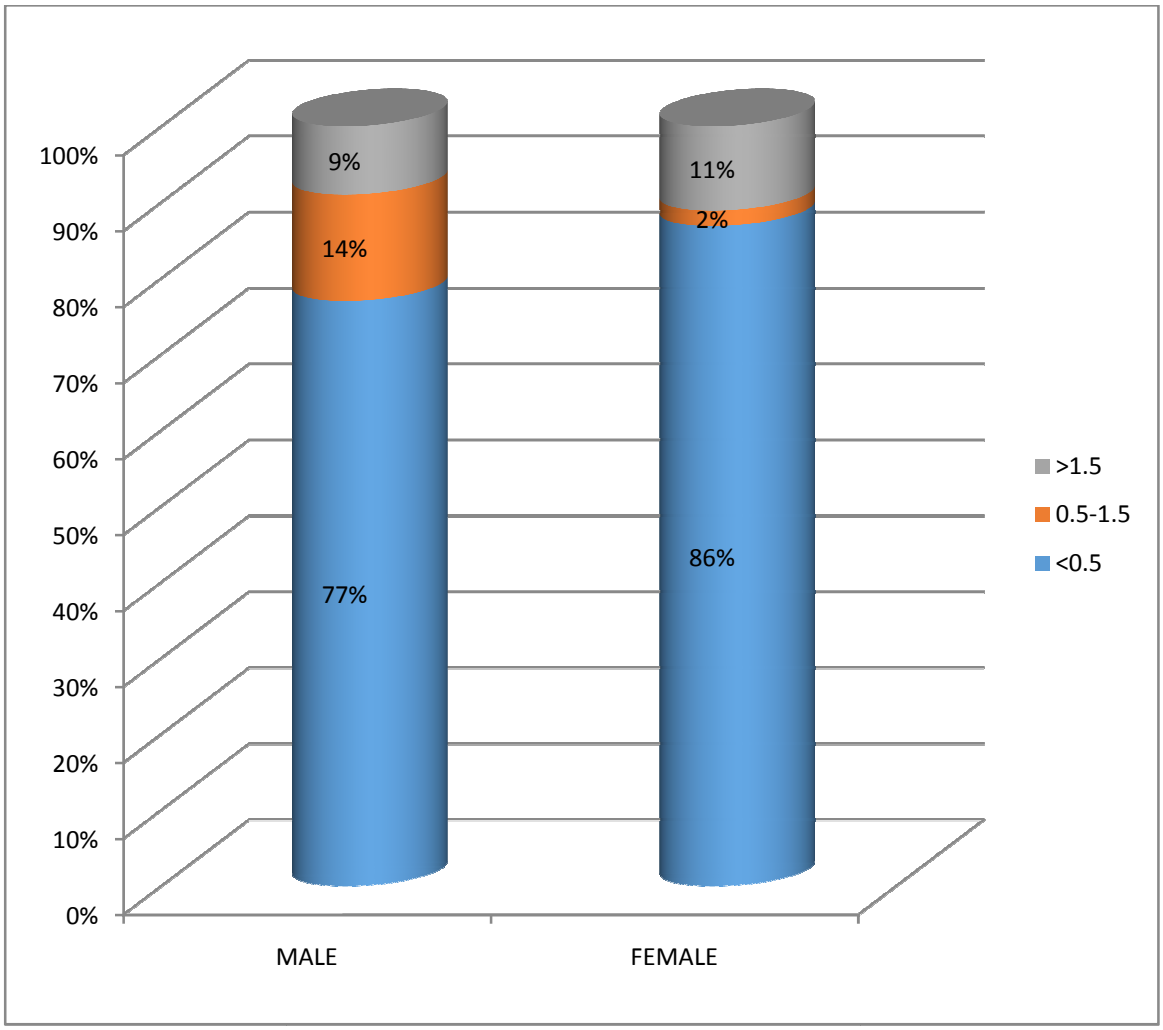
CROSSTABULATION CORRELATING APRI SCORE AND SEX DISTRIBUTION

CROSSTAB			SEX		Total
			MALE	FEMALE	
APRI_SCORE	<0.5	Count	43	38	81
		% within SEX	76.8%	86.4%	81.0%
	0.5-1.5	Count	8	1	9
		% within SEX	14.3%	2.3%	9.0%
	>1.5	Count	5	5	10
		% within SEX	8.9%	11.4%	10.0%
Total		Count	56	44	100
		% within SEX	100.0%	100.0%	100.0%

Pearson Chi-Square = 4.376 P= 0.112

From the given table, it is depicted that there is no male to female significance among APRI score. As the Pearson's Chi – square value is 0.112, implies that sex distribution among APRI score is not significant.

BAR DIAGRAM CORRELATING APRI SCORE AND SEX DISTRIBUTION



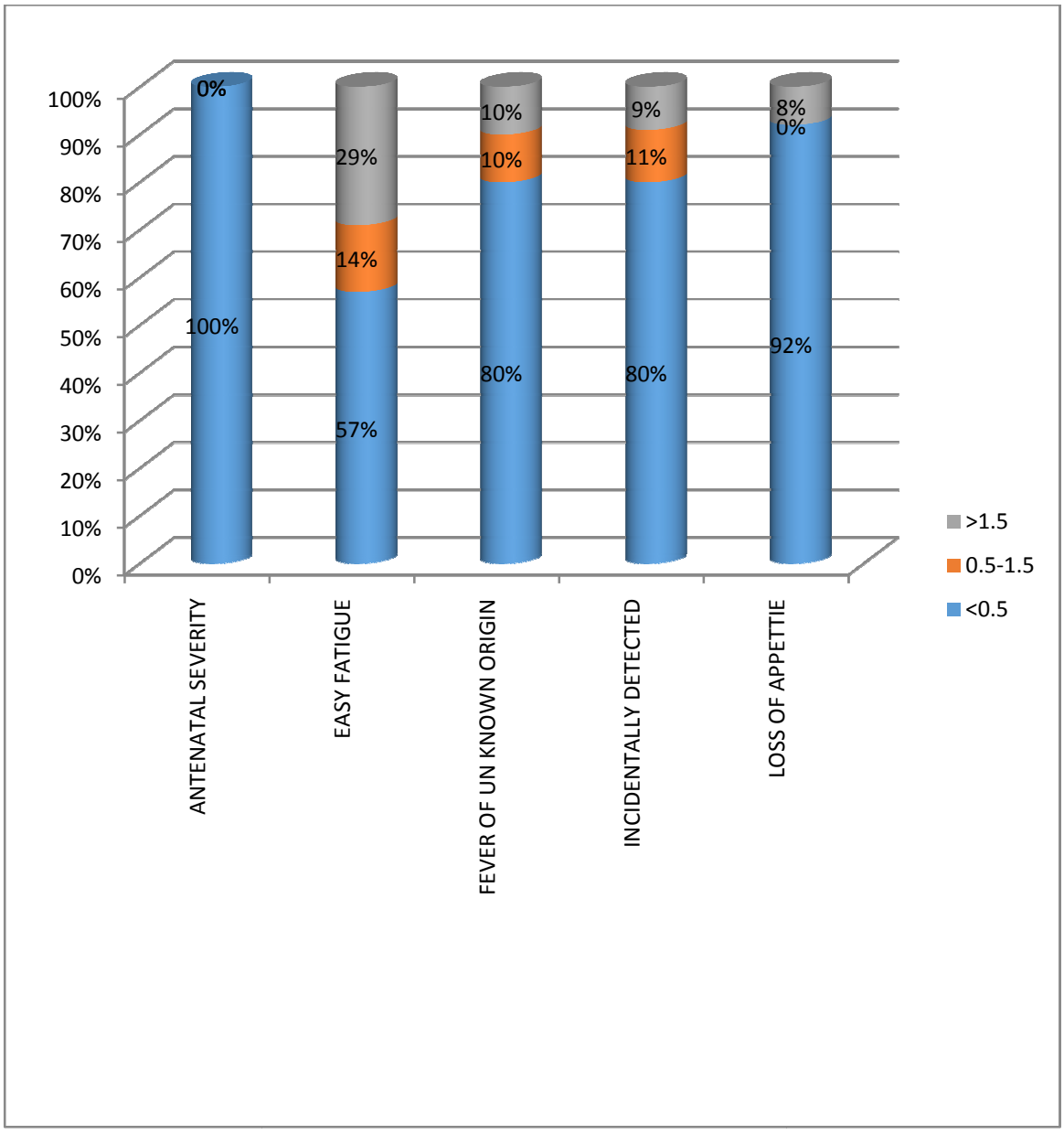
CROSS TABULATION CORRELATING HISTORY DURING DETECTION OF HBSAG/ HCV WITH APRI SCORE

