SERUM INTERLEUKIN 6 LEVEL IN PATIENTS WITH LIVER CIRRHOSIS OF ANY CAUSE AND ITS CORRELATION WITH CHILD PUGH SCORE IN ASSESSING DISEASE SEVERITY

Submitted in partial fulfilment of Requirements for

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CERTIFICATE

This is to certify that this dissertation entitled **"SERUM INTERLEUKIN 6 LEVEL IN PATIENTS WITH LIVER CIRRHOSIS OF ANY CAUSE AND ITS CORRELATION WITH CHILD PUGH SCORE IN ASSESSING DISEASE SEVERITY**" submitted by **Dr. M.MOHAMED KILJI** appearing for M.D. Branch I - General Medicine Degree examination in March 2013 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfilment of regulations of the TamilNadu Dr. M.G.R. Medical University, Chennai. I forward this to the TamilNadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation titled **"SERUM INTERLEUKIN 6 LEVEL IN PATIENTS WITH LIVER CIRRHOSIS OF ANY CAUSE AND ITS CORRELATION WITH CHILD PUGH SCORE IN ASSESSING DISEASE SEVERITY"** is done by me at Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai during 2012 under the guidance and supervision of **Prof.Dr.A.RADHAKRISHNAN., M.D.** The dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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ABBREVIATIONS

MELD	- Model for end stage liver disease
AUDIT	- Alcohol use disorder identification test
MAST	- Michigan alcohol screening test
CRP	- C-reactive protein
SHT	- Systemic hypertension
DM	- Diabetes mellitus
ESR	- Erythrocyte Sedimentation Rate
IL-1	- Interleukin 1
IL-6	- Interleukin 6
TNF alpha	- Tumor necrosis factor alpha
TGF-β	- Transforming growth factor beta
INR	- International normalized ratio
PT	- Prothrombin time
apTT	- Activated partial thromboplastin time

CONTENTS

INTRODUCTION

INTRODUCTION:

Ancient world had known well about the liver and diseases associated with liver. Egyptian scriptures and books of Talmud described about the problems with the liver and remedies associated with altered function of this essential organ. The word 'cirrhosis' is actually derived from Greek medicine and means that diseased liver with orange yellow in colour.

Cirrhosis of liver which is having characteristic histological features resulting from various insult or injury to this organ whatever it would be, account for fourth major cause of mortality worldwide, and one of the leading cause of mortality in India.

Since the diagnosis of liver diseases went through various stages of development from the ancient period such as ultrasonogram abdomen portal doppler study, CT scan of abdomen, OGD scopy and recently developed fibro-scan which is a non-invasive modality for the diagnosis of cirrhosis, still History and Clinical examination are much more important in diagnosing liver disorders while coming across the evaluation of liver involvement, either primary or secondary to other systemic disorders.

To aid this evaluation further, various scores have been devised for the bed side identification of quantum of injury and to decide on therapeutic options whether liver transplantation needed or still medical management will be effective for decompensated and compensated liver diseases respectively.

Of these, scores currently in use are modified child pugh score and model for end stage liver diseases score. The modified child pugh score of 7 and above signifies the need for liver transplantation and scores below 7 indicates medical management which can sustain the process of liver injury and associated complications. The model for end stage liver diseases score of 18 and above indicates poor prognosis concerned for liver diseases.

Though various sequential pathogenic processes are involved to end in final stage of cirrhosis such as fatty liver, alcoholic hepatitis and fibrosis , one of mechanism for the progression of spectrum of pathological changes is inflammatory process upon which treatment modalities are proved to be effective also.

Various inflammatory marker are involved in this process such as IL 1, IL 6, TNF-α, IL-1β, IL-2R, IL-8. Of these I have taken serum interleukin 6 as a Inflammatory marker for liver diseases particularly liver cirrhosis since elevated

level of this marker is significantly proved in studies. Moreover, this elevation is independent of aetiology such as alcoholism and viral infections and etc.

Here one of above mentioned scoring system named child pugh score is correlated with level of interleukin 6 in patients with liver cirrhosis to facilitate the assessment of disease severity. If elevated level can be found statistically significant in this study, this marker even can be used as surrogate marker in assessment of disease severity in liver cirrhosis of various causes.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES:

To estimate SERUM INTERLEUKIN 6 level in patients with LIVER CIRRHOSIS of any cause

To find out the CORRELATION BETWEEN SERUM INTERLEUKIN 6 LEVEL AND CHILD PUGH SCORE in assessing DISEASE SEVERITY

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

Physicians have well known problems with liver from the olden period that details have been mentioned in lot of age old literatures. Egyptian scriptures mentioned about liver diseases with explanations and references on medicine. Talmud books described issues about liver and liver diseases. About 1500 years ago middle east areas were reported to know about treatment modalities of various illness about 1500 years ago.

Here I am going to discuss about “correlation of increasing levels of serum Interleukin 6 in liver cirrhosis patients with child pugh score to assess the disease severity with available references.

CIRRHOSIS

The word "cirrhosis" is actually coined in greek medicine and means that orange yellow colour of the diseased liver. Laennec also coined the name cirrhosis while he was working for stethoscope well before knowledge about this entity was described in the middle period of medicine. Details about shrunken liver were given in various ancient medical scriptures in detail including their management. [1]

Cirrhosis is actually defined as a disease process in which fibrosis and nodule formation are the major components. There are so many causes for cirrhosis, but ultimately leading to same end result that is cirrhotic process. Liver can react to

the injurious processes in multiple ways of which liver lobule collapse and formation of fibrous septa which is diffuse in nature are the important pathological processes. Another response from the liver which is important is nodule formation.

So whatever the cause for the liver injury, the final end histological picture is supposed to be ultimately unique. Necrosis of liver hepatocytes is usually followed by fibrotic process. Portal to portal bridging process occurring in zone 1 of liver histology is interface hepatitis which is actually the key process. Further collectively occuring necrotic processes leads to the formation of central to portal bridging process. Ultimately loss of cell mass in the liver leads to the formation of nodules. This nodular architecture of liver actually disturbs the original structure of liver and full blown cirrhosis picture will develop later on.

The complex process involving several key components in particular are the stellate cells, cytokines, and proteinases and their inhibitors the important components requiring for the multistep process of organization of normal liver to fibrotic liver and finally formation of cirrhosis. Cytokines play an important role in the stimulation stellate cells in this complex process. These are TGF-1b, IL1b and TNF. Byproducts of lipid peroxidation also involved in this complex process. Alcohol metabolism which gives rise to acetaldehyde as an intermediate taking part in this processes also.

Formation of matrix and its fate and discrepancies involved in this process play a major role in this complex process. Fate of matrix will be decided by those such

as metallo proteinases, tissue inhibitors of metallo proteinases and enzymes like stromelysin .There is alteration of interstitial matrix in such a way that normal basement membrane is degraded more and type collagen present in the interstitium will be degraded less in terms of amount and speed. These are the important pathological changes occurring during liver injury.

Activation of stellate cell leads to the formation of myofibroblast which is morphologically similar, but functionally different from stellate cell and contractile function of these myofibroblast is well described.

This function is expressed well over sinusoids leading to the local constriction and regulation of blood flow is attained well thereafter. This process is accomplished by two more biochemical substances such as nitric oxide and endothelin. Contraction is facilitated by decrease in nitric oxide level and increase in endothelin level [8, 9].

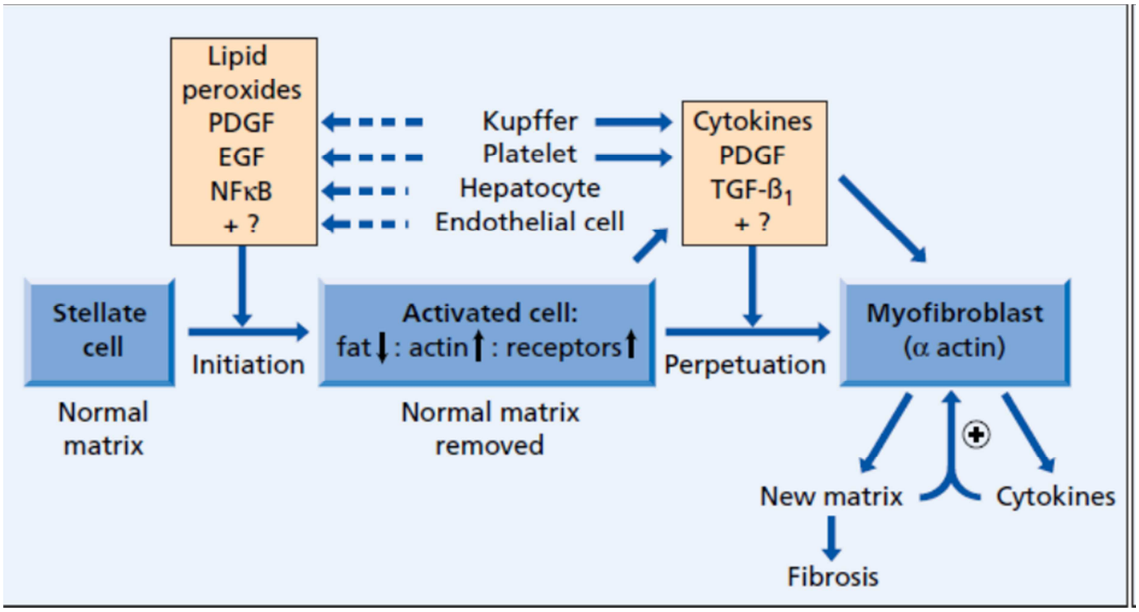
The Kupffer cells are important in the production of certain cytokines such as TNF-a, IL1 and IL6 and also produced by hepatocytes to the smaller extent.

Liver is involved in the clearance of these circulating cytokine and failure of this process leads to the level of certain cytokines to be elevated. This part of discussion is important since this could be probable mechanism for the elevation of certain cytokines in liver cirrhosis. Certain cytokines are involved in giving negative effect for regeneration of liver cells. These are IL6, IL1 and TNF [10].

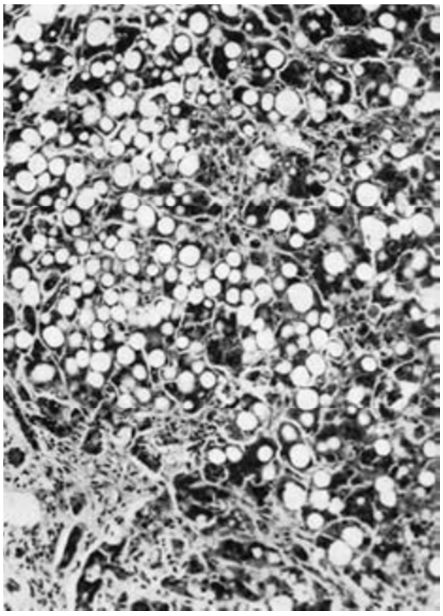
CLASSIFICATION OF CIRRHOSIS

Morphological classification

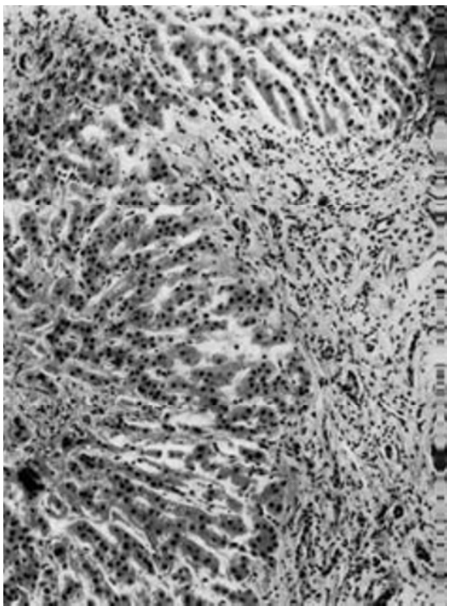
Morphologically cirrhosis is classified into macro-nodular cirrhosis, micro-nodular cirrhosis and mixed type which contains both the components of micro and macro nodular cirrhosis.



MECHANISM OF CIRRHOTIC PROCESS



HISTOLOGY OF MICRO-NODULAR CIRRHOSIS



HISTOLOGY OF MACRO-NODULAR CIRRHOSIS

Etiological classification

While mentioning about causes for cirrhosis liver, Viral hepatitis is particularly important. It is caused by Hepatitis b virus and hepatitis c virus and occasionally by the combination of Hepatitis b and d virus called delta virus. Alcohol is the important etiological factor involved in the causation of cirrhosis and is separately discussed below.

Metabolic causes like Wilson's disease in which abnormal copper metabolism is involved in the pathological process of cirrhosis formation also well known. Other metabolic causes such as type 4 glycogenolysis, congenital tyrosinosis, non alcoholic steatohepatitis and α -1 antitrypsin deficiency also well described as causes for cirrhosis. Cholestatic conditions either intrahepatic cholestasis or extra hepatic cholestasis is important causes and needed some invasive investigation to get diagnosed. Conditions causing obstruction to the blood flow from the liver such as Budd Chiari syndrome, occlusive disease of the venous system and constrictive pericarditis are also etiological factors for hepatic cirrhosis.

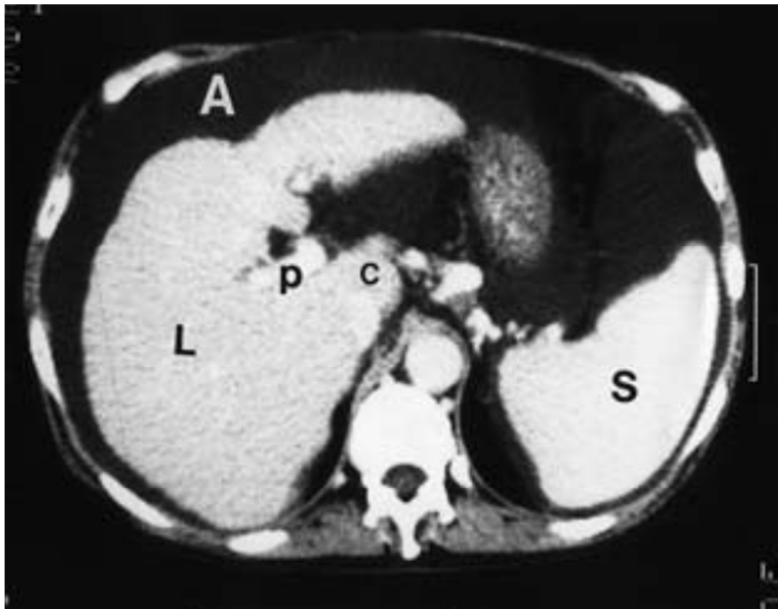
Autoimmune disease of the liver is also described to end in cirrhotic process of liver. This condition may be diagnosed with various autoimmune antibodies such as antinuclear antibodies, anti-smooth muscle antibodies and anti LKM antibody etc. Various toxins are described in the process of cirrhosis formation. Arsenic and phosphorus poisoning and therapeutic agents like methotrexate and amiodarone are known to cause cirrhosis liver. Indian childhood cirrhosis is rare

but known entity to cause liver cirrhosis.

Syphilis causes cirrhosis in neonates but not in adults. Schistosomiasis is another infectious cause reported to cause this disease process. Brucellosis, tuberculosis and sarcoidosis which causes focal granuloma, heal with fibrosis, but the liver does not show nodular regrowth. Cryptogenic cirrhosis is another rare entity in which the etiology is not known.

Diagnosis of cirrhosis

For the diagnosis of cirrhosis radiological investigations are much more important routine investigations. Nodules in the liver can be best suggested by ultrasonogram abdomen, but still it is not confirmatory for the diagnosis for particular liver pathology expected. Portal vein diameter and phasic flow changes in the portal vein are specific parameters for the detection of portal hypertension. In our study Portal vein diameter of greater than 13mm is considered to be a cut of value for the presence of portal hypertension. With both of these methods sensitivity goes up to 87% [11, 12]. Computerized Tomography is another important investigation used to diagnose presence of cirrhosis and its consequences.



CT SCAN SHOWING CIRRHOSIS AND ASCITES

Liver biopsy is ultimately confirmatory for the identification of pathological changes, particularly cirrhosis. But sensitivity of this invasive method is around 62% only. The Stains commonly used for the histopathology are collagen and reticulin. Van Giesen stain is used for the identification of scars, Specific portal zones. Elastin and silver stain used for sinusoids and reticulin fibres respectively.

Cirrhosis results in two major events apart from causing other features depending on the cause. On history, details regarding stomach pain, fatigue ,loss of appetite ,loss of weight, nonspecific gastrointestinal symptoms, yellowish discoloration of conjunctiva, Color of urine and altered color of faeces, Bilateral swelling of lower limbs and abdomen, bleeding from nose, gums, skin and alimentary tract, decreased libido should be asked about.