CROSSTAB			HISTORY					Total
			Antenatal severity	Easy fatigue	Fever of un known origin	Incidentally detected	Loss of appetite	
APRI SCORE	<0.5	Count	6	4	8	52	11	81
		% within HISTORY	100.0%	57.1%	80.0%	80.0%	91.7%	81.0%
	0.5-1.5	Count	0	1	1	7	0	9
		% within HISTORY	0.0%	14.3%	10.0%	10.8%	0.0%	9.0%
	>1.5	Count	0	2	1	6	1	10
		% within HISTORY	0.0%	28.6%	10.0%	9.2%	8.3%	10.0%
Total		Count	6	7	10	65	12	100
		% within HISTORY	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Pearson Chi-Square = 6.098 P= 0.636

In the table given above, it is evident that history at the time of detection of HBSAG / HCV doesnot correlate with APRI score. Our p value was also 0.636 showing that it is insignificant in correlating history with APRI score.

BAR DIAGRAM CORRELATING HISTORY DURING DETECTION OF HBSAG/ HCV WITH APRI SCORE



CROSS TABULATION CORRELTING PLATELET COUNT WITH APRI SCORE

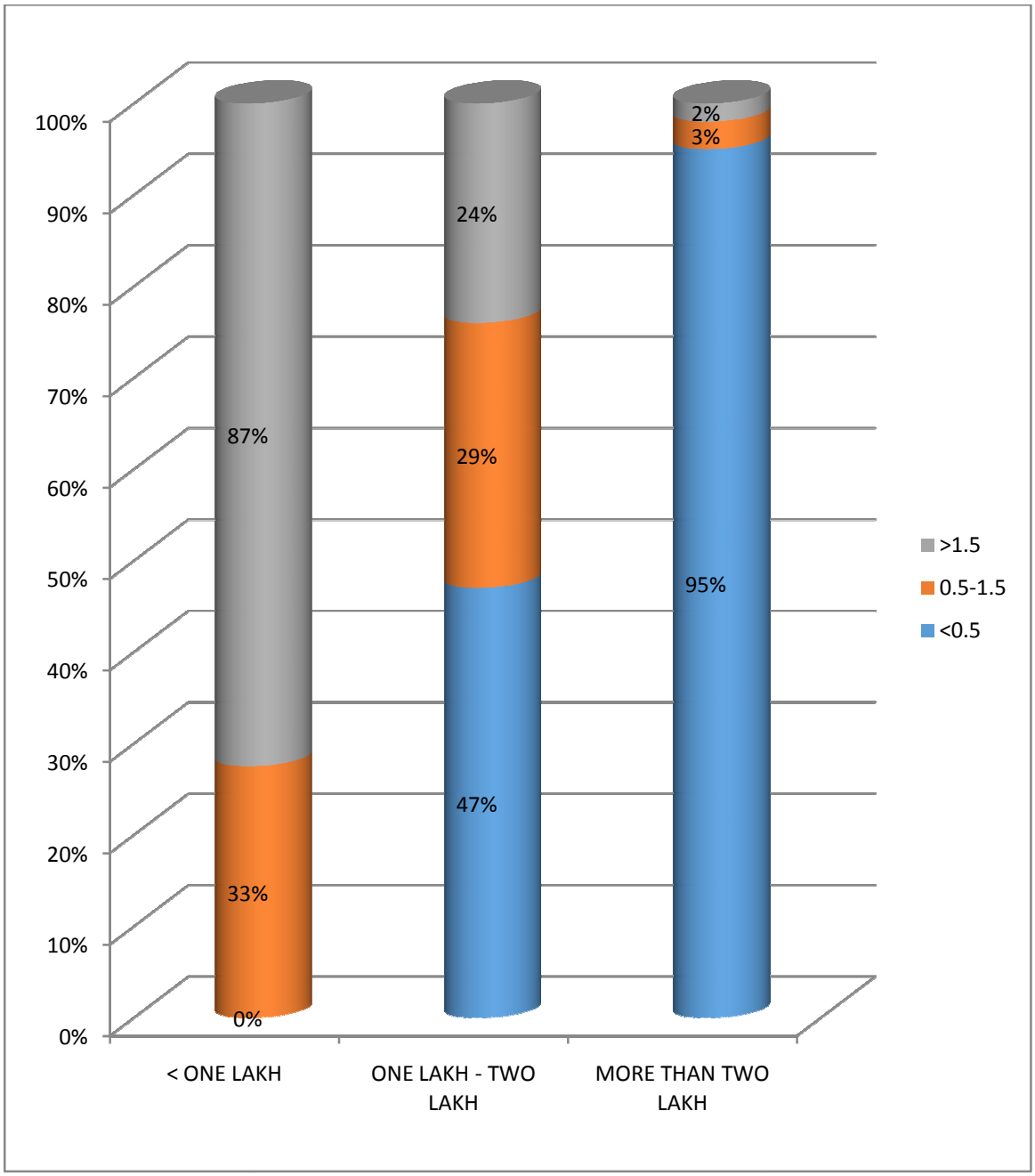
CROSSTAB			PLATELET_COUNT			Total
			< One lakh	One lakh - two lakh	More than two lakh	
APRI SCORE	<0.5	Count	0	8	73	81
		% within PLATELET_COUNT	0.0%	47.1%	94.8%	81.0%
	0.5-1.5	Count	2	5	2	9
		% within PLATELET_COUNT	33.3%	29.4%	2.6%	9.0%
	>1.5	Count	4	4	2	10
		% within PLATELET_COUNT	66.7%	23.5%	2.6%	10.0%
Total		Count	6	17	77	100
		% within PLATELET_COUNT	100.0%	100.0%	100.0%	100.0%

Pearson Chi-Square = 51.012 ** P<0.001

In our study score, around 73 patient had platelet value > 2,00,000 cells / ul correlating with APRI score < 0.5.Similarly, we had 4 patient with thrombocytopenia correlating well with an APRI score of >1.5.

From the given table, it is evident that as the platelet count reduces, the APRI score value increases. Since the p value appears to be <0.001, it is considered significant and well correlating.

BAR DIAGRAM CORRELTING PLATELET COUNT WITH APRI SCORE



CROSS TABULATION CORRELATING PRESENCE OF HBSAG AND / HCV WITH APRI SCORE

CROSS TAB			HBSAG	HCV	BOTH	TOTAL
APRI SCORE	<0.5	Count	62	14	5	81
		% within HBSAG	83.8%	73.7%	71.4%	81.0%
	0.5-1.5	Count	6	3	0	9
		% within HBSAG	8.1%	15.8%	0.0%	9.0%
	>1.5	Count	6	2	2	10
		% within HBSAG	8.1%	10.5%	28.6%	10.0%
Total		Count	74	19	7	100
		% within HBSAG	100.0%	100.0%	100.0%	100.0%

Pearson Chi-Square = 4.628 P= 0.328

From the above table, it is evident that patients with coinfection with HBSAg and HCV are more prone for fibrosis / cirrhosis, in comparison to patients with HBSAg or HCV infection separately.

Since the p value appears to be 0.328 , it predicts that this correlation between presence of HBSg / and HCV with APRI SCORE is not significant.

BAR DIAGRAM CORRELATING PRESENCE OF HBSAG AND / HCV WITH APRI SCORE

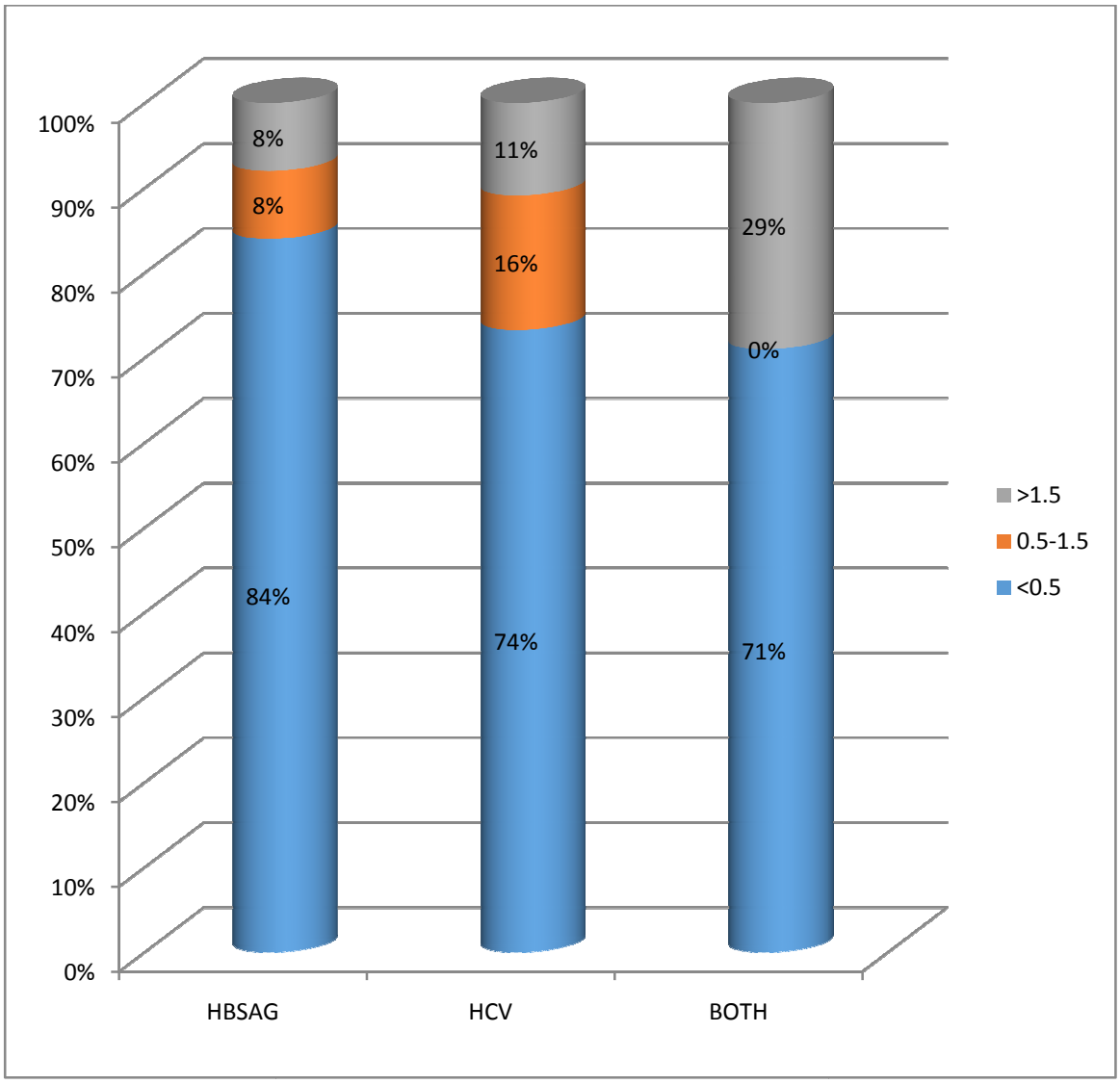


TABLE CORRELATING AGEWISE DISTRIBUTION WITH FIBROSCAN SCORE

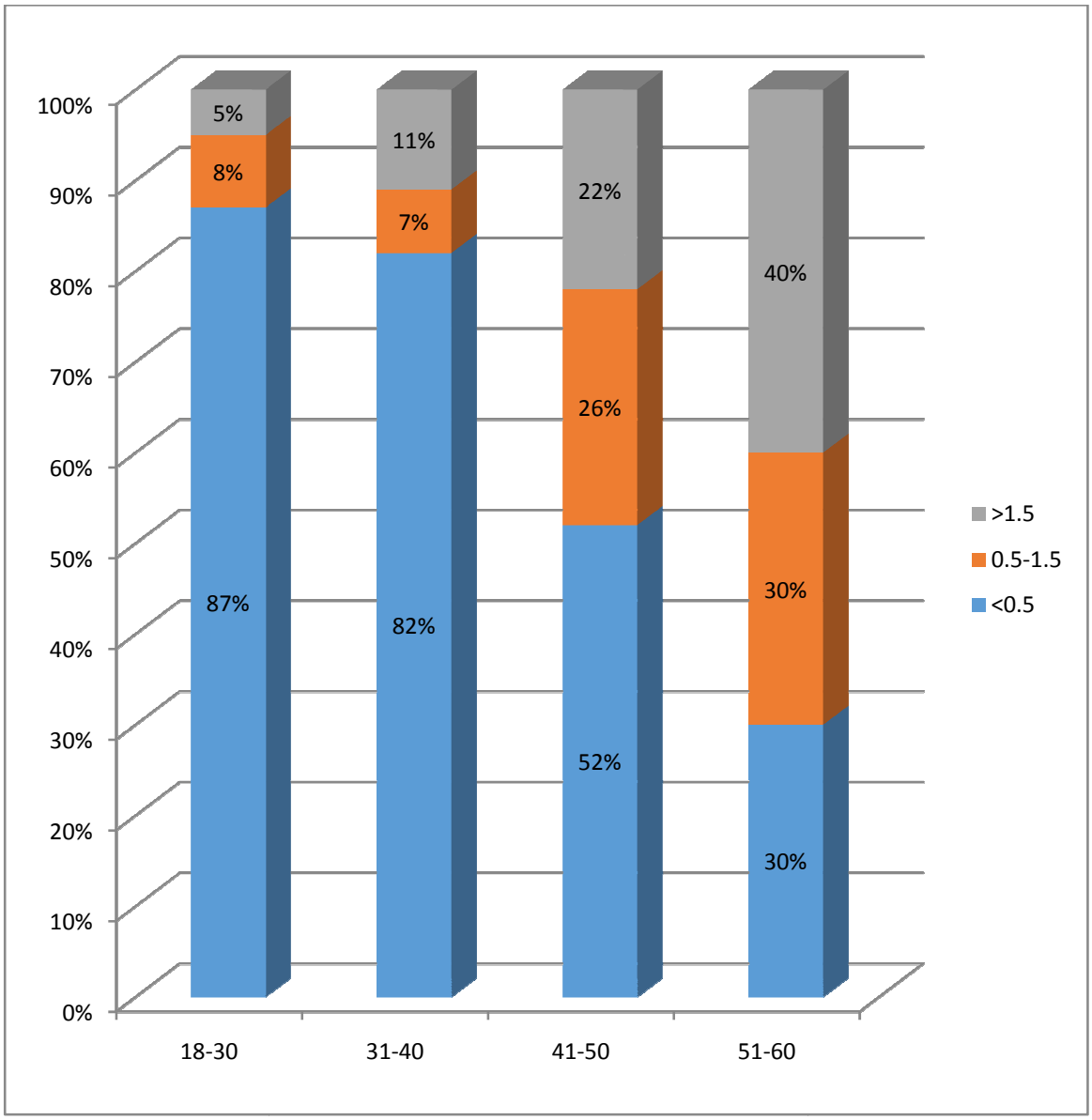
CROSSTAB			AGE_SCORE				Total
			18-30	31-40	41-50	51-60	