Past history about other relevant significant history about diabetes mellitus,

systemic hypertension, coronary heart disease, kidney disease details of drugs ingested and blood transfusion before 1986 and 1992 to rule out possibility of hepatitis B and hepatitis C should be asked. History of any particular illness running in the family should be asked. History of alcoholism consumption should be described in detail.

The clinical examination is important and should be correlated with history. More focus on nutritional status of the patient is needed and may give clue regarding chronicity of the problem. If the patient is febrile importantly spontaneous bacterial peritonitis should be ruled out and common causes of febrile illness should be also borne in mind. Details regarding fetor hepaticus, jaundice, pigmentation, purpura, should be also noted.

Finger clubbing which may occur in inflammatory bowel diseases may narrow down the diagnosis if correctly identified. Other Important signs such as koilonychia due to hypo albuminemia, spider nevi which also mimic like venous star, erythema involving inner hand, breast enlargement, reduced testicular size with loss of testicular sensation, Parotid gland enlargement which is specific for male alcoholics.

Dupuytren's contracture and distribution of body hair may direct the physician to search for other signs of liver cell failure .Note regarding peripheral edema should be made and cardiac, renal other causes of edema also should be ruled out.

On Per Abdomen examination evidence for free fluid in the abdomen like shifting

dullness or fluid thrill should be elicited. If not elicited with conventional methods puddle sign may help us to detect minimal fluid as little as 120 ml. Abdominal wall veins if noted their direction should be specified since pattern in Portal hypertension is just the exaggeration of normal pattern and should be examined in sitting or standing posture if possible.

Liver span should be measured since it may be reduced in cirrhosis of liver. Palpation of the spleen should be done since its presence signify the presence of portal hypertension. If not palpable, try to find splenic enlargement with percussion methods like Nixon's, castell's and traube's method.

Central nervous system examination is critical since it helps in the diagnosis of hepatic encephalopathy and may change the direction of the management, particularly drug prescription. Tests to detect minimal hepatic encephalopathy can be done at bed side and the presence of asterixis should not be missed and other causes of flapping tremor should be also borne in mind.

All routine investigations such as Complete blood count, Renal function tests, liver function tests which includes Total bilirubin, direct bilirubin, indirect bilirubin, Aspartate aminotransferase, Alanine amino transferase, alkaline phosphatase, Gamma glutamyl trans-peptidase, total protein, serum albumin level, serum globulin level and chest x ray, electrocardiogram, urine analysis should be done. Prothrombin time including INR, apTT should be done.

If ascites present, ascitic fluid analysis should be sent with aseptic diagnostic paracentesis. Daily weight chart and abdominal girth chart should be maintained.

Simple urine analysis for presence of albumin in the urine may give additional clue to the diagnosis.

Various antibodies are important if diagnosis of autoimmune hepatitis is contemplated. Anti-nuclear antibodies, anti-smooth muscle cell antibodies, anti mitrochondrial antibodies and anti LKM -1 antibody can be helpful in ruling out this condition. Viral markers such as HBs Ag, anti-HCV and other markers of hepatitis should be done if viral hepatitis comes across the diagnostic work up. Alpha fetoprotein which may be elevated in malignancy should be done if relevant.

Endoscopy may help to grade varices and to plan treatment also. Hepatic CT scan or ultrasound to confirm the presence of cirrhosis is ideal in the diagnostic work up. Use of Invasive procedures is limited in the diagnostic work up particularly if diagnostic work up is inconclusive after all possible diagnostic tests have been done.

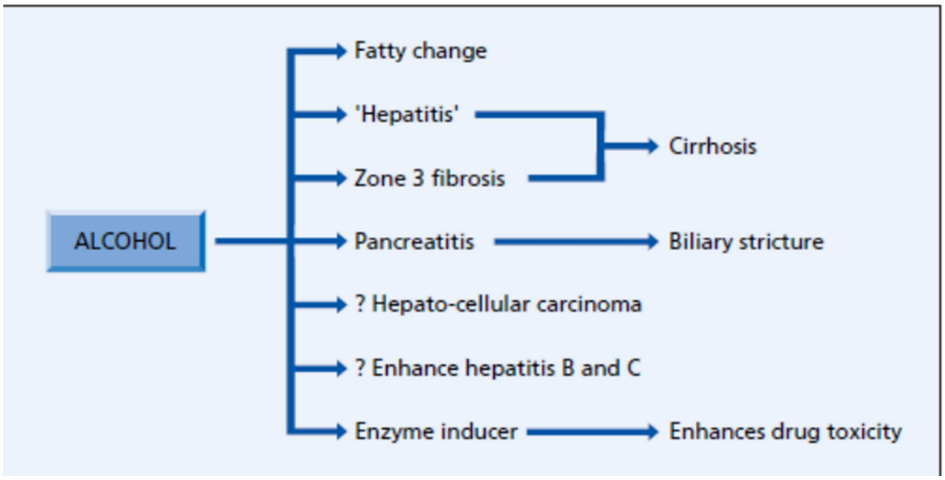
History of Mood disturbances, altered sensorium and loss of sleep are specified by attenders, central nervous system involvement can be better evaluated with EEG. Since most of the patients included in our study are alcoholic, discussion related with alcohol induced liver diseases is done here in detail.

Alcohol is the important causative factor worldwide. During the period of 10,000 B.C Alcohol have been used for its euphoric and recreational effects [2]. In Iron evidences were found for utensils used to prepare alcohol related drinks about 5000 B C [3]. In the Bible also evidences for alcohol use were found of that the

holy messenger Noah used to drink alcohol [4].Increase in taxes have been laid upon alcohol and related beverages in England in 1726 due to its increasing side effects on health.[5]. Once prime minister of Great Britain have talked and enumerated regarding the evil effects of alcohol to working people his country in a formal meeting advised them to quit from drinking. Ultimately strict laws were enhanced there to restrict their use and reduce their effect on health and sickness absenteeism.[6,7].

Liver damage doesn't develop in all those taking alcohol. Only 10-15% of those taking alcohol will develop fibrotic changes in the liver [14]. If males consume alcohol for about nearly eight year period, they may develop cirrhotic changes [15].The danger dose in most individual is higher than 80 g of alcohol /day. Religious beliefs, customs, cost of the alcohol.

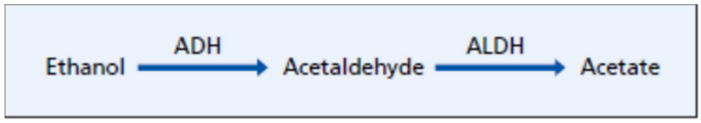
Economic status of the individual largely plays a role in the determination of the prevalence of alcoholic liver disease. If cost of the alcohol is lower, more socio economic group will be affected. Moreover, the type of beverage has no role in quantum of liver injury, but its alcohol content accounts. Alcohol content of 10 grams will be present in 30 ml of whisky, 100ml of wine and 250 ml of beer.



HEPATO-BILIARY EFFECTS OF ALCOHOL

Comparatively women are more prone to ill effects of alcohol more than males. They usually have the propensity for hastened pathological processes to cirrhosis much earlier than o males get their ill effects. Frequent relapses are also reported and the real reason behind this propensity is still under investigation. Even if they stop alcohol they may show disease progression [16].

Genetic studies have been carried out to reason out rate of elimination of alcohol in different people and gene polymorphism of enzyme system could be the probable cause [17].The rate at which alcohol is removed from our body is decided by different iso-enzyme pattern of enzyme mentioned below in the picture description. Actually alcohol supplies nutritionally valueless calories. 1 gram of alcohol supplies 7 calories.200 gram supplies approximately 1400 calories.



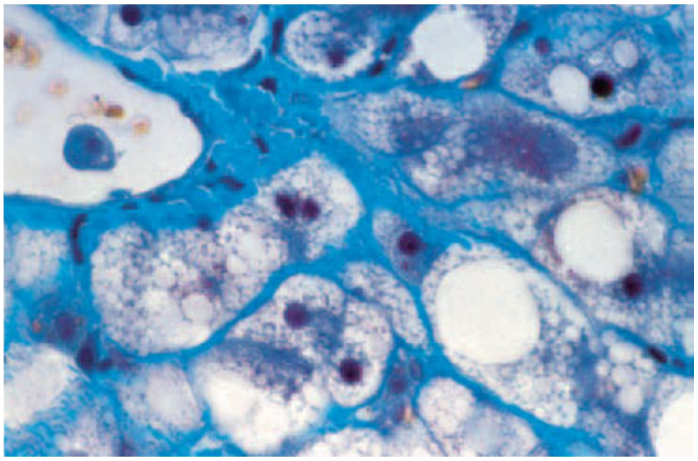
Alcohol metabolism in the liver. ADH, alcoholdehydrogenase; ALDH, aldehyde dehydrogenase

Hepatotoxic effects of acetaldehyde:

1. Increased lipid peroxidation
2. Binding with plasma membranes
3. Problems of electron transport chain of mitochondria
4. Inhibition DNA repair process
5. Micro tubular functional abnormality
6. Protein adduct formation
7. Activation of complement Stimulates superoxide formation by Neutrophil produces super oxide radicals due to complement activation.
8. Hastened and altered synthesis of collagen

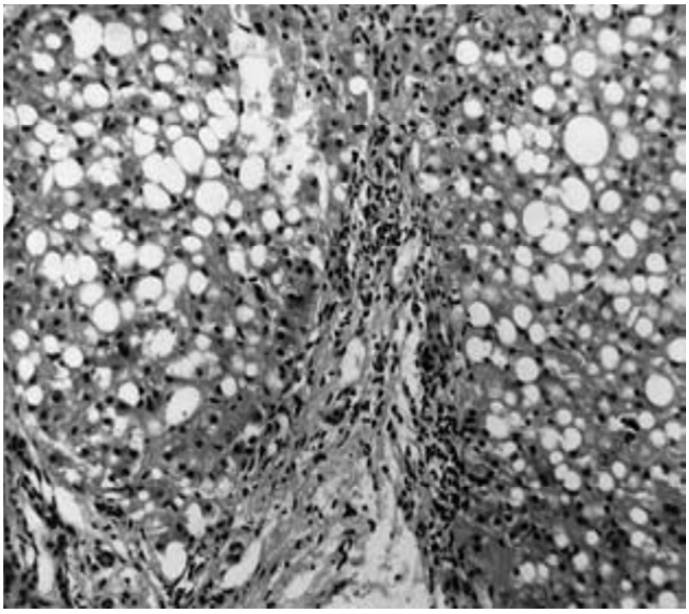
Morphological changes occuring in alcoholics are divided into,

1. Fatty liver
2. Alcoholic hepatitis
3. Cirrhosis



HISTOLOGY OF ACUTE ALCOHOLIC HEPATITIS.

Alcoholic hepatitis histologically described with the following features such as Mallory bodies, Balloon degeneration, Sclerosing hyaline necrosis, Acidophilic bodies, Mallory bodies, Giant mitochondria.



HISTOLOGY OF CIRRHOSIS

Cirrhosis in alcoholics is classically micro nodular. But macro nodular pattern of cirrhosis will develop along with micro nodular pattern with the attainment of reduced fibrosis. Histologically it is very difficult to ascertain the cause of cirrhosis when this end stage of histological picture results. In approximately one third of alcoholics there will be increased hepatic iron.

Screening of alcohol use and its overuse can be better detected by specific questionnaires which used to ascertained dependence of substance use and its abuse and these include the CAGE [18] ,The MAST and The AUDIT[19].

The CAGE questionnaire includes the letters such as C, A, G and E. Each alphabet denotes one question to be asked from the patient who should answer in the presence of observer. It He says ‘ yes’ for one question it signifies alcohol use and if answered for two questions it is concluded that alcohol dependence status to further evaluated in the given patient and treatment direction may be changed further.

Another questionnaire used in the screening of alcohol abuse alcohol dependence is AUDIT questionnaire. This is difficult to use at bed side, but valuable in screening alcoholics.

Questions	0	1	2	3	4
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
3. How often doyou have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. how often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10. Has a relative, friend, doctor or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year

To score the AUDIT questionnaire, sum the scores for each of the 10 questions. A total ≥ 8 for men up to age 60, or ≥4 for women, adolescents, or men over age 60 is considered a positive screening test.

Score of our study to be correlated with serum interleukin level in assessing disease severity is child pugh score which includes scores from five to fifteen. It contains the following entities such as prothrombin time in seconds, serum albumin level, and serum bilirubin level. Scores of 5 and 6 being Child class A means the score of five and six and said that patient is in compensated state of cirrhosis. Child class B includes scores of seven to nine, and Child class C includes scores of ten to fifteen.

This scoring system was initially devised to stratify patients into risk groups prior to undergoing portal decompressive surgery. The Child-Pugh score is a reasonably reliable predictor of survival in many liver diseases and predicts the likelihood of major complications of cirrhosis such as bleeding from varices and spontaneous bacterial peritonitis. It was used to assess prognosis in cirrhosis and to provide the standard criteria for listing liver transplantation (Child-Pugh class B).

Patient survival rate at one and two year can be better with this scoring system. For Class A, it is100% and 85% respectively; for Class B It is 80% and 60% percent respectively and for Class C it is 45% and 35% respectively[24,25]. Patients with a Child pugh score of less than 8 had a higher survival rate at 90 days compared with patients whose score was 8 or greater(95 versus 30 percent)[27].

CHILD PUGH SCORE	1	2	3	Score	Child cl
Ascites	None	slight	moderate	5-6	A
Encephalopathy	None	Grade1 to 2	Grade 3 to 4	7-9	B
Serum bilirubin	<2.0	2.0-3.0	>3.0	10-15	C
Serum Albumin	>3.5	3.5-2.8	<2.8		
PT(sec inc more than control)	0-4	4-6	>6		

Another similar classification system related with child pugh classification and not used in our study is Child turcotte classification system which was originally proposed more than 30 years ago [28]. It was originally designed for predicting the outcome after surgery for portal hypertension in patients with cirrhosis. The variables used are level of ascites, level of encephalopathy, serum bilirubin level, serum albumin level and nutritional status of the patient [28].A modified version of child's score which was discussed and used in our study was proposed 20 years ago [29].

CHILD TURCOTTE SCORE	A	B	C
Ascites	none	Easily controlled	Poorly controlled
Encephalopathy	none	mild	advanced
Serum bilirubin	<2.0	2.0-3.0	>3.0
Serum Albumin	>3.5	3.5-3.0	<3.0
Nutrional status	excellent	good	Poor

The most used one and simple to use is Maddrey (modified) Discriminant Function score [20]. It contains two variables such as difference in prothrombin time and total bilirubin in mg/dl. Here is the formula to calculate modified discriminant function.

Modified Discriminant Function = 4.6* (PT patient-PT control) +serum bilirubin. It indicates poor prognosis if score is greater than thirty two in alcoholic hepatitis. One month mortality rate is calculated with this formula that if score is greater than or equal to 32 are at increased risk of mortality which is between thirty and fifty percent [21].

Other system has also been proposed to stratify patients and includes serum bilirubin, serum creatinine and International normalized ratio. It is called model for end stage liver disease score [22].The formula used to calculate MELD score is as follows,

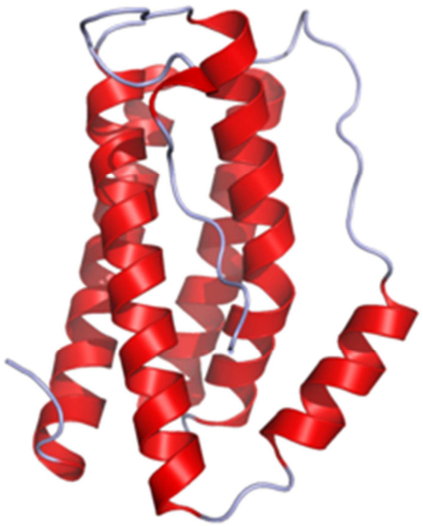
Model for end stage liver disease score = 3.8 * loge (serum total bilirubin) + 11.2 * loge (International normalized ratio) + 9.6 *loge (serum creatinine) + 6.4

If MELD score is greater than 18, it indicates poor prognosis in alcoholic hepatitis.

One more score is there to assess the prognosis of alcoholic hepatitis. It is Alcoholic Hepatitis score of glasgow. Variables used are patient's age, blood urea level, white ell count, PT ratio and bilirubin in mg/dl. If score is greater than 8, it is considered to be poor.