FIBROSCAN SCORE	<7	Count	34	23	12	3	72
		% within AGE_SCORE	87.2%	82.1%	52.2%	30.0%	72.0%
	7-11	Count	3	2	6	3	14
		% within AGE_SCORE	7.7%	7.1%	26.1%	30.0%	14.0%
	>11	Count	2	3	5	4	14
		% within AGE_SCORE	5.1%	10.7%	21.7%	40.0%	14.0%
Total		Count	39	28	23	10	100
		% within AGE_SCORE	100.0%	100.0%	100.0%	100.0%	100.0%

Pearson Chi-Square = 19.852 * P= 0.003

In our study, the above table depicts that as the age increases , the incidence of fibrosis/ cirrhosis increases as evidenced by increased Fibroscan values (<11)

The table had good correlation between agewise distribution and Fibroscan values, as the p value is significant (0.003).

BAR DIAGRAM CORRELATING AGEWISE DISTRIBUTION WITH FIBROSCAN SCORE



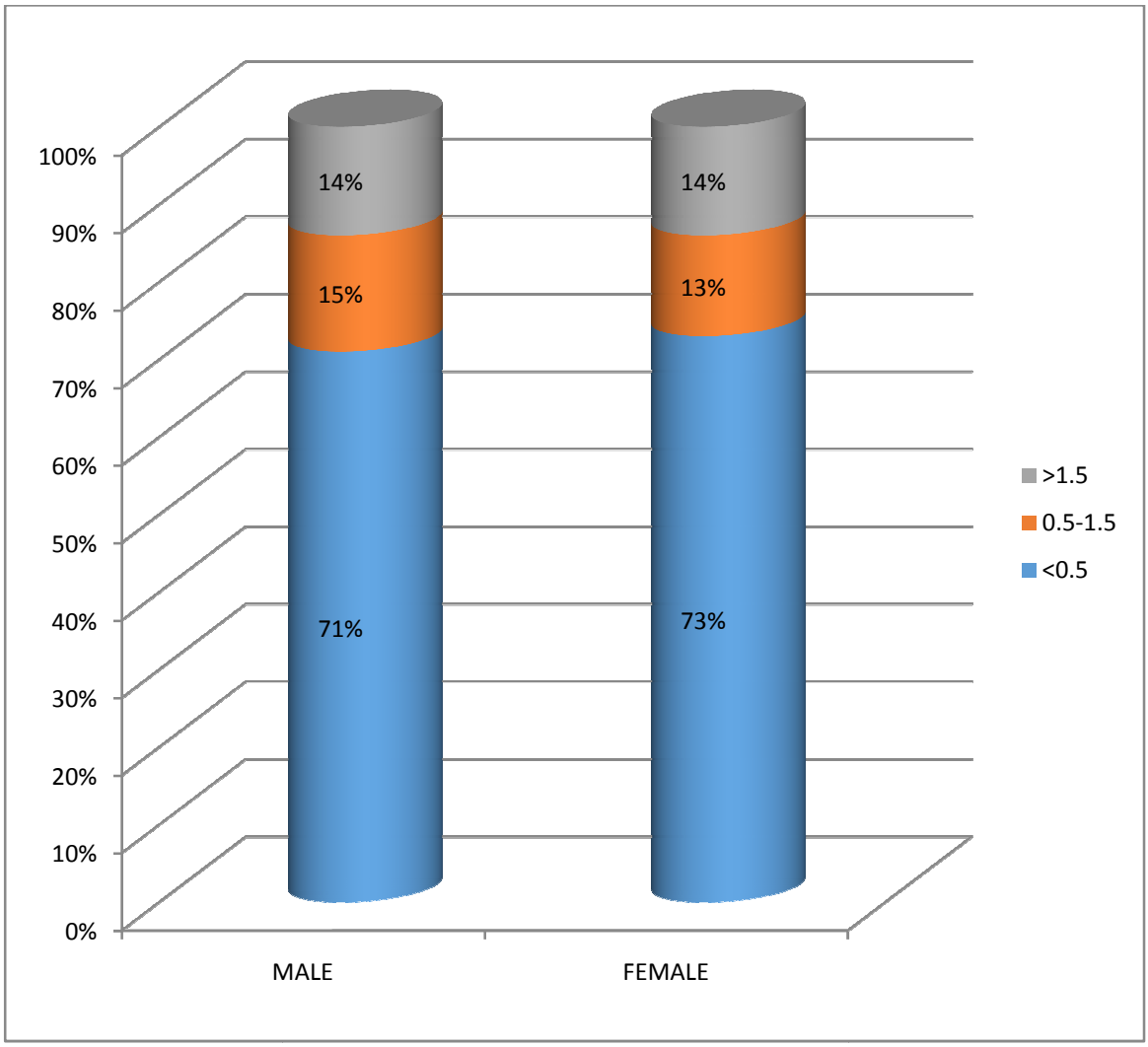
CROSS TABULATION CORRELATING SEX DISTRIBUTION WITH FIBROSCAN VALUES

CROSSTAB			SEX		Total
			MALE	FEMALE	
FIBROSCAN SCORE	<7	Count	40	32	72
		% within SEX	71.4%	72.7%	72.0%
	7-11	Count	8	6	14
		% within SEX	14.3%	13.6%	14.0%
	>11	Count	8	6	14
		% within SEX	14.3%	13.6%	14.0%
Total		Count	56	44	100
		% within SEX	100.0%	100.0%	100.0%

Pearson Chi-Square = 0.021 P= 0.990

The table above shows that there is no significance between sex distribution and Fibroscan values , as confirmed by p value that is 0.990.