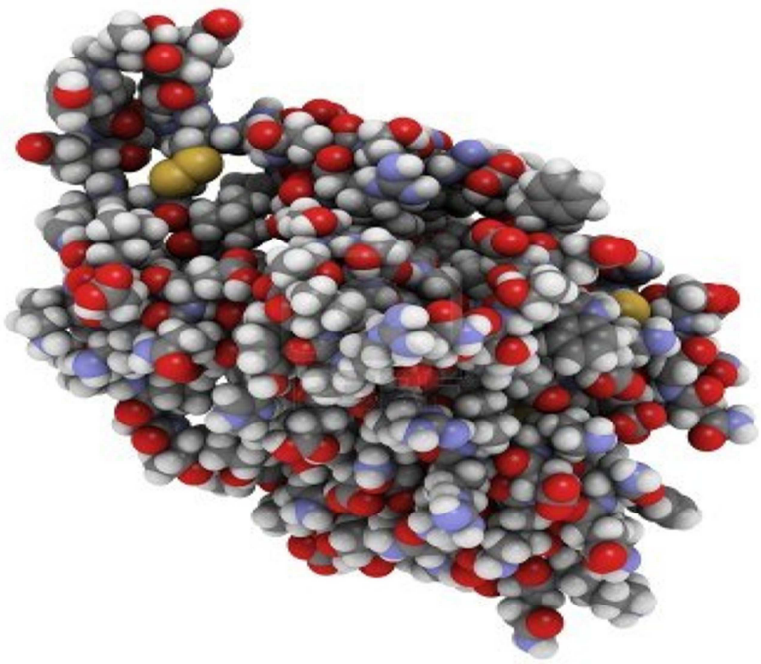
Interleukin 6

Interleukin-6 is the serum substance of which level is correlated in our study with modified child pugh score in liver cirrhotics. Certain properties of Interleukin 6 are discussed here.



CRYSTAL STRUCTURE OF IL-6

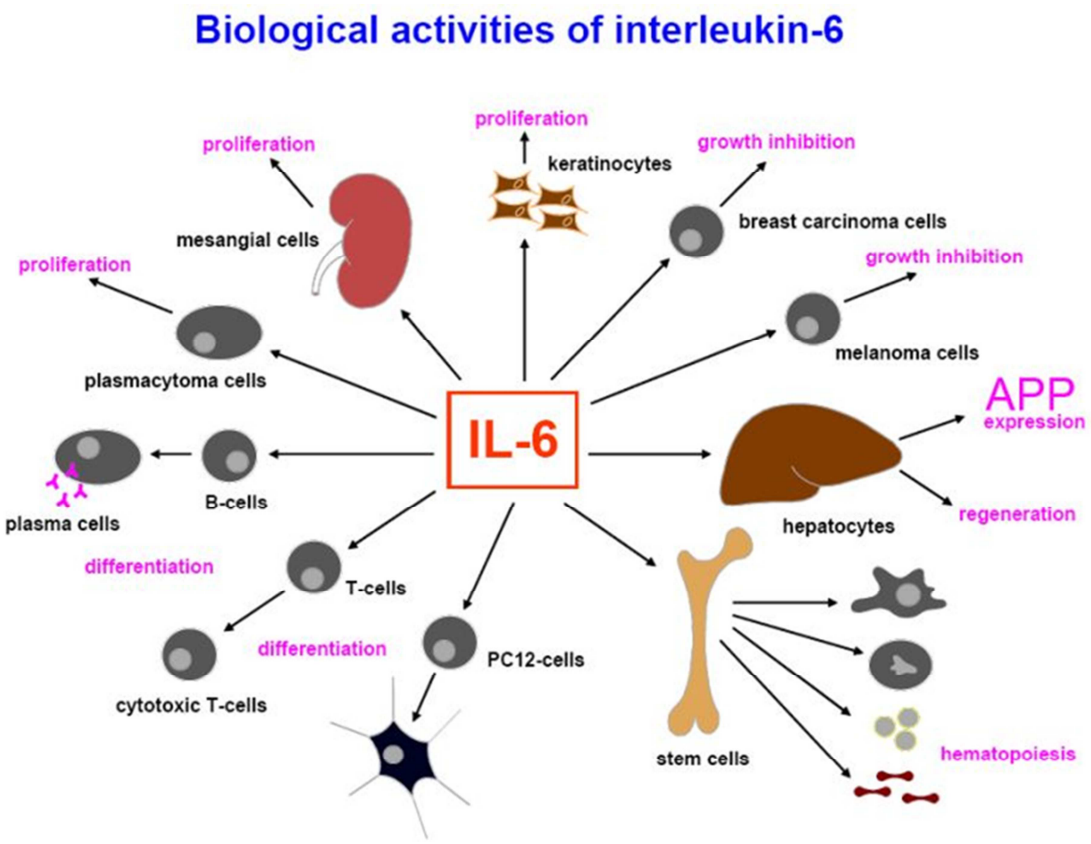
Interleukin-6, a monomer of 184 amino acids, is a multifunctional pleotropic cytokine having important function in the regulation of immunity, inflammatory reaction in various sites of our body, haematopoiesis and cancer biosynthesis. Its functions are shared by other cytokines like leukemic inhibitory factor, ciliary neutrotrophic factor, and oncostatin [30].



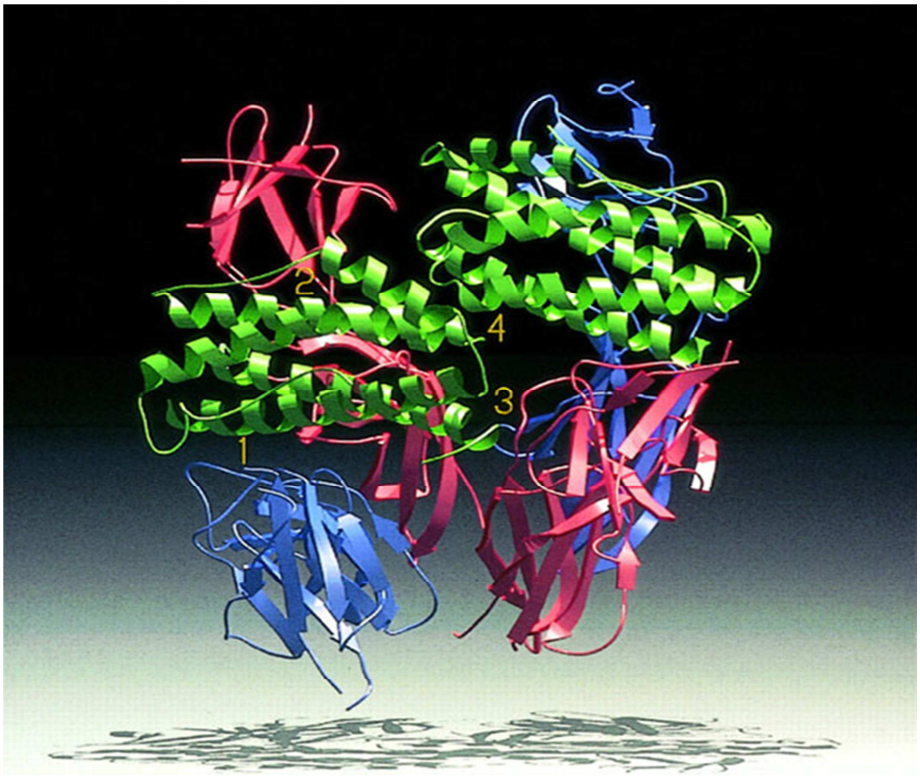
CHEMICAL STRUCTURE OF IL6

Interleukin 6 has its own exclusive system which consists of two components such as a Receptor specific for IL-6 andgp130, the common signal transducer of cytokines related to IL-6[31, 32, 33]. The transduction through gp 130 is processed through two important pathways of which the JAK STAT pathway and the RAS MAP kinase pathway and their individual structure and function specifically identified [34].

Both anti-inflammatory and pro-inflammatory properties of this cytokine are well elucidated .Gene is located in 7 p 21 chromosome in human beings [35]. Both T cells and macrophages release interleukin 6 to augment immune response.



Interleukin-6 is also important in fighting against infection, One important bacteria, pneumococci is inhibited with the help of interleukin 6.This study was conducted in mice and proved [36]. During muscle contraction it has been shown that level of this cytokine will be elevated. So it is also called myokine [37]. Mobilization of substances into cell will be accomplished with the help of this cytokine while doing exercise and hormone like action is expressed here. [38]



IL-6 WITH ITS RECEPTOR (IL 6R IN BLUE)

Osteoclast is formed due to stimulation by interleukin 6 which production by osteoclast is well documented. Middle layer of blood vessel also produce Interleukin 6.It inhibits other cytokine such as TNF-α and IL-1 and so exhibiting anti-inflammatory action which also done with stimulation of Interleukin 1 and Interleukin 10.It is one of the important mediator of acute phase response and of fever. It can invade central nervous system and start prostaglandin synthesis thereby regulating body's temperature [39].

Macrophages also secrete IL-6 in response to Specific microbial molecules. Cloning process well utilizes Interleukin 6 for the growth of cells and proved to be

effective. Estrogen use in the treatment of osteoporosis especially in old aged Women. Obese individuals are known to have higher level of interleukin 6 and subsequent studies showed that adipocytes could be also a source of this cytokine [40].

IL-6 is involved in many diseases such as diabetes mellitus [41], fat metabolism atherosclerosis [42], depressive illness and other psychiatric illnesses [43], alzhiemer's disease [44], lupus disease [45], cancer of prostate gland [46], and rheumatoid arthritis and related disorders [47]. Patients with advanced malignancy are proved to have elevated level of interleukin 6 [48].

Synthesis of steroids also is controlled by this cytokine since its action on hypothalamus and pituitary gland could be the possible mechanism. Stimulation of growth hormone secretion and inhibits TSH secretion are also part of the endocrine function of this hormone.

During stress its level is elevated and is positively controlled by catecholamines. In steroid withdrawal syndrome there will be elevate level of Serum Il-6. Normal process of aging is also involved elevated level of Interleukin 6[49].

Correlation of IL-6 level with CHILD PUGH score

It is found that Serum Interleukin 6 level is elevated in liver cirrhosis. In one study both cases of viral hepatitis and alcoholic liver diseases were included as causative factors. Serum Il-6 values are increased with progressive detioration of liver function. Interleukin 6 level in patients with child class C higher than with

child class B and A [50].Cirrhosis patients are reportedly known to have elevated level of Interleukin 6[51].

Positive correlation has been mentioned in one study that several serum inflammatory cytokines including IL-6 and severity of liver cirrhosis are well described. Moreover this correlation is independent of etiological factors like alcoholic liver diseases and viral hepatitis [52].In one study increasing values of IL-6 and TNF alpha are proved in concordance with severity of cirrhosis. For IL 6 child class A/B/C-(8.8/12.3/18.9pg/ml) respectively and for TNF alpha (36.9/42/51.7 pg/ml)[53].

The mechanism of raised serum IL-6 level in patients can be explained from the details of following study. Decreased hepatic uptake of Interleukin 6 is a reason due to which increase in the level of serum Interleukin 6 observed in cirrhosis. Healthy liver extracted 43% of portal vein derived IL-6, but cirrhotic liver only extracted 6.3% of IL-6 and showing that decreased removal by cirrhotic liver. Cause of liver cirrhosis did not affect hepatic removal rate telling that elevate level of Interleukin 6 synthesis in liver cirrhosis [54].

In another study it was highlighted that increased levels of serum IL 6 in patients with liver diseases may be protective, since IL-6 deficient mice is reported to have higher propensity for alcohol mediated injury, and exposure with IL-6 improved hepatic steatosis in these IL-6 deficient mice [55].To support this above mentioned issue, another study saying that in the protection of ethanol mediated liver injury IL-6 plays an important role. The expression of anti-apoptotic Bcl-2,

Bcl-xL proteins in the liver of chronically ethanol fed mice and human ALD is induced by elevated level of IL-6.So in the treatment of acute fulminant hepatic failure IL-6 could be used [56].

Serum concentration of IL-6 and IL-18 may be useful to discriminate cirrhotic patients with and without MHE, since there is a positive correlation between the level of IL-6 and IL-18 in patients with hepatic encephalopathy [57]. So by proving increasing levels of serum interleukin 6 in patients with and without portal hypertension, we can say that serum IL6 can be used as a marker with which severity of liver cirrhosis can be better assessed apart from other markers used in the assessment of severity of liver diseases.

MATERIALS AND METHODS

MATERIALS AND METHODS:

The center of study is Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai – 3.

Study Design : Cross sectional study.

Venue : Rajiv Gandhi Government General Hospital, Chennai

Collaborating Departments:

Institute of Biochemistry, MMC&RGGGH, Ch-3

Institute of Medical gastroenterology, MMC&RGGGH, Ch-3

Barnard Institute of Radiology, MMC&RGGGH, Ch-3

Duration : Study was conducted from June 2012 to November 2012

About fifty patients who attended our outpatient or got admitted in emergency department with history of Abdominal pain, Abdominal distention, Swelling of legs, jaundice, yellowish disc of urine reduced urine output, haemetemesis, melena, haemetochezia, fever, chills, rigor, loss of weight, loss of appetite, altered sensorium, mood changes and sleep disturbances were selected randomly. A complete history was taken either from the patient or his/ her attender including past history of jaundice, DM, hypertension, coronary artery disease, seizures, Cerebro vascular

accidents, COPD, history of prior surgery, malignancy, blood transfusion. His/her personal habits were enquired.

A complete physical examination was done with monitoring of vitals (temperature, pulse rate, respiratory rate and blood pressure) every day or frequently as the patient condition demanded. A battery of blood investigations were done including renal functions, liver functions test, Complete blood count, ECG, HBs Ag, HIV, Anti HCV, prothrombin time, apTT, Urine analysis Lipid profile, serum IL 6, Chest X ray, USG abdomen, Portal Doppler study, Ascitic fluid analysis and OGD scopy.

Serum Interleukin 6 level was measured **by ELISA method**. Pyrogen/Endotoxin free collecting tubes are used for sample collection. Serum is removed rapidly and carefully from the red cells after clotting. Following clotting, centrifugation done at approximately 1000 x g for 10 min and Serum removed. Shortly after collection, samples are aliquoted (250-500µl) to avoid repeated freeze-thaw cycles and stored frozen at –70°C.

The sensitivity, minimum detectable dose of IL-6 using this IL-6 ELISA kit is found to be less than 2pg/ml. The assay recognizes both natural and recombinant human IL-6. To define the specificity of this ELISA several proteins were tested for cross reactivity. There was no cross reactivity observed for any protein tested (IL-1a, IL-1b, IL-10, IL-12, IFN gamma, IL-4, TNF alpha, IL-8 and IL-13).

The overall intra-assay coefficient of variation has been calculated to be 4.2%. The calculated overall inter-assay co-efficient of variation was 7.7%. This immunoassay is calibrated against the International Reference Standard NIBSC 89/548. NIBSC 89/548 is quantitated in International Units (IU). 1IU is corresponding to 11pg of this given ELISA kit measurement of IL-6.

Inclusion Criteria:

Recently diagnosed/Known cases of cirrhosis of any cause with or without portal hypertension.

Age group: 25-50 years.

Exclusion criteria:

1. Cirrhosis with SBP
2. Hypertensive patients
3. Diabetic patients
4. Dyslipidemic patients

5. Connective tissue disorders

6. Any chronic inflammatory condition

7. Autoimmune liver diseases

8. Malignancy/metastasis

9. Haematological malignancy

10. Known coronary artery disease patients

Other co morbidities (COPD, pre-existing renal disease, thyroid disorders)

Statistical Analysis Plan:

Data analyzed using statistical package - SPSS EPI INFO Software

Consent

All participants / attenders gave written informed consent.

Ethical Committee Approval

Institutional Ethics Committee of Madras Medical College approved the study

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS:

In the study of fifty cases of Cirrhosis of varying causes admitted in Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai, the following observations were made in sex incidence, age distribution, distribution of duration (with Child class, Child score and Mean IL 6 level respectively), Child class with Mean IL6, Child class with Variceal grading, Child class with Mean Portal vein diameter, Child class with Mean SAAG, Child class with serum albumin, Child class with Mean total protein, Child class with Mean Hb %, Child class With Mean Platelet, Hb % with Mean IL 6, Platelet with Mean IL 6, Prothrombin time with Mean IL 6, No of HbsAg Positives and negatives, No of HCV Positives and Negatives, Serum albumin with Mean IL 6, SAAG with Mean IL 6, Portal vein diameter with Mean IL 6, Variceal grading with Mean IL 6 and Child class With Hb% as follows:

Total number of patients : 50

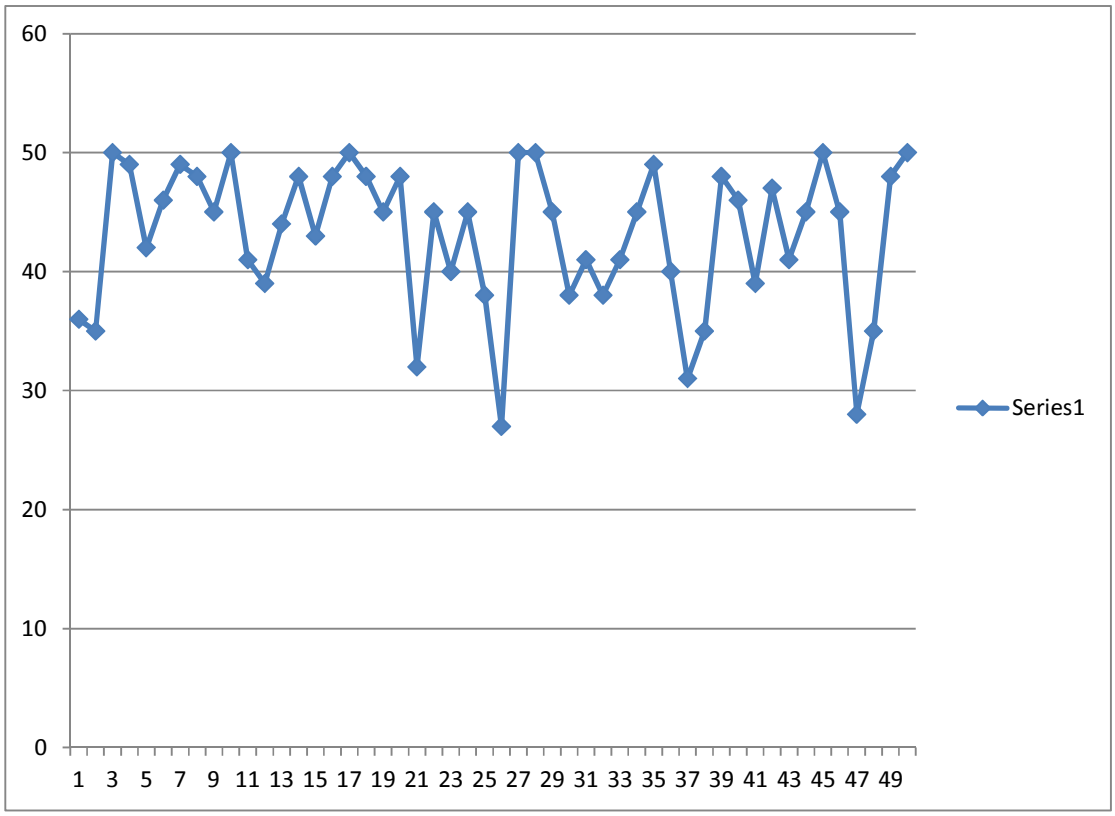
Total number of males : 47 (94%)

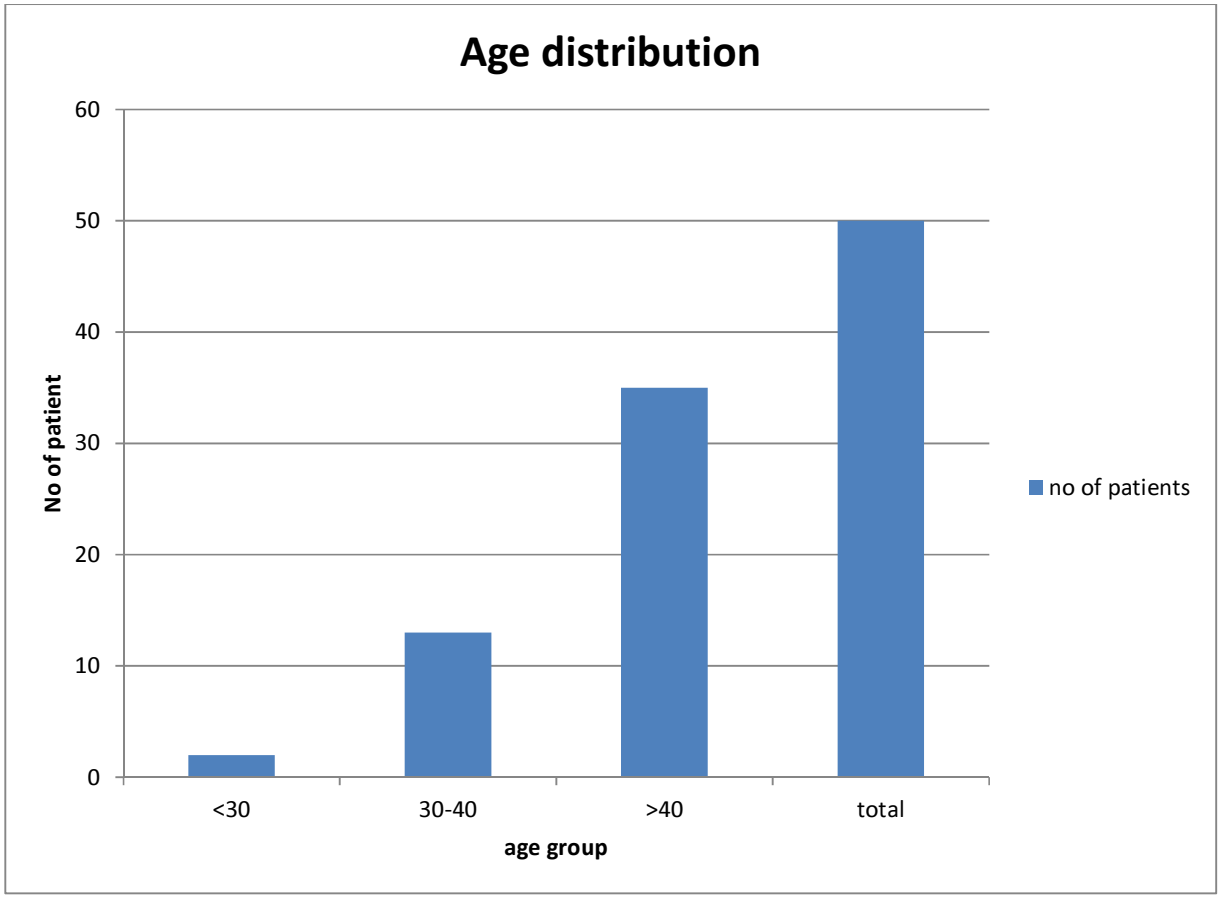
Total number of females : 3 (64%)

Age distribution

Age	No of patients	Percent
< 30	2	4.0
-40	13	26.0
> 40	35	70.0
Total	50	100.0

TABLE NO: 1





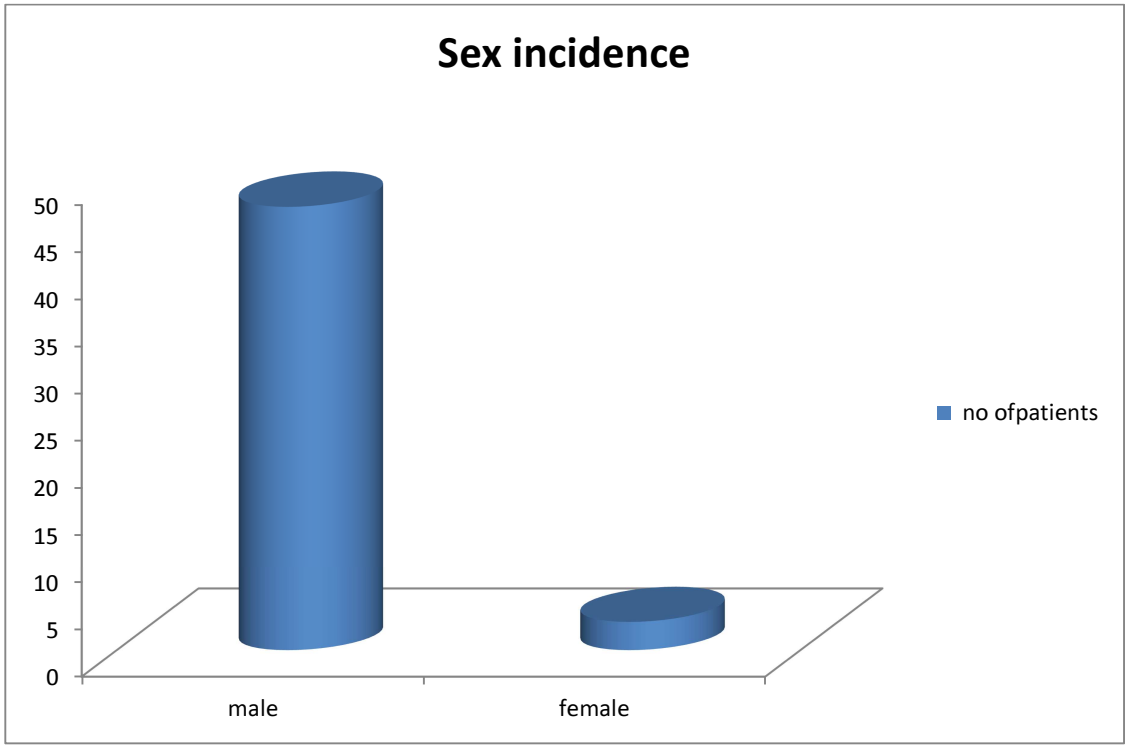
Patients with Age between 40 -50 were around 35(70%) and Patients with age less than 30 were just 2 in number.

So this study may tell u more about correlation of Child pugh score with Serum IL6 values in the age group of between40 and 50.

Sex incidence

Sex	Frequency	Percent
Male	47	94.0
Female	3	6.0
Total	50	100.0

TABLE NO: 2

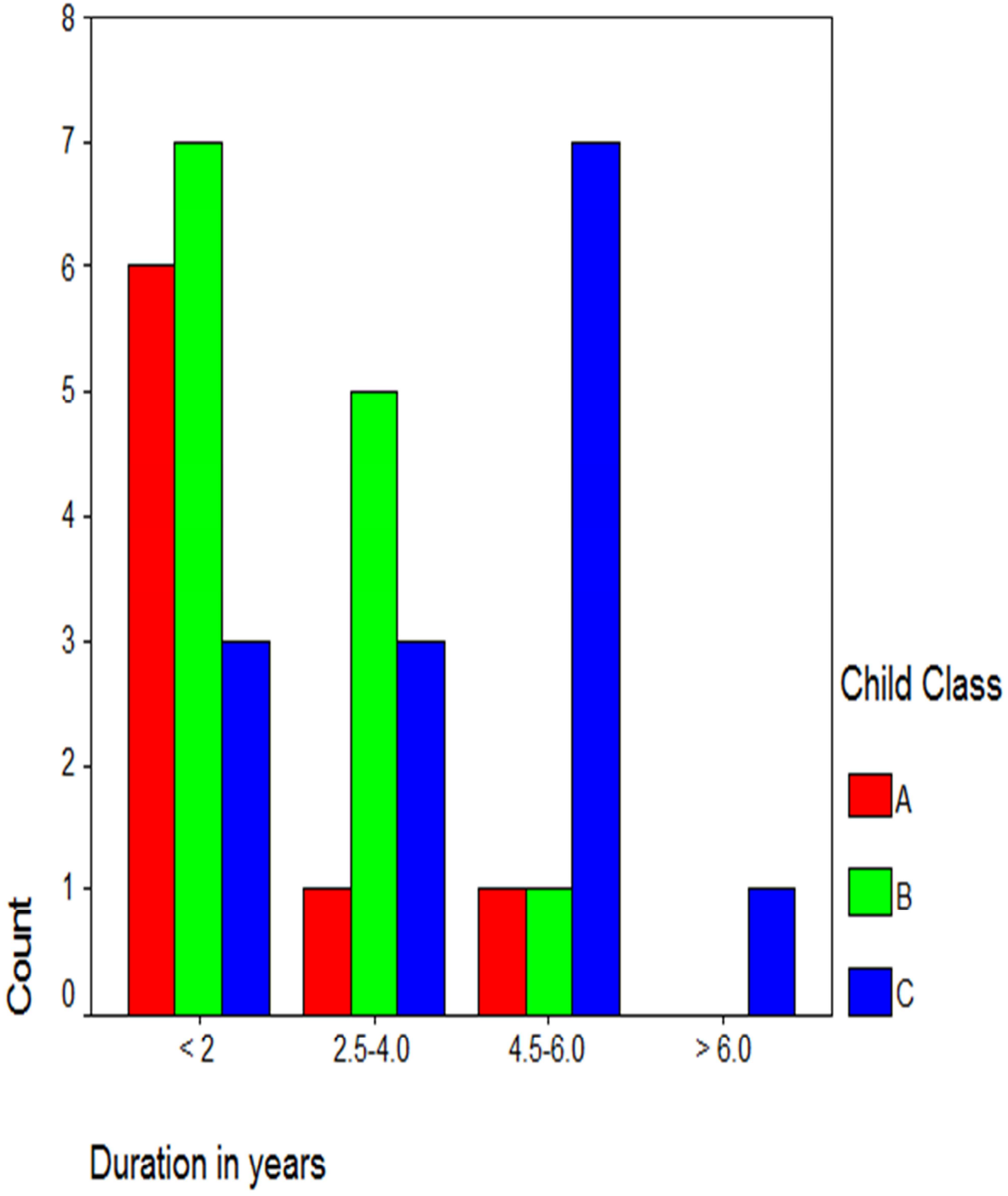


Total number of males included in this study was 47 and females 3 accounting for 94% and 6% respectively. Since Prevalence of Alcoholism was significantly higher in our study population and particularly in Males, males are higher in number in our study.

Duration of illness and Child class

Duration in years		Child Class			
		A	B	C	Total
< 2	Count	6	7	3	16
	% within Duration in years	37.5%	43.8%	18.8%	100.0%
	% within Child Class	75.0%	53.8%	21.4%	45.7%
2.5-4.0	Count	1	5	3	9
	% within Duration in years	11.1%	55.6%	33.3%	100.0%
	% within Child Class	12.5%	38.5%	21.4%	25.7%
4.5-6.0	Count	1	1	7	9
	% within Duration in years	11.1%	11.1%	77.8%	100.0%
	% within Child Class	12.5%	7.7%	50.0%	25.7%
> 6.0	Count	0	0	1	1
	% within Duration in years	.0%	.0%	100.0%	100.0%
	% within Child Class	.0%	.0%	7.1%	2.9%
Total	Count	8	13	14	35
	% within Duration in years	22.9%	37.1%	40.0%	100.0%
	% within Child Class	100.0%	100.0%	100.0%	100.0%

TABLE NO: 3



The p value is 0.065

Distribution of duration of illness with child class is explained here. Patient's duration of illness around 2 years is higher among all other groups such as group of 2.5 to 4 years, 4.5 to 6 years and > 6 years. Comparision of distribution of duration with Child class is no statistically significant since P value is 0.065.

Duration and child score

Duration in years		Child Score		
		< 10	> 10	Total
< 2	Count	14	2	16
	% within Duration in years	87.5%	12.5%	100.0%
	% within Child Score	48.3%	33.3%	45.7%
2.5-4.0	Count	8	1	9
	% within Duration in years	88.9%	11.1%	100.0%
	% within Child Score	27.6%	16.7%	25.7%
4.5-6.0	Count	6	3	9
	% within Duration in years	66.7%	33.3%	100.0%
	% within Child Score	20.7%	50.0%	25.7%
> 6.0	Count	1	0	1
	% within Duration in years	100.0%	.0%	100.0%
	% within Child Score	3.4%	.0%	2.9%
Total	Count	29	6	35
	% within Duration in years	82.9%	17.1%	100.0%
	% within Child Score	100.0%	100.0%	100.0%

TABLE NO: 4

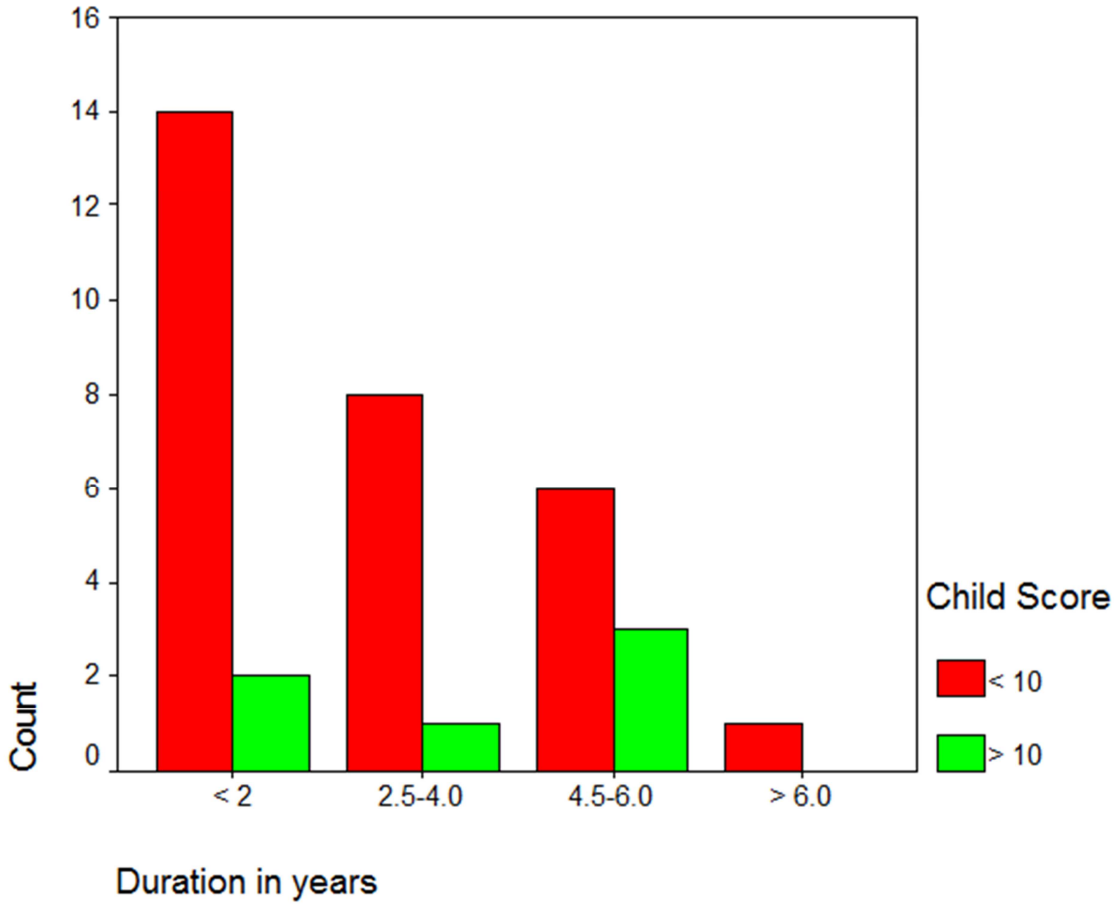
The p value is 0.505

Comparision of distribution of duration with Child pugh score is done here. Patients with child score less than 10 in the duration group of 2 years are 14(87.5%) and with greater than 10 is 2(12.5%).