BAR DIAGRAM CORRELATING SEX DISTRIBUTION WITH FIBROSCAN VALUES



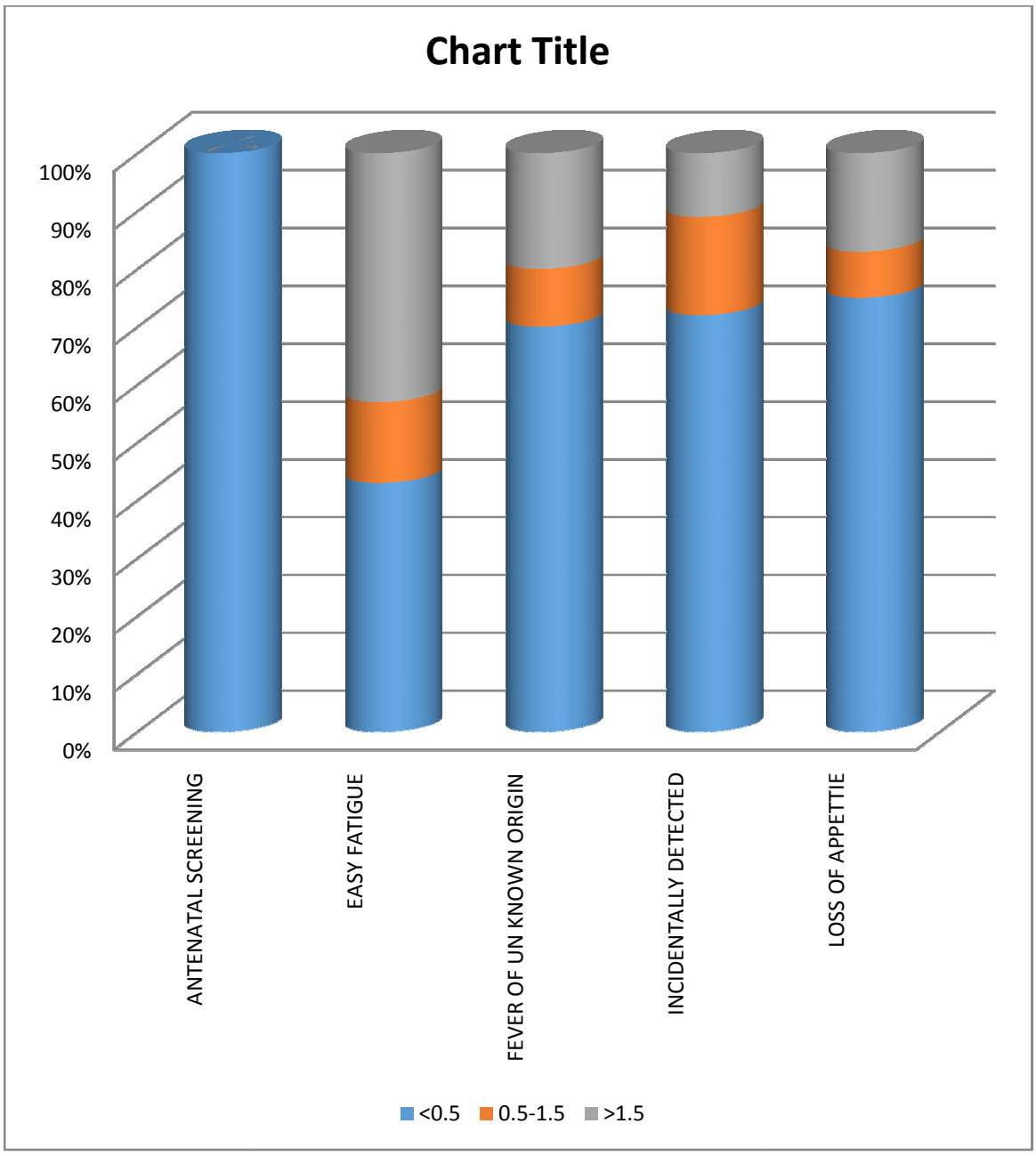
CROSS TABULATION DEPICTING RELTIONSHIP BETWEEN HISTORY AT THE TIME OF DIAGNOSIS AND FIBROSCAN SCORE

CROSSTAB			HISTORY					Total
			Antenatal Screening	Easy fatigue	Fever of un known origin	Incidentally detected	Loss of appettie	
FIBROSCAN SCORE	<7	Count	6	3	7	47	9	72
		% within HISTORY	100.0%	42.9%	70.0%	72.3%	75.0%	72.0%
	7-11	Count	0	1	1	11	1	14
		% within HISTORY	0.0%	14.3%	10.0%	16.9%	8.3%	14.0%
	>11	Count	0	3	2	7	2	14
		% within HISTORY	0.0%	42.9%	20.0%	10.8%	16.7%	14.0%
Total		Count	6	7	10	65	12	100
		% within HISTORY	100.0%	100.0 %	100.0%	100.0%	100.0%	100.0 %

Pearson Chi-Square = 8.933 P= 0.348

It is clear from the above table that there is no signifance in correlating history at the time of detection of HBSAg / HCV, as suggested by p value that is 0.348.

BAR DIAGRAM DEPICTING RELTIONSHIP BETWEEN HISTORY AT THE TIME OF DIAGNOSIS AND FIBROSCAN SCORE



CROSS TABULATION CORRELATING PLATELET COUNT WITH FIBROSCAN SCORE

CROSSTAB			PLATELET_COUNT			Total
			< One lakh	One lakh - two lakh	More than two lakh	
FIBROSCAN SCORE	<7	Count	2	6	64	72
		% within PLATELET_COUNT	33.3%	35.3%	83.1%	72.0%
	7-11	Count	0	6	8	14
		% within PLATELET_COUNT	0.0%	35.3%	10.4%	14.0%
	>11	Count	4	5	5	14
		% within PLATELET_COUNT	66.7%	29.4%	6.5%	14.0%
Total		Count	6	17	77	100
		% within PLATELET_COUNT	100.0%	100.0%	100.0%	100.0%

Pearson Chi-Square = 30.683 ** P<0.001

In our study score, around 72 patients had platelet value > 2,00,000 cells / ul correlating with FIBROSCAN SCORE <7. Similarly, we had 4 patient with thrombocytopenia correlating well with an FIBROSCAN SCORE >11.

From the given table, it is evident that as the platelet count reduces, the FIBROSCAN value increases. Since the p value appears to be <0.001, it is considered significant and well correlating.