Patients with child score less than 10 in the duration group of 2.5 to 4 years are 8 (88%) and with greater than 10 is 1(11%).

Patients with child score less than 10 in the duration group of 4.5 to 6 years are 6(66%) and with greater than 10 are 3(33%). Patients with child score less than 10 in the duration group of greater than 6.5 years is 1 and with greater than 10 is 1.

This correlation is not statistically significant since the P value is 0.505.



DURATION AND mean IL6

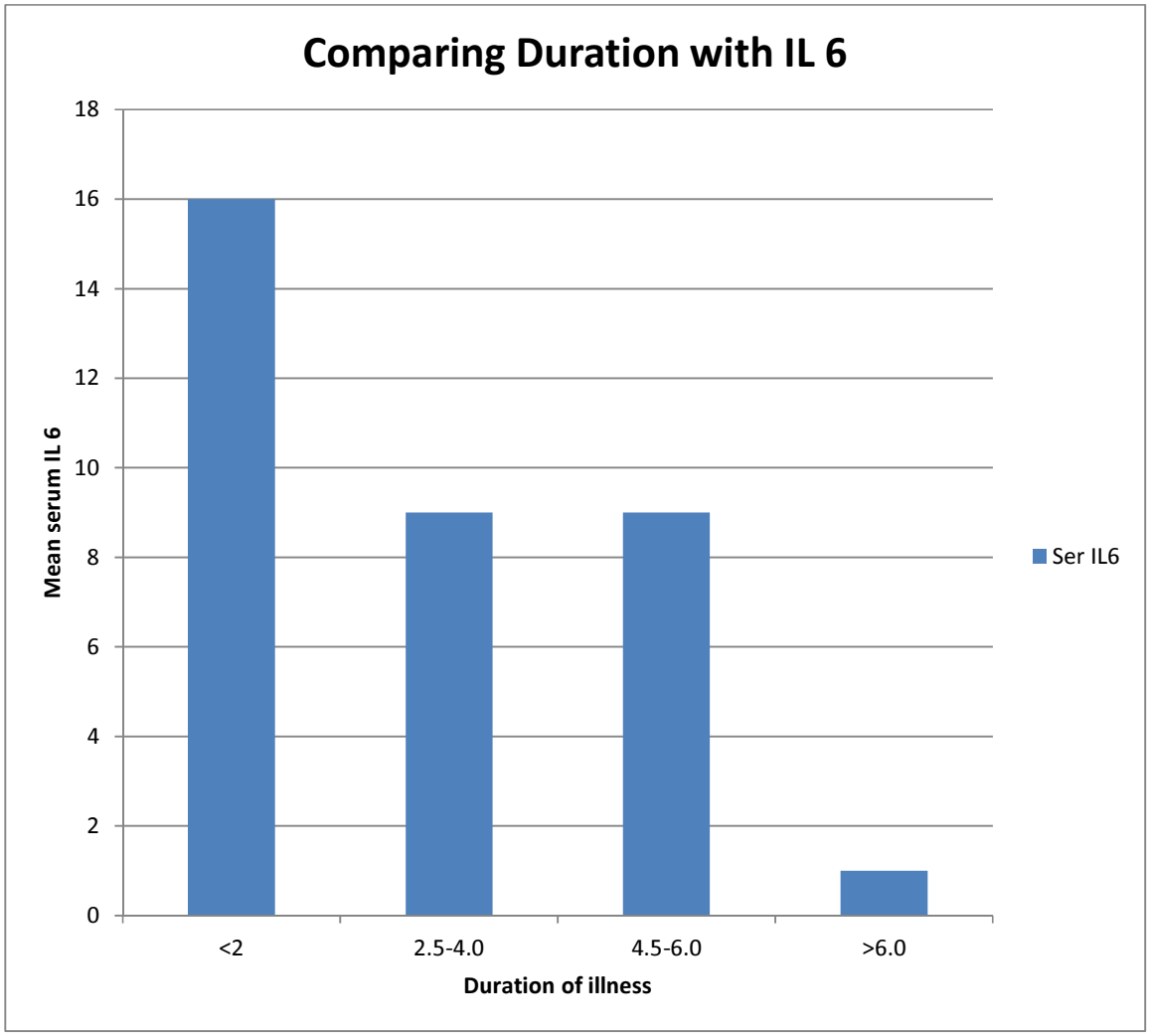
The p value is 0.061

Comparison of duration with mean IL 6value is done here. Mean IL 6 value of Patients with duration of illness less than 2 years is 12.281. Mean IL 6 value of Patients with duration of illness 2.5 to 4 years is 14.278. Mean IL 6 value of

Patients with duration of illness 4.5 to 6 years is 17.067. Mean IL 6 value of Patients with duration of illness greater than years is 16.400. Higher number of patient is in the duration group of less than 2 years. This comparison is not statistically significant since the p value is 0.061.

Duration in years	No of patients	Mean IL 6(pg/ml)
< 2	16	12.281
2.5-4.0	9	14.278
4.5-6.0	9	17.067
> 6.0	1	16.400
Total	35	14.143

TABLE NO: 5

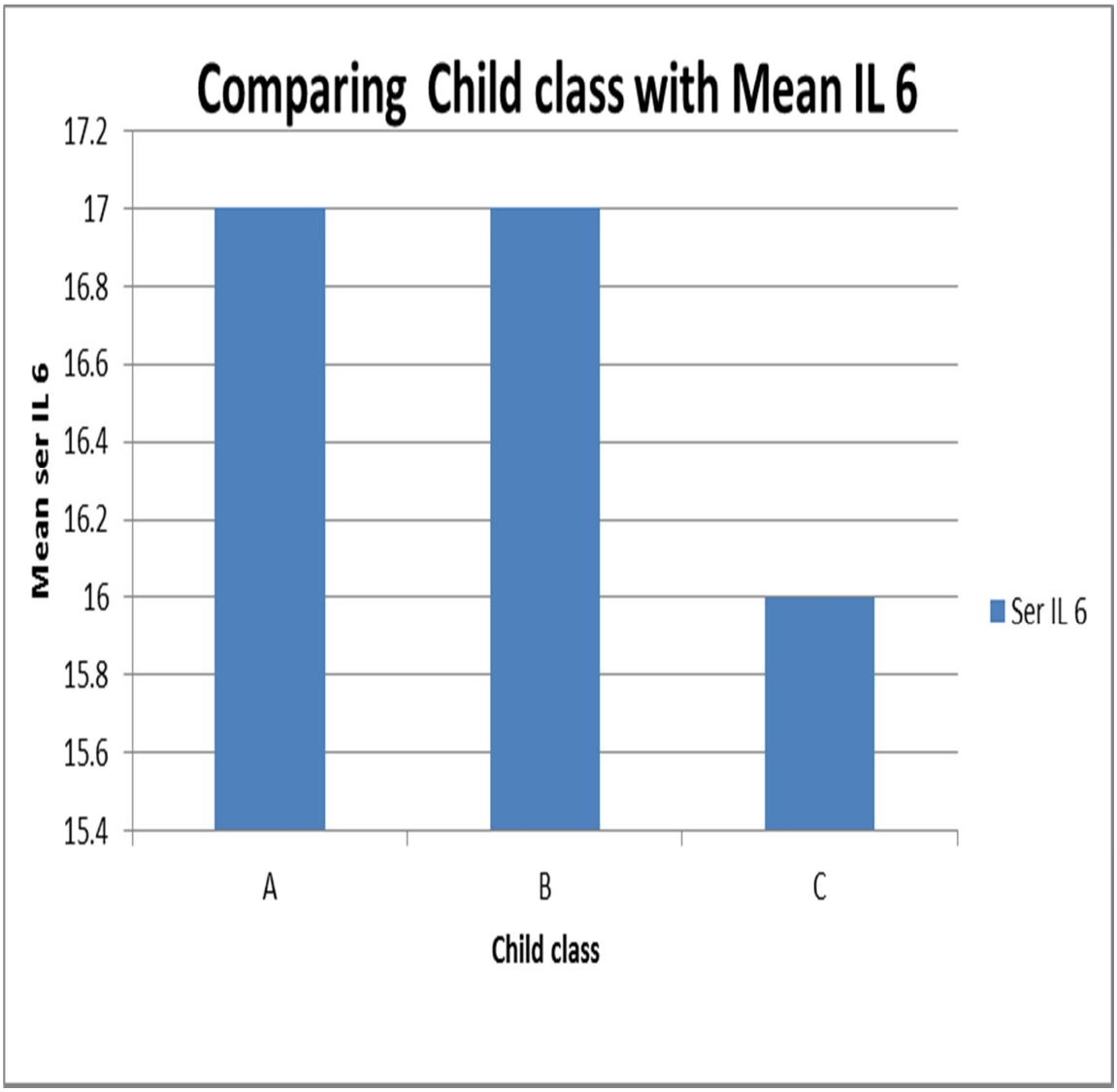


Child class and IL6

P value is .001

Here the comparison of Child class with Mean IL 6 value is done. Mean IL 6 value of Patients with Child class A, B and C are 8.876, 13.041 and

18.612pg/ml respectively. Increasing values of Mean IL 6 are proved here if Child classis increasing from A to C. So main objective of our study is statistically significant since p value is 0.001



Child class	No of patients	Mean IL 6(pg/ml)
A	17	8.876
B	17	13.041
C	16	18.612
Total	50	13.408

TABLE NO: 6

Child class and variceal grading

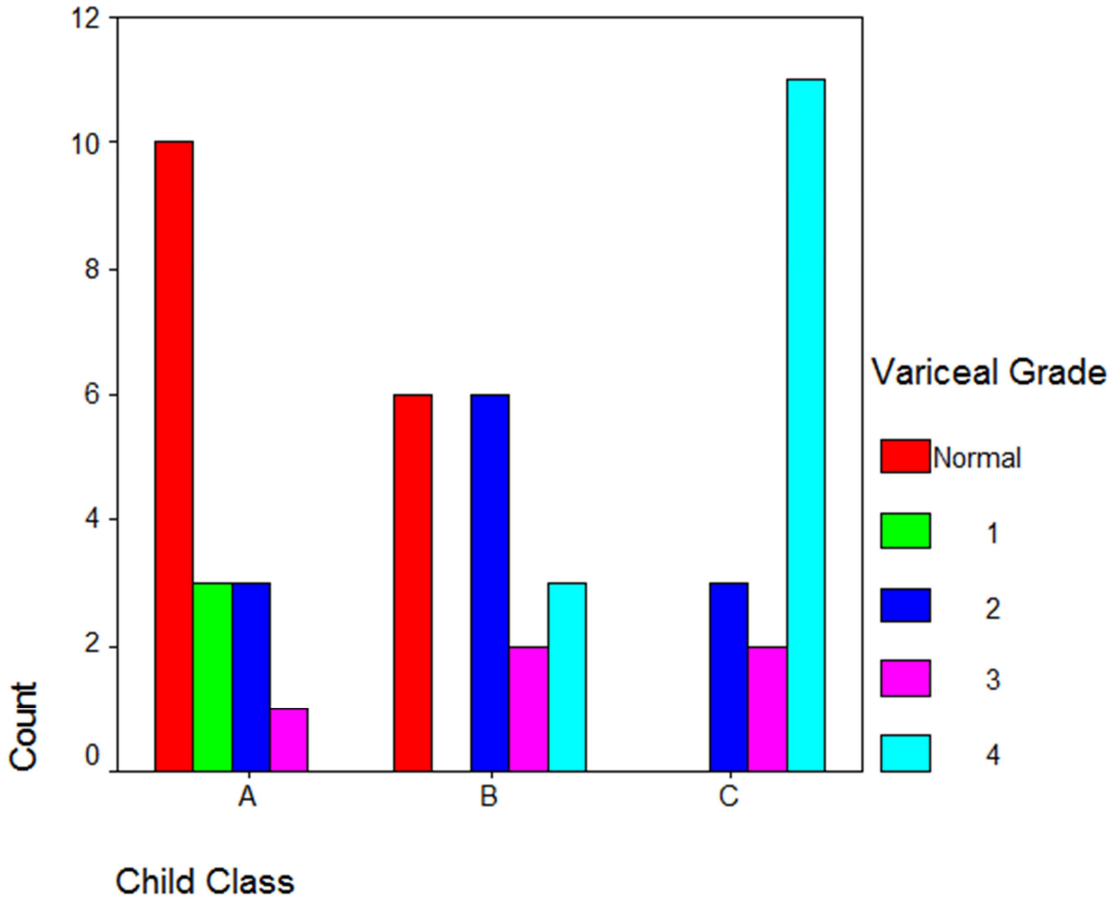
P value is .001

Here the comparison of Child class and variceal grading is done. Child class A having total number of patients 17 is observed here to have normal OGD scopy for 10 patients and variceal grading of 1 and 2 with number of patients each 3 respectively.