BAR DIAGRAM CORRELATING PLATELET COUNT WITH

FIBROSCAN SCORE

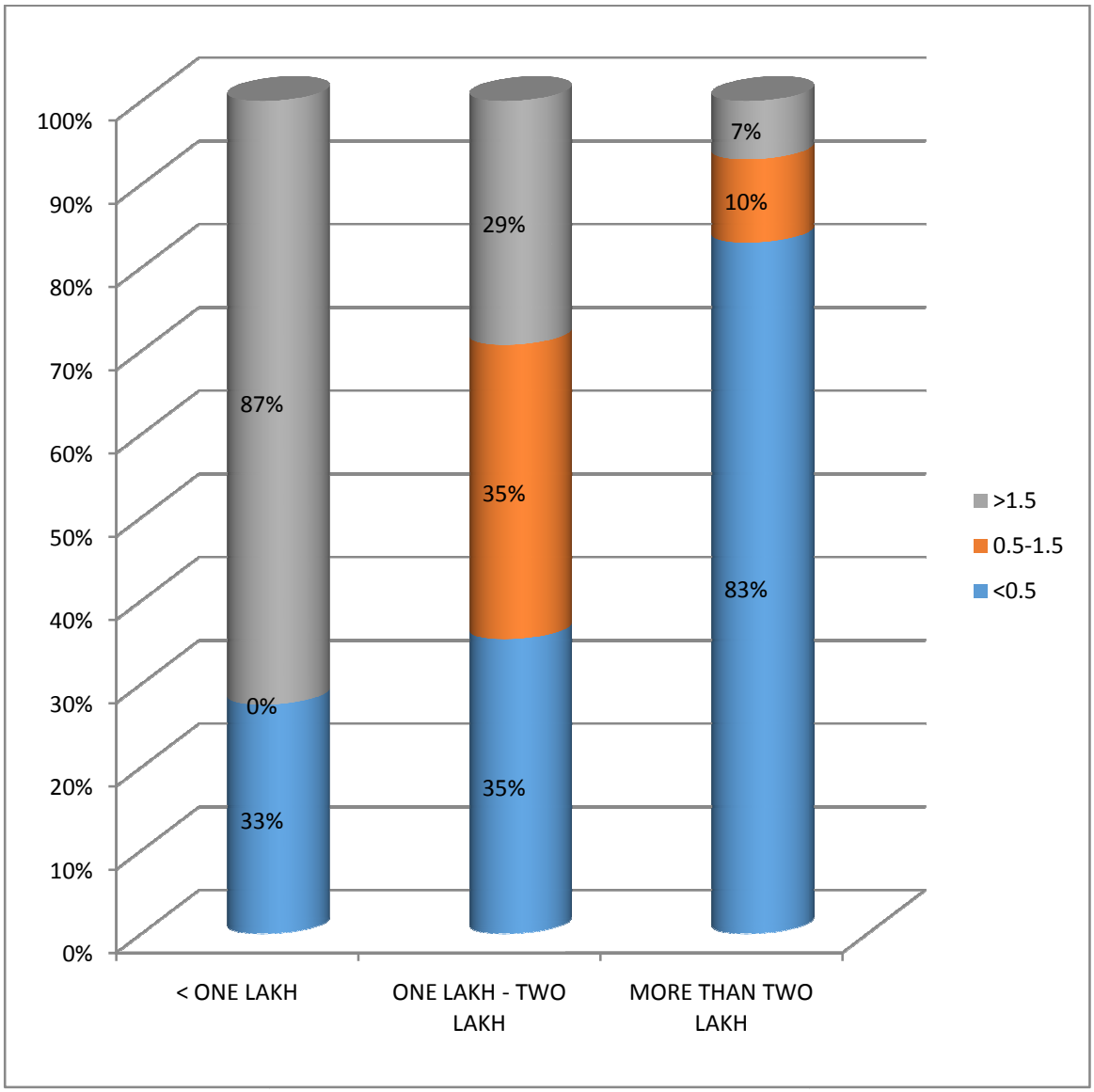


TABLE DEPICTING CORRELATION BETWEEN TYPE OF HEPATITIS VIRUS INFECTION (HBSAG / AND HCV) AND FIBROSCAN SCORE

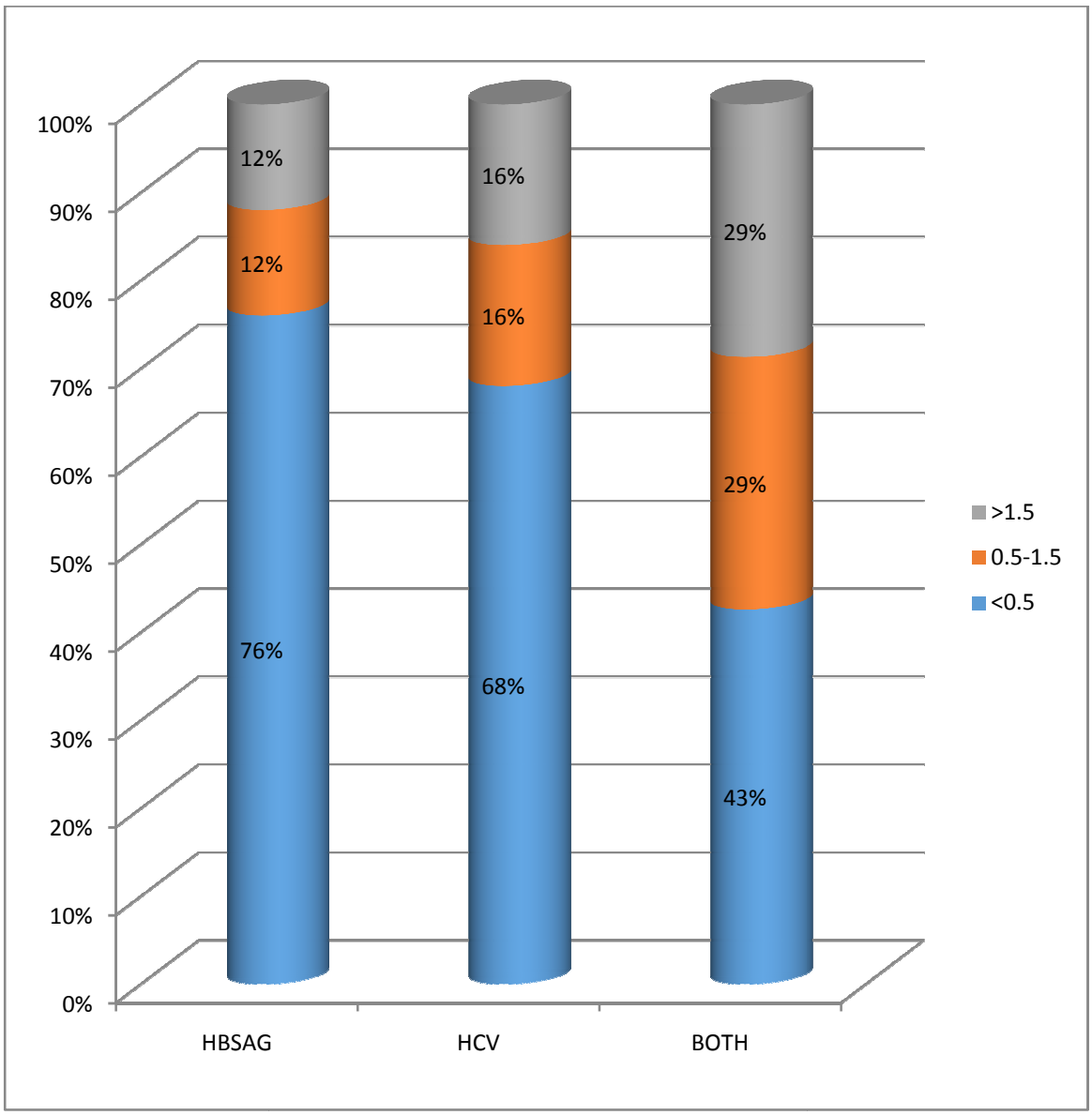
CROSSTAB			HBSAG			Total
			HBSAG	HCV	BOTH	
FIBROSCAN SCORE	<7	Count	56	13	3	72
		% within HBSAG	75.7%	68.4%	42.9%	72.0%
	7-11	Count	9	3	2	14
		% within HBSAG	12.2%	15.8%	28.6%	14.0%
	>11	Count	9	3	2	14
		% within HBSAG	12.2%	15.8%	28.6%	14.0%
Total		Count	74	19	7	100
		% within HBSAG	100.0%	100.0%	100.0%	100.0%

Pearson Chi-Square = 3.566 P= 0.468

From the above table, it is evident that patients with coinfection with HBSAg and HCV are more prone for fibrosis / cirrhosis , in comparison to patients with HBSAg or HCV infection separately.