Child class C having total number of patients 16 is observed to have normal OGD scopy for 0 and grade 4 for 11 patients and grade 3 for 2 patients. So increasing values of variceal grading is observed if Child class is increasing. This correlation is statistically significant since p value is 0.001

Child Class		Variceal Grade					Total
		Normal	1	2	3	4	
A	Count	10	3	3	1	0	17
	% within Child Class	58.8%	17.6%	17.6%	5.9%	.0%	100.0%
	% within Variceal Grade	62.5%	100.0%	25.0%	20.0%	.0%	34.0%
B	Count	6	0	6	2	3	17
	% within Child Class	35.3%	.0%	35.3%	11.8%	17.6%	100.0%
	% within Variceal Grade	37.5%	.0%	50.0%	40.0%	21.4%	34.0%
C	Count	0	0	3	2	11	16
	% within Child Class	.0%	.0%	18.8%	12.5%	68.8%	100.0%
	% within Variceal Grade	.0%	.0%	25.0%	40.0%	78.6%	32.0%
Total	Count	16	3	12	5	14	50
	% within Child Class	32.0%	6.0%	24.0%	10.0%	28.0%	100.0%
	% within Variceal Grade	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

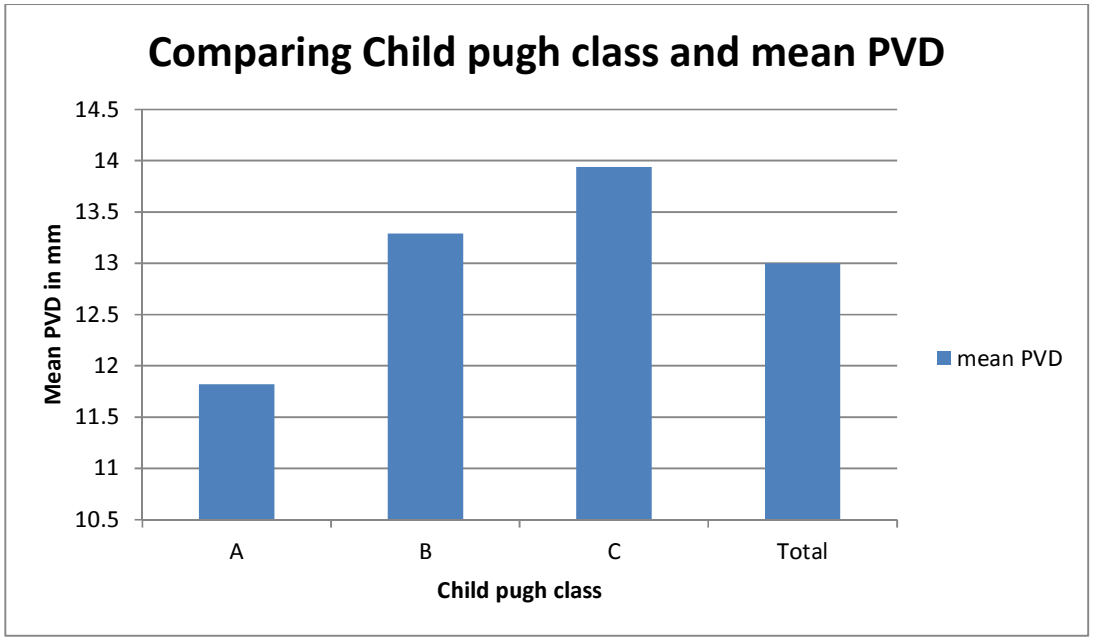
TABLE NO: 7



Child score and Portal vein diameter

Child class	No of patients	Mean PVD(mm)
A	1	11.82
B	17	13.29
C	16	13.94
Total	34	13.00

TABLE NO: 8



The p value is .001

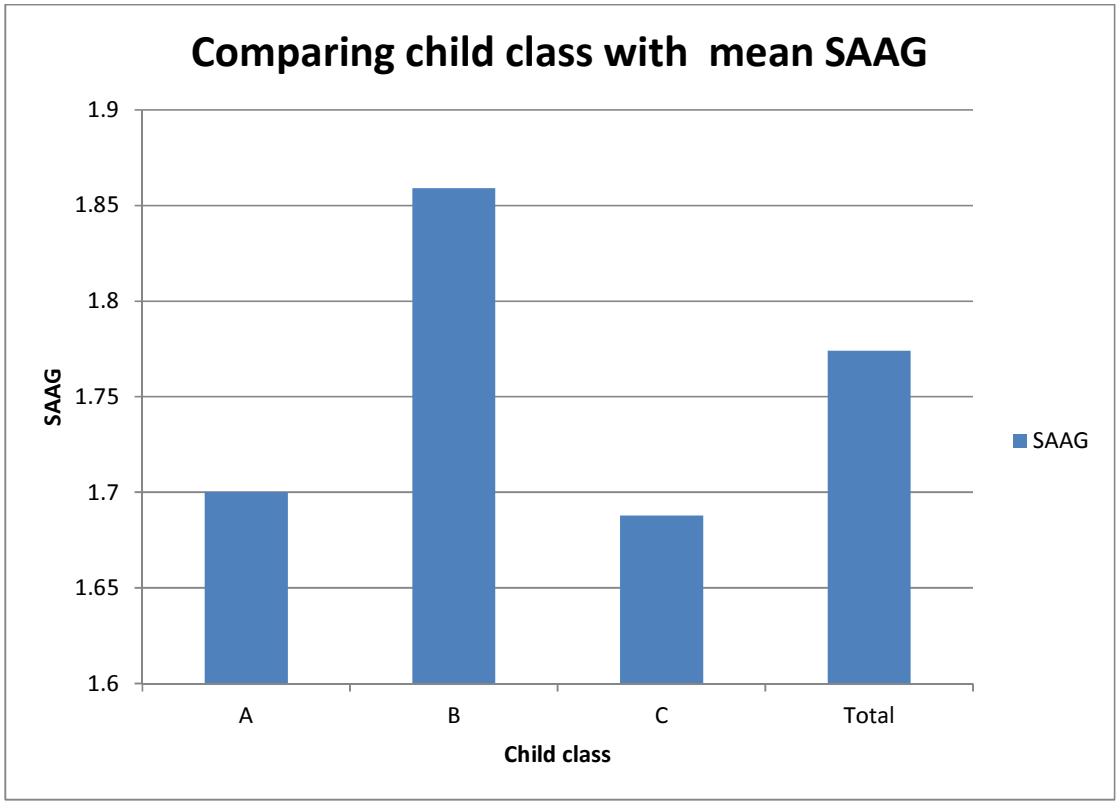
Here the comparison of Child pugh score with Portal vein diameter is done. Mean Portal vein diameter is increasing if Child class increases.

The mean Portal vein diameter of 11.82mm is obtained for child class A. The mean portal vein diameter of 13.29 mm is obtained for child class B. The mean portal vein diameter of 13.94 mm is obtained for child class C. The mean portal vein diameter of 13.00 mm is obtained for all patients in this study. This increase is statistically significant since p value for this comparison is 0.001

Child class and SAAG

Child class	No of patients	Mean SAAG
A	1	1.700
B	17	1.859
C	16	1.688
Total	34	1.774

TABLE NO: 9



The p value is 0.449

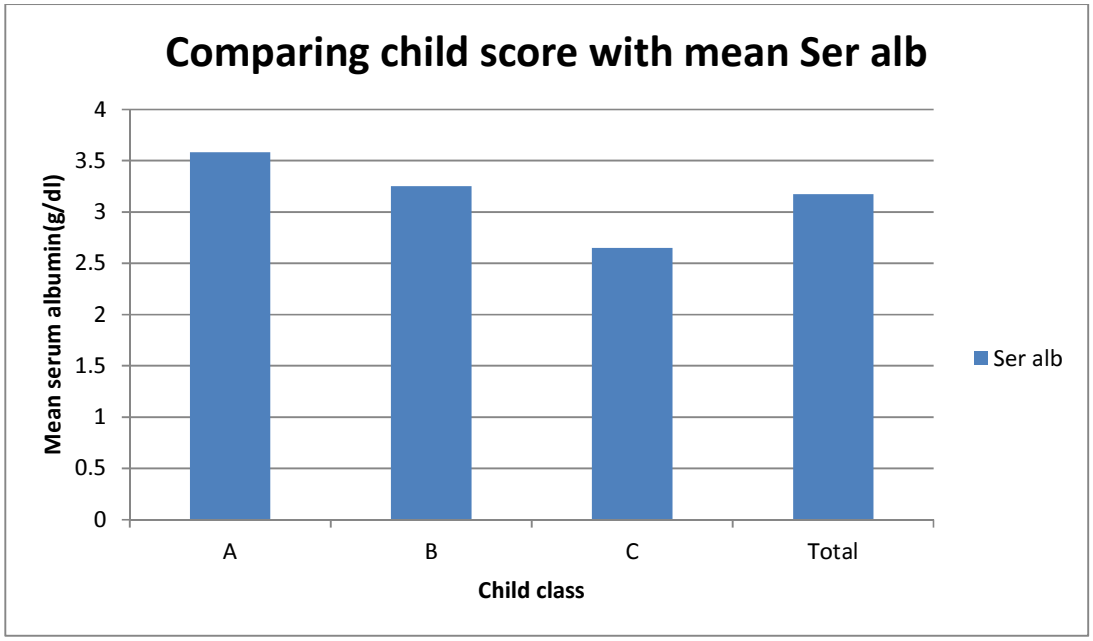
Here the comparison of Child class with mean SAAG value is done. The mean SAAG value for child class A is 1.700. The mean SAAG value for child class B is 1.859. The mean SAAG value for child class C is 1.688. The mean SAAG value for all patients is 1.774.

This correlation is not statistically significant since the p value is 0.449. Though the SAAG is very important to differentiate patients with and without portal hypertension, in our study it is not correlating well for the required work.

Child class and Serum albumin

Child class	No of patients	Serum Albumin(g/dl)
A	17	3.582
B	17	3.253
C	16	2.650
Total	50	3.172

TABLE NO: 10



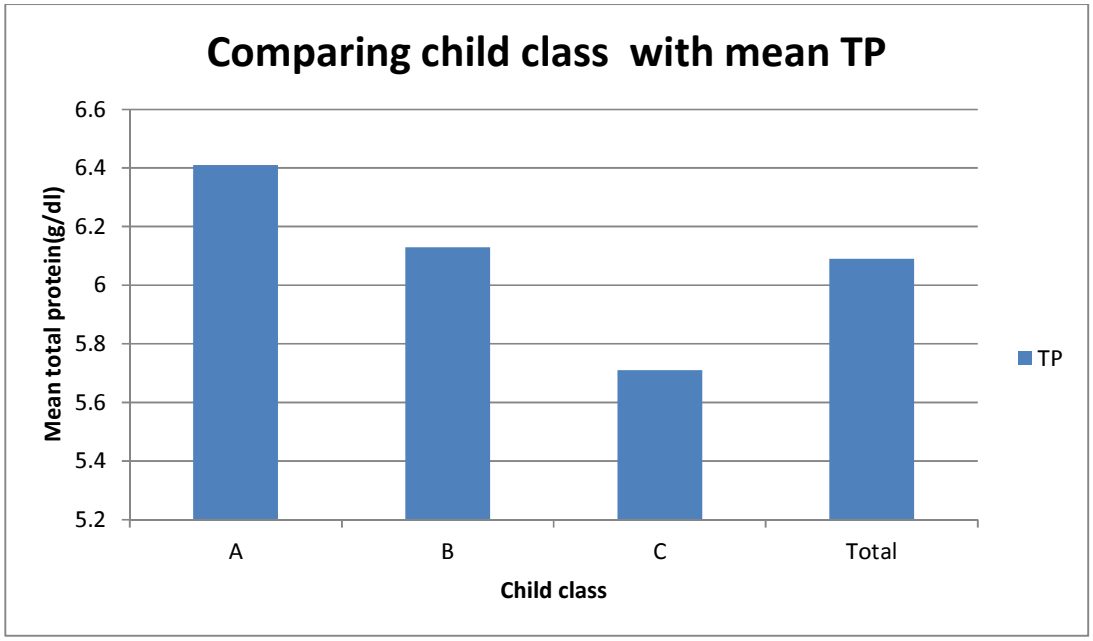
The p value is 0 .001

Here the comparison of Child class with mean Serum Albumin value is done. Serum albumin value decreases if child score increases from A to C. This correlation is statistically significant since the p value is 0.001

Child pugh score and Mean Total protein

Child class	No of patients	Mean Total protein(g/dl)
A	17	6.41
B	17	6.13
C	18	5.71
Total	50	6.09

TABLE NO: 11



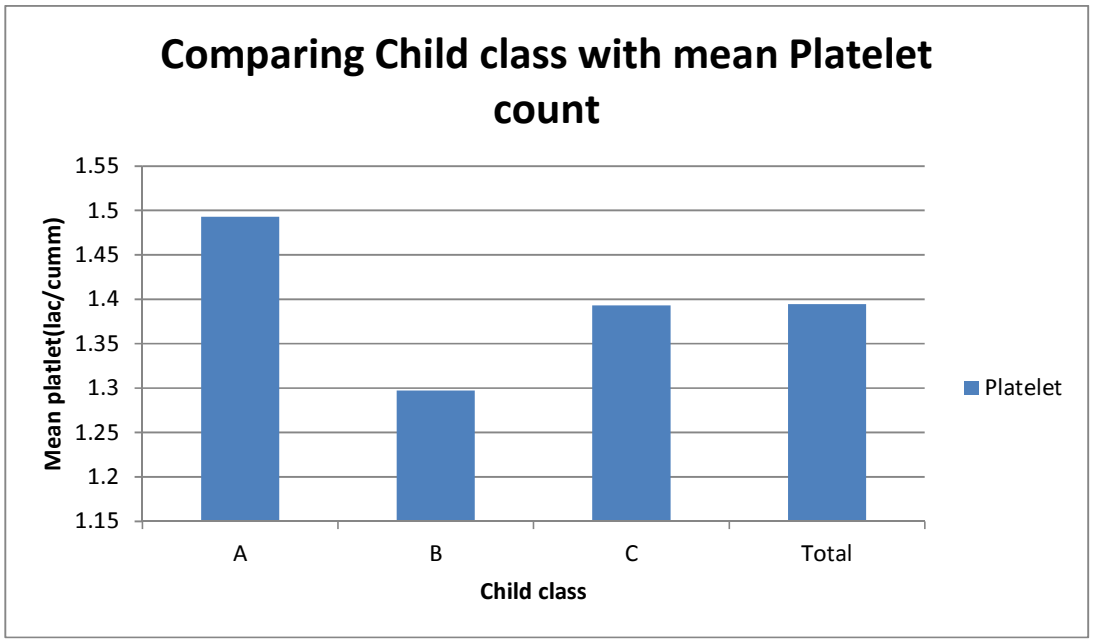
The p value is 0 .006

Here the comparison of Child class with mean Total protein value is done. Serum Total protein value increases if child score increases from A to C. This correlation is statistically significant since the p value is 0.006

Child pugh score and Platelet count

Child class	No of patients	Mean Platelet count(lac/cumm3)
A	17	1.4929
B	17	1.2971
C	18	1.3931
Total	50	1.3944

TABLE NO: 12



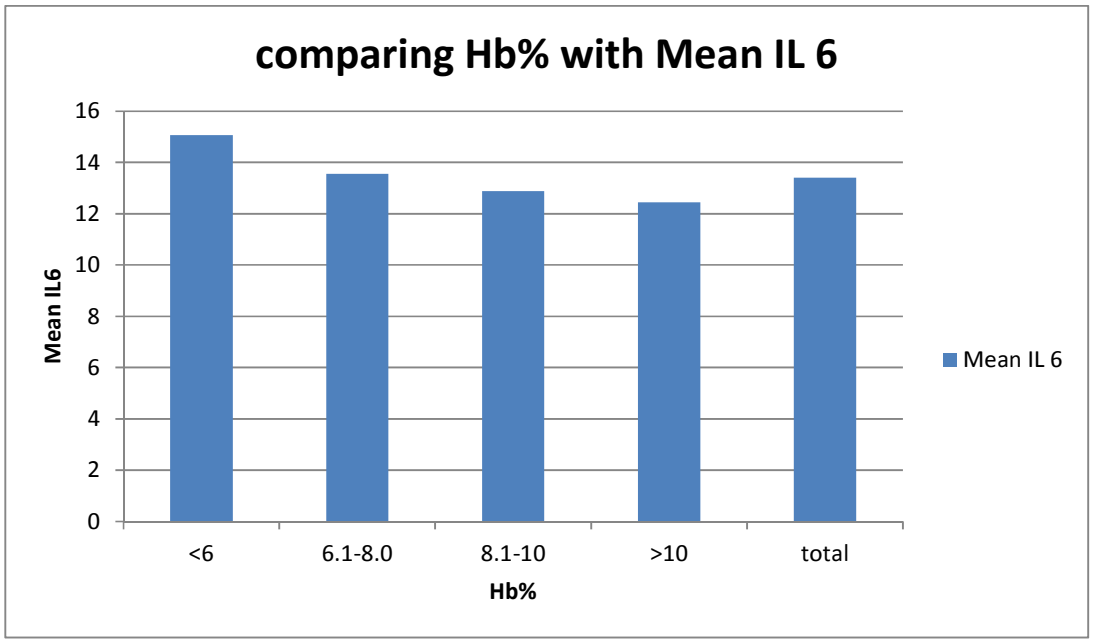
The p value is 0 .675

Here the comparison of Child class with mean platelet value is done. This correlation is not statistically significant since the p value is 0.675

IL 6 and Hemoglobin%

Hb%	No of patients	Mean IL 6(pg/ml)
< 6	11	15.064
6.1-8	12	13.558
8.1-10	14	12.871
> 10	13	12.446
Total	50	13.408

TABLE NO: 13



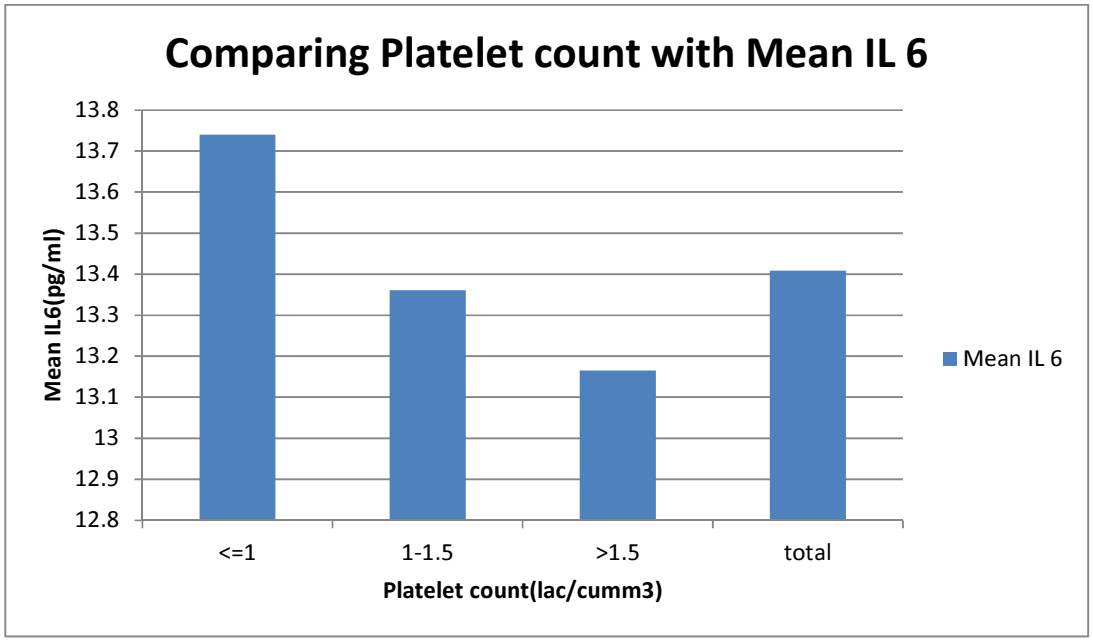
The p value is 0.536

Here the comparison of Hemoglobin with mean IL 6 value is done. This correlation is not statistically significant since the p value is 0.536