Since the p value appears to be 0.468 , it predicts that this correlation between presence of HBSg / and HCV with FIBROSCAN SCORE is not significant.

BAR CHART DEPICTING CORRELATION BETWEEN TYPE OF HEPATITIS VIRUS INFECTION (HBSAG / AND HCV) AND FIBROSCAN SCORE



DISCUSSION

DISCUSSION

This study was conducted as a prospective and retrospective observational study in patients attending Hepatology OPD at Madras Medical College and Rajiv Gandhi Government General Hospital. Sample size is 100. After getting the informed consent of the patients and their attending close relatives, the patients were subjected to history taking, physical examination and relevant laboratory testing and imging. These were done to identify the presence/ absence of fibrosis /cirrhosis in the patient.

A study by Hind I. Fallatah and Alyaa M. Fallatah et al also showed that APRI SCORE can be compared to fibroscan for Assessment of Liver Fibrosis.

Another study by Wenwen Jin, Zhonghua Lin et al showed diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio (APRI) index for the assessing of hepatitis B-related fibrosis and found that it had almost equal sensitivity and specificity as Fibroscan in predicting fibrosis.

Liver biopsy is presently the standard available for assessment of liver fibrosis and necrotic inflammatory activity. Being an invasive procedure subjected to inter-observer variability and sampling error is up

to 33% of biopsies. Furthermore the biopsy might have complications ,for example bleeding, pain or injury of the neighbouring organs such as kidney, lung or colon.

Due to these limitations, liver biopsy could not be performed in such patients. The severity of Liver fibrosis and the degree of liver damage in patients of chronic hepatitis B/ and C acan be assessed using other simple noninvasive tests .

Notable among these are fibrotest and hepascore which exhibit near diagnostic accuracy.

An ideal non-invasive test for assessing liver fibrosis should be a simple, readily available, inexpensive, and must be accurate. AST/ ALT ratio was used for the diagnosis of cirrhosis.

The aspartate aminotransferase-to-platelet count ratio index (APRI), an index with limited expense and widespread availability, is a noninvasive alternative to liver biopsy in detecting hepatic fibrosis. The objective of this study was to systematically review the performance of the APRI in predicting significant fibrosis and cirrhosis in hepatitis B /and C -related fibrosis.

The combination of Fibroscan and APRI, provides a valuable approach for assessing hepatic fibrosis. This can eliminate the need for liver biopsy in patients without clear indication.

Liver enzymes are measured using a dimension clinical chemistry system (Flex Reagent Cartridge). APRI score can be determined using the following equation :

$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

The limitation of the score is due to inability to identify various stages of fibrosis, it can however, only differentiate mild from significant fibrosis or mild/moderate from severe fibrosis.The interval between the diagnostic cut-offs ≤ 0.90 and ≥ 1.5 is the major grey zone where the patients tends to remain unclassified. In these patients hepatic biopsy needs to be performed for appropriate classification.

LIMITATIONS OF THE STUDY

A multi centric study with a large sample size and further longer follow up is essential in order to assess the predictive power of these prognostication tools in a much more comprehensive manner.

CONCLUSION

CONCLUSION

From our study results, it could be concluded that ASPARTATE AMINOTRANSFERASE –PLATELET COUNT RATIO INDEX (APRI) SCORE has sensitivity and specificity around 80-90% as comparable to Fibroscan scores in assessing hepatic fibrosis in patients with chronic hepatitis B virus / and C infection.

Hence, it can be used as a non-invasive tool in predicting cirrhosis in primary care settings where Fibroscan would not be available. In other centres, it can be used in combination with Fibroscan to assess fibrotic status of liver in patients with Hepatitis B virus / and C infection.

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BIBLIOGRAPHY

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ANNEXURES

ABBREVIATIONS

APRI	-	ASPARTATE AMINOTRANSFERASE PLATELET COUNT RATIO INDEX
AST	-	ASPARTATE AMINOTRANSFERASE
ALT	-	ALANINE AMINOTRANSFERASE
HCV	-	HEPATITIS C VIRUS
HBV	-	HEPTITIS B VIRUS
GGTP	-	GAMMA GLUTAMYL TRANSPEPTIDASE
DAA	-	DIRECTLY ACTING ANTIVIRALS
IFN	-	INTERFERON ALPHA
TMA	-	TRANSCRIPTION MEDIATED AMPLIFICATION
EIA	-	ENZYME IMMUNOASSAY
HRQOL	-	HELTH RELATED QUALITY OF LIFE
HDL	-	HIGH DENSITY LIPOPROTEIN
HBEAG	-	HEPATITIS B ENVELOP ANTIGEN
HCC	-	HEPATOCELLULAR CARCINOMA
MHC	-	MAJOR HISTOCOMPTIBILITY COMPLEX
CTL	-	CYTOTOXIC T LYMPHOCYTE

PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

OP/ NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

COMPLAINTS :

PAST HISTORY :

H/o blood transfusions
H/o previous surgeries
History of tattooing
H/o Intravenous drug abuse
H/o High risk behavior/HIV/CKD/ Bleeding diathesis/Alcohol related liver disease.
H/o chronic alcoholism >30g/day within past 6 months.

TREATMENT HISTORY :

GENERAL EXAMINATION

Pallor: Icterus: Cyanosis: Clubbing:

Lymphadenopathy: Edema:

VITALS

Pulse Rate: BP: Respiratory rate: Temperature:

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM :

RESPIRATORY SYSTEM :

ABDOMEN :

CENTRAL NERVOUS SYSTEM :

INVESTIGATIONS:

PLATELET COUNT-

ASPARTATE AMINOTRANSFERASE -

APRI SCORE:

(ASPARTATE AMINOTRANSFERASE PLATELET RATIO INDEX):

AST(U/L) / UPPER LIMIT OF AST(U/L) X 100

PLATELET COUNT(10^9 / L)

FIBROSCAN VALUE

THESIS APPROVAL CERTIFICATE

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.Vidhyalakshmi.C.K.
Post Graduate in M.D. (General Medicine)
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.Vidhyalakshmi.C.K.,

The Institutional Ethics Committee has considered your request and approved your study titled **"APRI SCORING AS A PREDICTOR OF HEPATIC FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B AND/OR C INFECTION IN COMPARISON WITH FIBROSCAN " - NO.(II) 09032016.**

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.