Platelet count with Mean IL6

Platelet count(lac/cumm3)	No of patients	Mean IL6(pg/ml
<= 1	15	13.740
1-1.5	18	13.361
> 1.5	17	13.165
Total	50	13.408

TABLE NO: 14



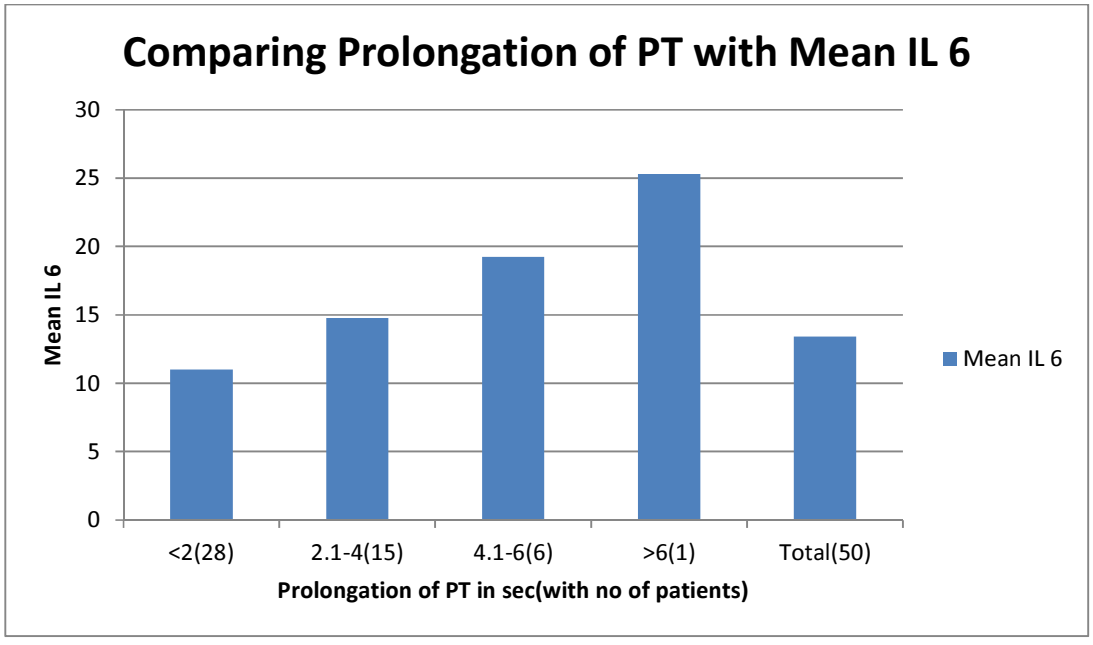
The p value is 0.939

Here the comparison of Platelet count with mean IL 6 value is done. This correlation is not statistically significant since the p value is 0.939

Prolongation of PT in sec with Mean IL6

Prolongation of PT(sec)	No of patients	Mean IL6(pg/ml)
< 2	28	11.011
2.1-4	15	14.760
4.1-6	6	19.233
> 6	1	25.300
Total	50	13.408

TABLE NO: 15



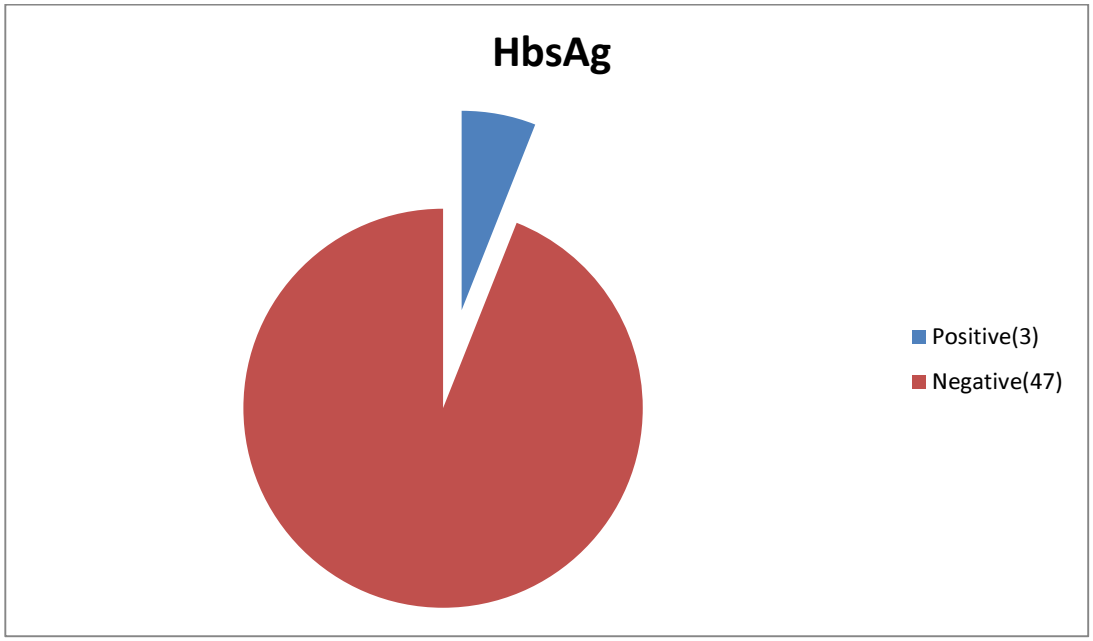
The p value is 0.001

Here the comparison of PT prolongation with mean IL 6 is done. This correlation is statistically significant since the p value is 0.001

HbsAg Positivity and Negativity

HbsAg	No of patients
Positive	3
Negative	47

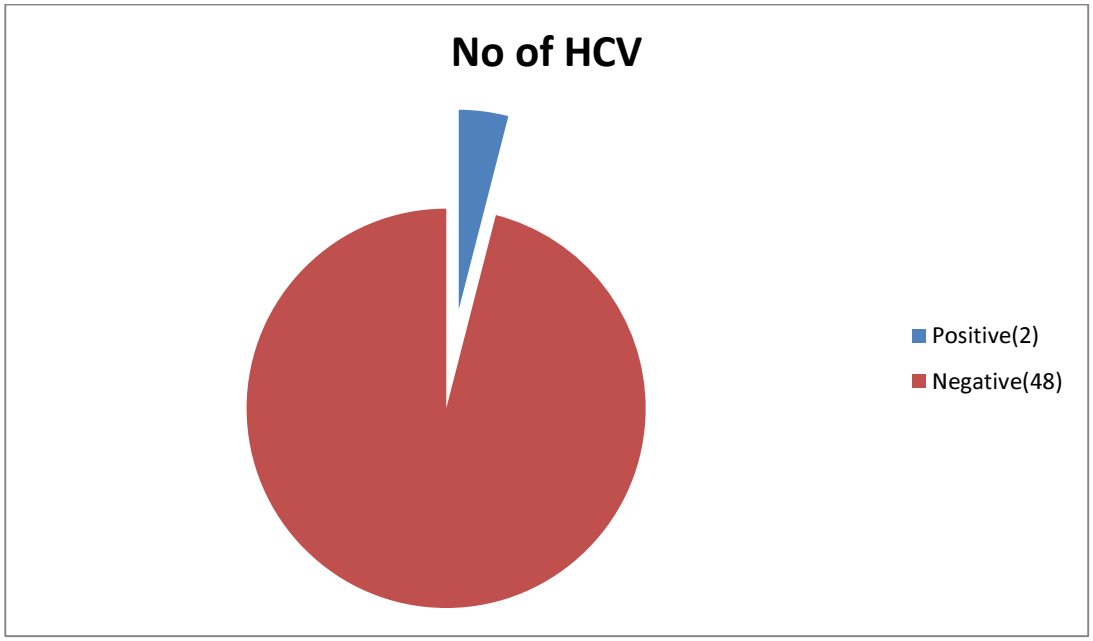
TABLE NO: 16



HCV Positivity and Negativity

HCV	No of patients
Positive	2
Negative	48

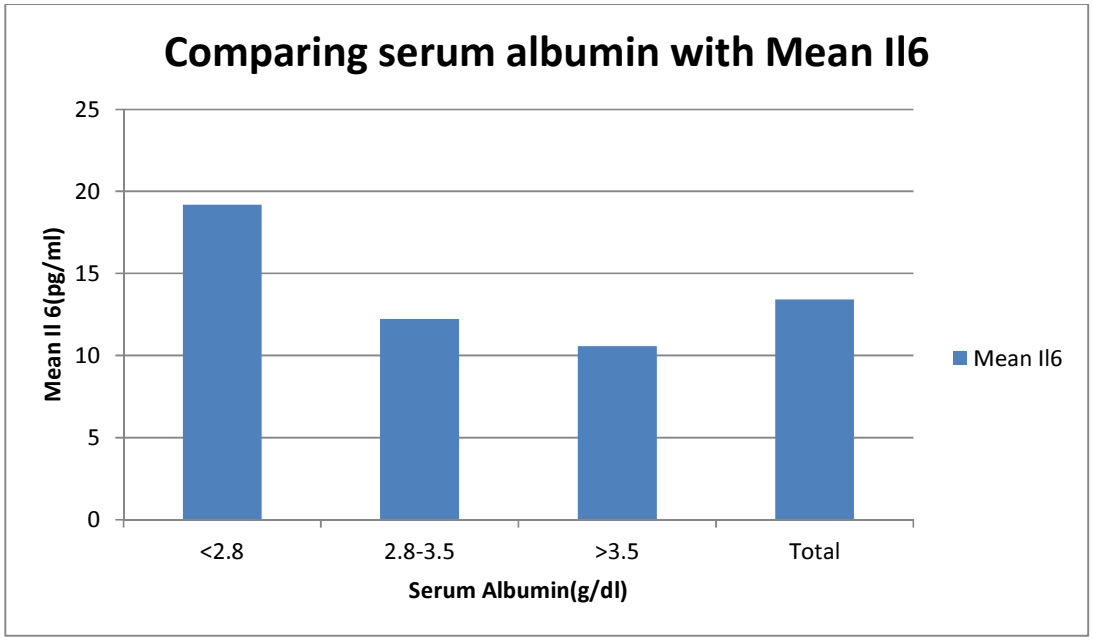
TABLE NO: 17



Albumin and Mean IL 6

Serum albumin(g/dl)	No of patients	Mean IL 6(pg/ml)
< 2.8	12	19.192
2.8-3.5	23	12.243
> 3.5	15	10.567
Total	50	13.408

TABLE NO: 18



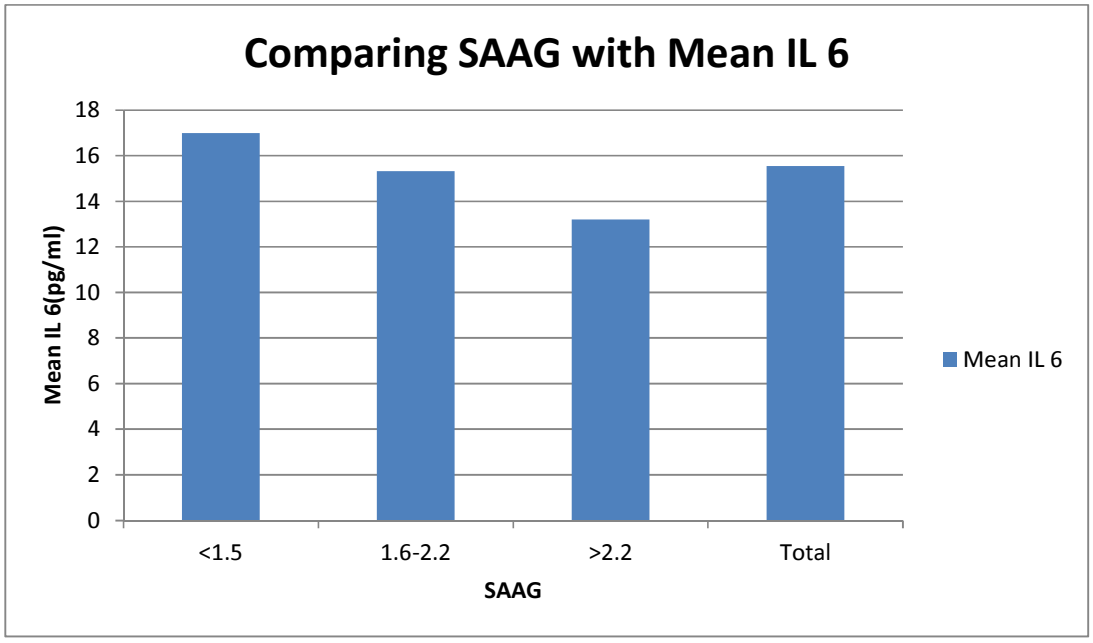
The p value is 0.001

Here the comparison of serum albumin with mean IL 6 is done. This correlation is statistically significant since the p value is 0.001

SAAG with Mean IL 6

SAAG	No of patients	mean IL 6(pg/ml)
< 1.5	10	16.990
1.6-2.2	20	15.310
> 2.2	4	13.200
Total	34	15.556

TABLE NO: 19



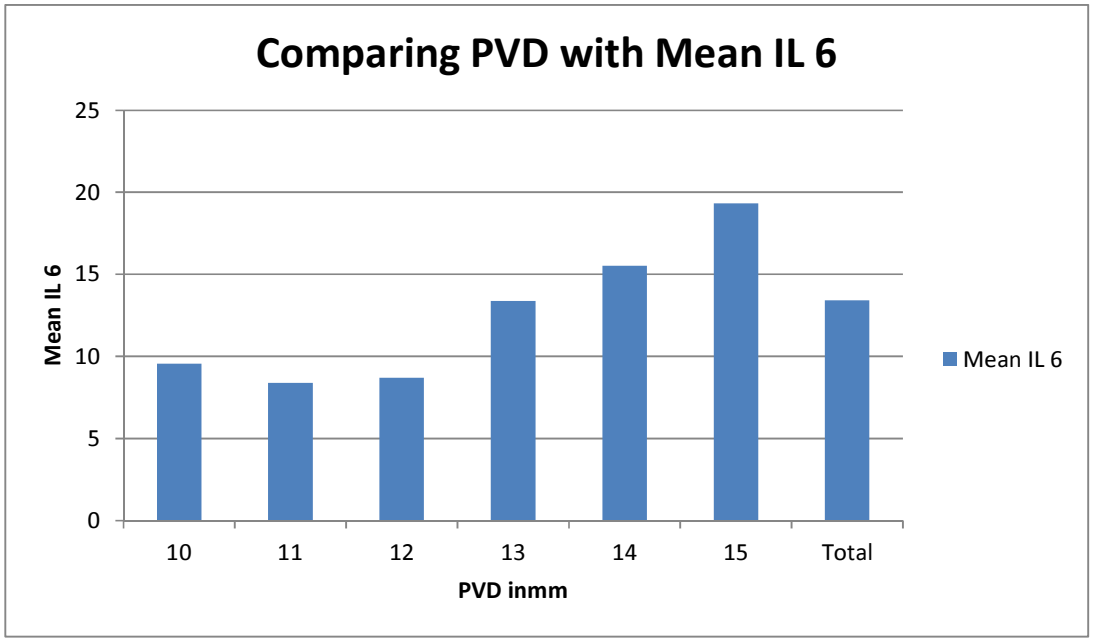
The p value is 0.215

Here the comparison of SAAG with mean IL 6 is done. This correlation is not statistically significant since the p value is 0.215

Portal vein diameter and Mean IL6

Portal vein diameter in mm	No of patients	mean IL 6(pg/ml)
10	3	9.567
11	5	8.380
12	3	8.700
13	20	13.365
14	16	15.525
15	3	19.333
Total	50	13.408