Member Secretary – Ethics Committee

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

31 MAR 2016

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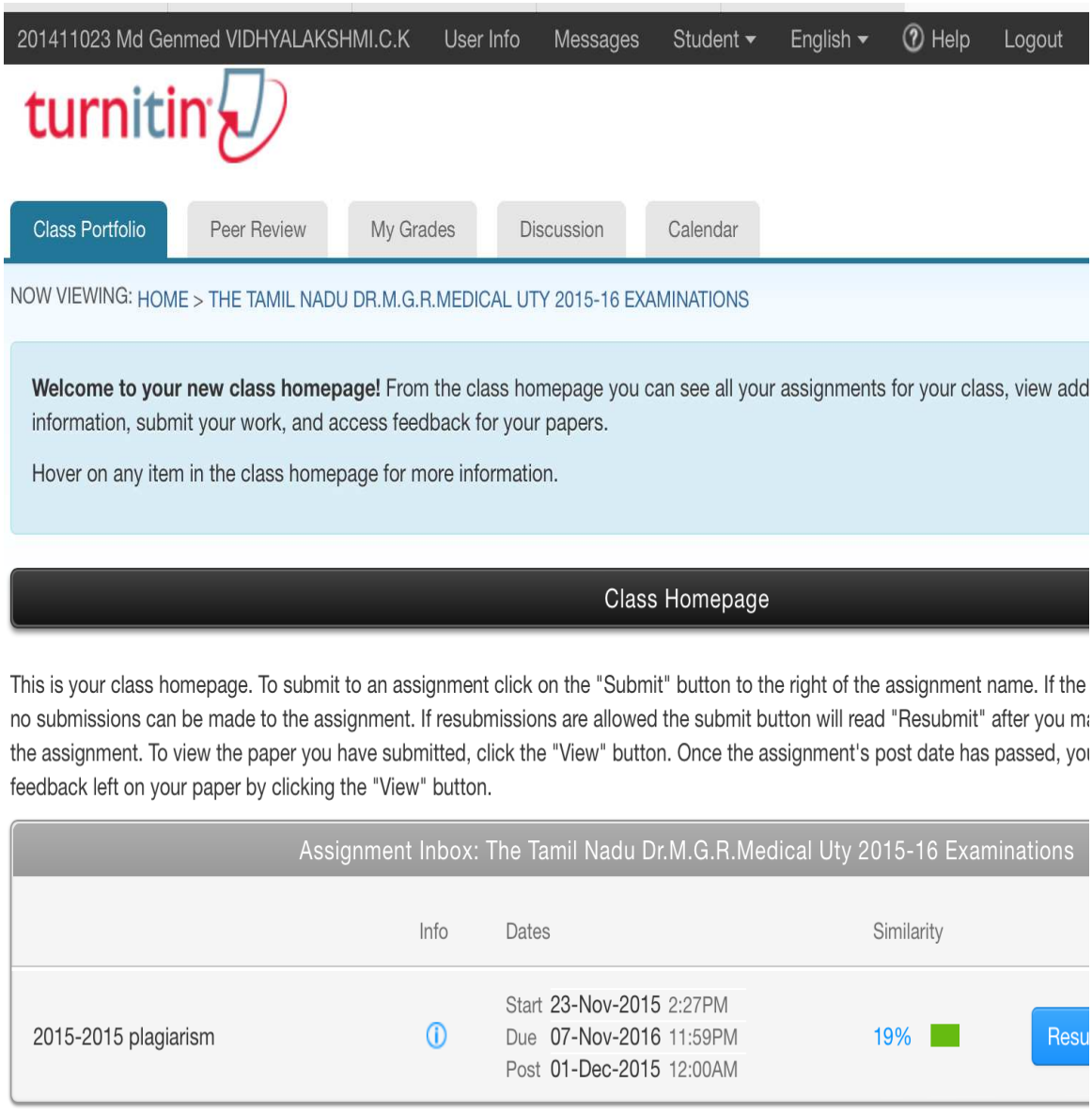

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INFORMATIONSHEET

We are conducting a study on "APRI SCORING AS A PREDICTOR OF HEPATIC FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B AND/OR C INFECTION IN COMPARISON WITH FIBROSCAN " among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your co- operation to undergo PLATELET COUNT ,LIVER FUNCTION TEST,FIBROSCAN may be valuable to us.

The purpose of this study is to use APRI scoring as a predictor of hepatic fibrosis in patients with chronic Hepatitis B and/or C patients with Fibroscan being used as a tool to confirm hepatic fibrosis .

We are selecting certain cases and if you are found eligible, we would like to 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 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 ராஜீவ்காந்தி அரசு பொது மருத்துவமனையின் பொது மருத்துவத்துறையில் "அப்பாச்சி-2 மற்றும் சோஃபா அளவீடுகளை குறுதி நஞ்சு-பல்லுறுப்பு செயல் பிறழ்ச்சியின் இறப்பு விகிதத்தின் குறிகாட்டிகளாய் ஒப்பிட்டு ஆராய்தல்" பற்றிய ஆய்வு நடைபெறுகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதனால் தங்களது சிகிச்சையில் பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆய்வில் தங்களுக்கு மருத்துவபரிசோதனை, இரத்தப் பரிசோதனை, ஸ்கேன், சிறுநீர் பரிசோதனை மற்றும் எக்ஸ்ரே (X-Ray) பரிசோதனை செய்யப்படும்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

பங்கேற்பாளர் கையொப்பம்

ஆராய்ச்சியாளர் கையொப்பம்

நாள் :
இடம் :

PATIENT CONSENT FORM

Study Detail	:	"APRI SCORING AS A PREDICTOR OF HEPATIC FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B AND/OR C INFECTION IN COMPARISON WITH FIBROSCAN "
Study Centre	:	Department of Hepatology, 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

Investigator's Name:

Patient's Name and Address:

Dr.VIDHYALAKSHMI.C.K.

சுய ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு :

அப்பாச்சி 2 மற்றும் சோபா அளவீடுகளை, குறுதி நஞ்சு - பல்லுறுப்பு செயல் பிறழ்ச்சி நோயின் குறிகாட்டிகளாக ஒப்பிட்டு ஆராய்தல்

பெயர்	வயது
பால்	தேதி
உள் நோயாளி எண்	ஆராய்ச்சி சேர்க்கை எண்

இந்த ஆராய்ச்சியின் விவரங்களும் நோக்கங்களும் எனக்கு முழுமையாகவும் தெளிவாகவும் விளக்கப்பட்டன. எனக்கு விளக்கப் பட்ட விஷயங்களை நான் புரிந்து கொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

மேற்கொண்ட பரிசோதனையின் பொழுது ஏற்படக்கூடிய பின் விளைவுகளை உணர்ந்து இந்த பரிசோதனைக்கு மனமாற சம்மதிக்கிறேன்.

இந்த ஆய்வுக்கான பரிசோதனைகளை செய்து கொள்ள சம்மதிக்கிறேன். இந்த ஆராய்ச்சியின் விளக்க தாளை பெற்றுக்கொண்டேன். இந்த ஆய்வில் முழு சுதந்திரத்துடன் மற்றும் சுய நினைவுடன் பங்கு கொள்ள சம்மதிக்கிறேன்.

பங்கேற்ப்பாளர் / பாதுகாவலர் கையொப்பம்

தேதி