TABLE NO: 20



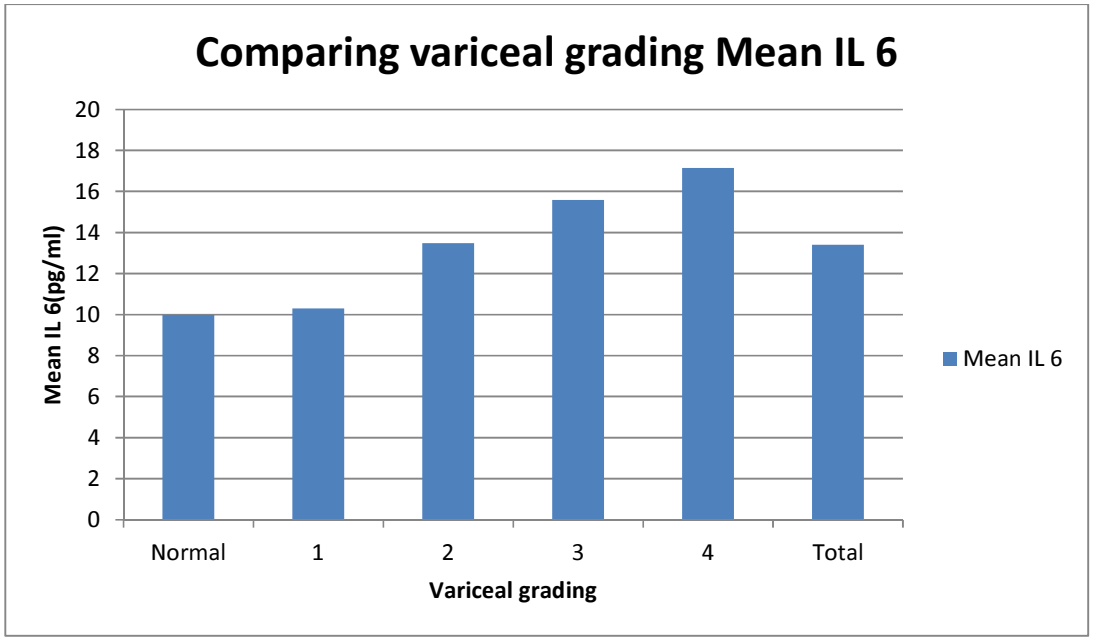
The p value is 0.001

Here the comparison of Portal vein diameter with mean IL 6 is done. This correlation is statistically significant since the p value is 0.001

Variceal grading and Mean IL6

Variceal grading	No of patients	mean IL 6(pg/ml)
Normal	16	9.975
1	3	10.300
2	12	13.483
3	5	15.580
4	14	17.157
Total	50	13.408

TABLE NO: 21



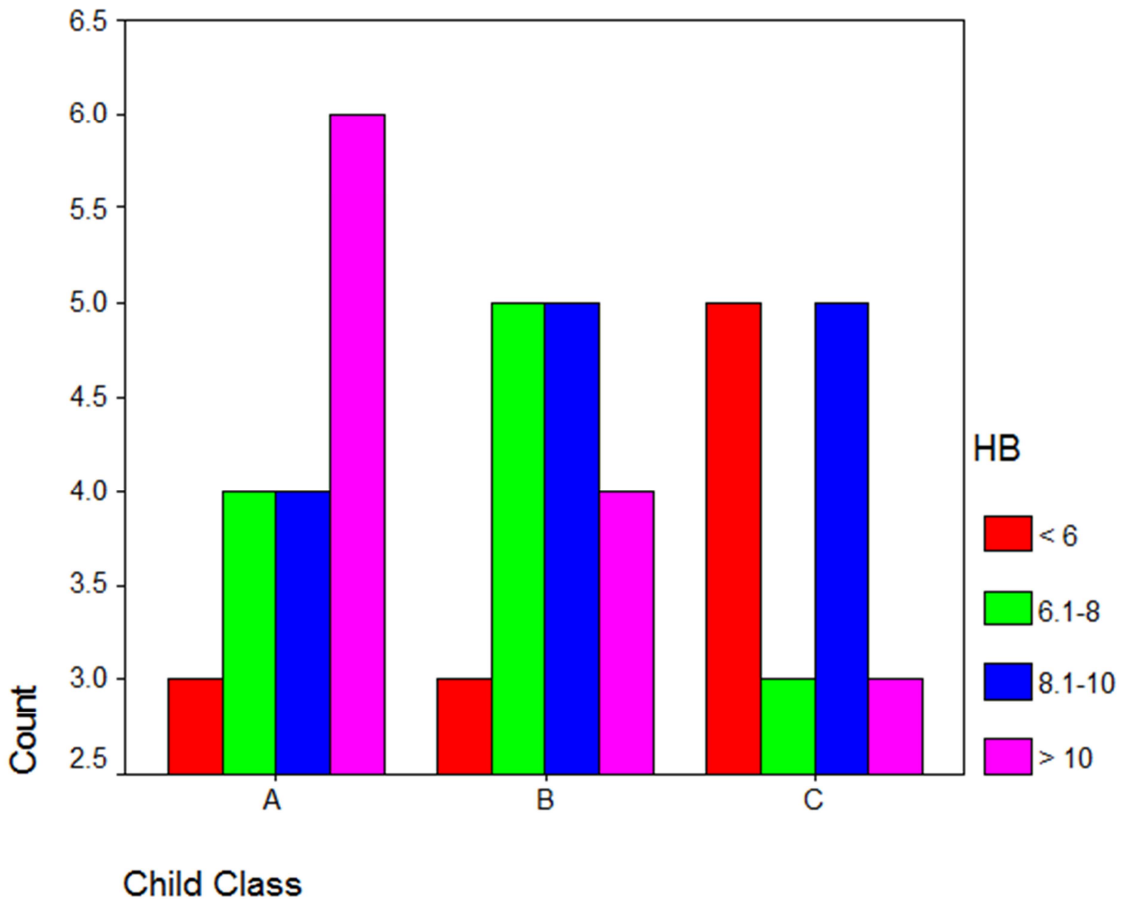
The p value is 0.001

Here the comparison of Portal vein variceal grading with mean IL 6 is done. This correlation is statistically significant since the p value is 0.001

Child class and Hb%

			Hb(gm%)				
			< 6	6.1-8	8.1-10	> 10	Total
Child Class	A	Count	3	4	4	6	17
		% within Child Class	17.6%	23.5%	23.5%	35.3%	100.0%
		% within HB	27.3%	33.3%	28.6%	46.2%	34.0%
	B	Count	3	5	5	4	17
		% within Child Class	17.6%	29.4%	29.4%	23.5%	100.0%
		% within HB	27.3%	41.7%	35.7%	30.8%	34.0%
	C	Count	5	3	5	3	16
		% within Child Class	31.3%	18.8%	31.3%	18.8%	100.0%
		% within HB	45.5%	25.0%	35.7%	23.1%	32.0%
Total		Count	11	12	14	13	50
		% within Child Class	22.0%	24.0%	28.0%	26.0%	100.0%
		% within HB	100.0%	100.0%	100.0%	100.0%	100.0%

TABLE NO:22



The p value is 0 .876

Here the comparison of Child class with Hemoglobin is done. This correlation is not statistically significant since the p value is 0.876

DISCUSSION

DISCUSSION:

Jolanta-Zuwala-Jagiello et al observed that rising values of serum IL 6 level in patients with cirrhosis of varying causes are correlated with child pugh score while assessing disease severity. The values are 8.8pg/ml, 12.3pg/ml and 18.9pg/ml for child pugh scrore A, B and C respectively [52].

In our study rising levels of serum IL 6 is noted while correlating with Child pugh score from A to C. The mean values of serum IL 6 level in patients with cirrhosis for Child class A, B and C are 8.876, 13.041 and 18.612 respectively. So our study is well correlating with the reference study since the p value for statistical significance is 0.001

From the above correlation mentioned serum IL 6 can be used as a marker while assessing disease severity in patients with liver cirrhosis in place of modified Child pugh score with acceptable statistical significance.

Total no of alcoholics included in our study from the study population (50) is 45 excluding 2 of hepatitis C and 3 of hepatitis B related cirrhosis. As vedat goral et

al mentioned, rising serum IL 6 level is independent of etiological factors [53] while assessing disease severity, this could not be possible in our study, since most of the patients included in our study are alcoholics with all other possible causes excluded.

Total number of males and females are 47(94%) and 3(6%) respectively. Since prevalence of alcohol use is higher among males in our country, sex relationship with rising level of IL 6 level in our study could not be done.

Not only the Child pugh score is correlating with serum interleukin 6 level with statistical significance, but also with other known parameters like mean total protein, Serum albumin, Portal vein diameter and Variceal grading on OGD scopy.

Coming to the correlation of Child pugh score with mean total protein, Child class A, B and C is having mean total protein values of 6.41, 6.13 and 5.71respectively. This correlation is observed to have statistical significance since the p value is 0.006. In this context, we can take even total protein values as a acceptable parameter to assess disease severity in place of modified child pugh score, particularly if there is difficulty in calculating this score.

The serum Albumin values for Child pugh class A, B and C are 3.582, 3.253, 2.650 respectively. While taking serum albumin alone in assessing disease severity in liver cirrhosis, the statistical significance is well appreciated. The p value is around 0.001.Comparatively Serum albumin is having more statistical significance than total serum protein.

Portal vein diameter calculated by Portal Doppler Study if greater than or equal to 13, it can be assumed that patient is having portal hypertension. In our study Portal vein diameter values for Child pugh class A, B and C are 11.82 mm, 13.29 mm and 13.94 mm respectively and for total 50 patients it is 13 mm. It is correlated statistically with Child pugh class with p value of 0.001. Patients with child pugh class B and C definitely having portal hypertension since the mean values are 13.29 mm and 13.94 mm than patients with Child pugh class A.

Variceal grading by OGD scopy is significantly correlated with modified child pugh scoring system. The p value for this correlation is 0.001. Child class A having total number of patients 17 is observed in our study to have normal OGD scopy for 10 patients and variceal grading of 1 and 2 with 3patients each respectively.

Child class C having total number of 16 patients is observed to have normal OGD scopy for 0 patients and grade 4 for 11 patients and grade 3 for 2 patients. So increasing values of variceal grading is observed if Child class is increasing.

Variceal grading also is correlated with serum IL 6 level with statistical significance. The p value for this correlation is 0.001. Raising levels are of mean serum interleukin 6 is proved with raising variceal grading score. The mean serum IL6 values for the variceal grading scores of normal, 1, 2, 3, 4 and 5 are 9.975, 10.300, 13.483, 15.580, 17.157 and 13.408.

So from this analysis we can consider serum IL 6 as a non-invasive parameter for the identification of varices in patients with liver cirrhosis, especially when facilities for OGD scopy are not available or when patient cannot be shifted to OGD room if extremely ill.

Portal vein diameter and serum interleukin 6 are correlated in patients with liver cirrhosis in our study. There is a positive correlation obtained with p value of 0.001. The mean IL 6 values for the portal vein diameter 10mm, 11 mm, 12 mm, 13 mm, 14 mm and 15 mm for 50 patients are 9.567, 8.380, 8.700, 13.365, 15.525, 19.333 and 13.408 pg/ml respectively.

Presence of portal hypertension is considered if portal diameter is greater than 13 mm. 39 patients having portal diameter of 13mm or greater have values of serum IL 6 between 13.365pg/ml and 19.333pg/ml. So serum IL 6 values greater than 13 pg/ml can be better taken as a cut of value to say that presence of portal hypertension is suggested in patients of liver cirrhosis of mostly having alcoholic etiology.

Though use of portal Doppler study is invaluable in patients with liver cirrhosis, IL 6 can be also considered as a marker for identification of portal hypertension as a noninvasive test. Statistical significance of correlation between serum IL 6 and serum albumin is also proved to be good, since the p value is 0.001. So worsening of liver function with increasing levels of serum IL 6 is another inference from this study.

Raising serum IL 6 level is correlated with prolongation of Prothrombin time. Significant statistical correlation is obtained with p value of 0.001. Mean serum interleukin values for prolongation of prothrombin time < 2, 2.1-4, 4.1-6, > 6 are11.011, 14.760, 19.233 and 25.300pg/ml. So by knowing the value of raised

serum interleukin 6 in patients with liver cirrhosis, we can assume risk of bleeding in patients with liver cirrhosis.

LIMITATIONS OF STUDY

LIMITATIONS OF STUDY:

Most of the patients included in this study are male. Since the prevalence of alcoholism is more in males in our country, Most of the patients included in this study are male alcoholics. So age and sex related correlation of this study are not possible.

Since most of the patients are having the problem for 2 years in this study, correlation of duration of illness with child pugh class is not significant.

Since prediabetes, prehypertension, and initial states of most of the inflammatory conditions are not considered in this study, confounding factors related with these factors are to be considered.

CONCLUSION

CONCLUSION :

Raised levels serum Interleukin 6 is correlated well with the modified child pugh scoring system in patients with liver cirrhosis of varying causes. So disease severity can be better assessed with Serum interleukin 6 in patients with liver cirrhosis alone or in association with modified child pugh score.

Cost is considered in doing serum interleukin 6 assays. Though difficult, making this test available to all care level, will be helpful in assessing disease severity in patients with liver cirrhosis and in taking decisions regarding treatment quickly.

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ANNEXURE

PROFORMA

MASTER CHART

INSTITUTIONAL ETHICS COMMITTEE

CERTIFICATE OF APPROVAL

PLAGIARISM LOADED COPY

PROFORMA

SERUM INTERLEUKIN 6 LEVEL IN PATIENTS WITH LIVER CIRRHOSIS OF ANY CAUSE AND ITS CORRELATION WITH CHILD PUGH SCORE IN ASSESSING DISEASE SEVERITY

Name: Age: Sex:

Address: Occupation:

Symptoms:

Abdominal pain
Abdominal distention
Swelling of legs
jaundice
yellowish disc of urine
reduced urine output
haemetemesis /melena
haemetochezia
fever/chills/rigor
loss of weight
loss of appetite
altered sensorium
mood changes
sleep disturbance

Past history:

Known case of cirrhosis and portal hypertention- (y/m)
Diabetes mellitus/Bronchial asthma/COPD
Hypertension/coronary artery disease
Tuberculosis/renal disorder/thyroid disorder
Previous h/o jaundice/blood transfusion/tattoing
h/o drug abuse
Other co-morbid illnesses

Personal history:

Smoking

Alcoholism: period (y/m)

Quantity (ml/day)

Alcohol %

Branded/unbranded

Diet: veg/nonveg/ mixed

General examination:

Anthropometry:

Height(in cm): Weight(in kg):

PULSE:

BLOOD PRESSURE: **RR:** **TEMP:**

GENERAL EXAMINATION:

SYSTEMIC EXAMINATION:

CVS: RS: ABDOMEN: CNS:

INVESTIGATIONS:

Hemogram			**RFT**		
TC		cells/mm^3	Glucose (F)		mg/dl
DC			Glucose (PP)		mg/dl
ESR		mm/hr	Urea		mg/dl
Hb		g/dl	Creatinine		mg/dl
PCV		%	Na+		mEq/l
Platelets		lakhs/mm^3	K+		mEq/l
RBCs		million/mm^3	**Urinanalysis**		
Lipid profile			Albumin		

Total cholesterol		mg/dl	Sugar	
LDL		mg/dl	Deposits	
HDL		mg/dl	**Microalbuminuria**	
Triglycerides		mg/dl	**Culture**	

ECG:

PT/INR: aPTT:

LFT		
TB		mg/dl
DB		mg/dl
IB		mg/dl
AST		IU
ALT		IU
ALP		IU
TP		mg/dl
ALB		mg/dl
GLO		mg/dl

Ascitic fluid analysis: albumin:
SAAG

Portal Doppler study:

CHILD PUGH SCORE	1	2	3	Score	Child cl
Ascites	none	Mild-mod	Sev/ref	5-6	A
Encephalopathy	none	Mild(I-II)	Mod/sev(II-IV)	7-9	B
Bilirubin(mg/dl)	<2	2-3	>3	10-15	C
Alb(g/dl)	>3.5	3.5-2.8	<2.8		
PT(sec inc)	1-3	4-6	>6		

ULTRASONOGRAM OF ABD:

SERUM IL6 LEVEL

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. M. Mohamed Kilji
PG in MD General Medicine
Madras Medical College, Chennai -3

Dear Dr. M. Mohamed Kilji

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Serum interleukin 6 levels in patients with liver cirrhosis of any cause and its correlation with child pugh score in assessing disease severity" No.30062012.

The following members of Ethics Committee were present in the meeting held on 19.06.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. K. Ramadevi MD Prof of Biochemistry, MMC, Ch-3	-- Member
3.	Prof. R. Nandhini MD Director, Inst. of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
6.	Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member

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

Sd/ Chairman & Other Members

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

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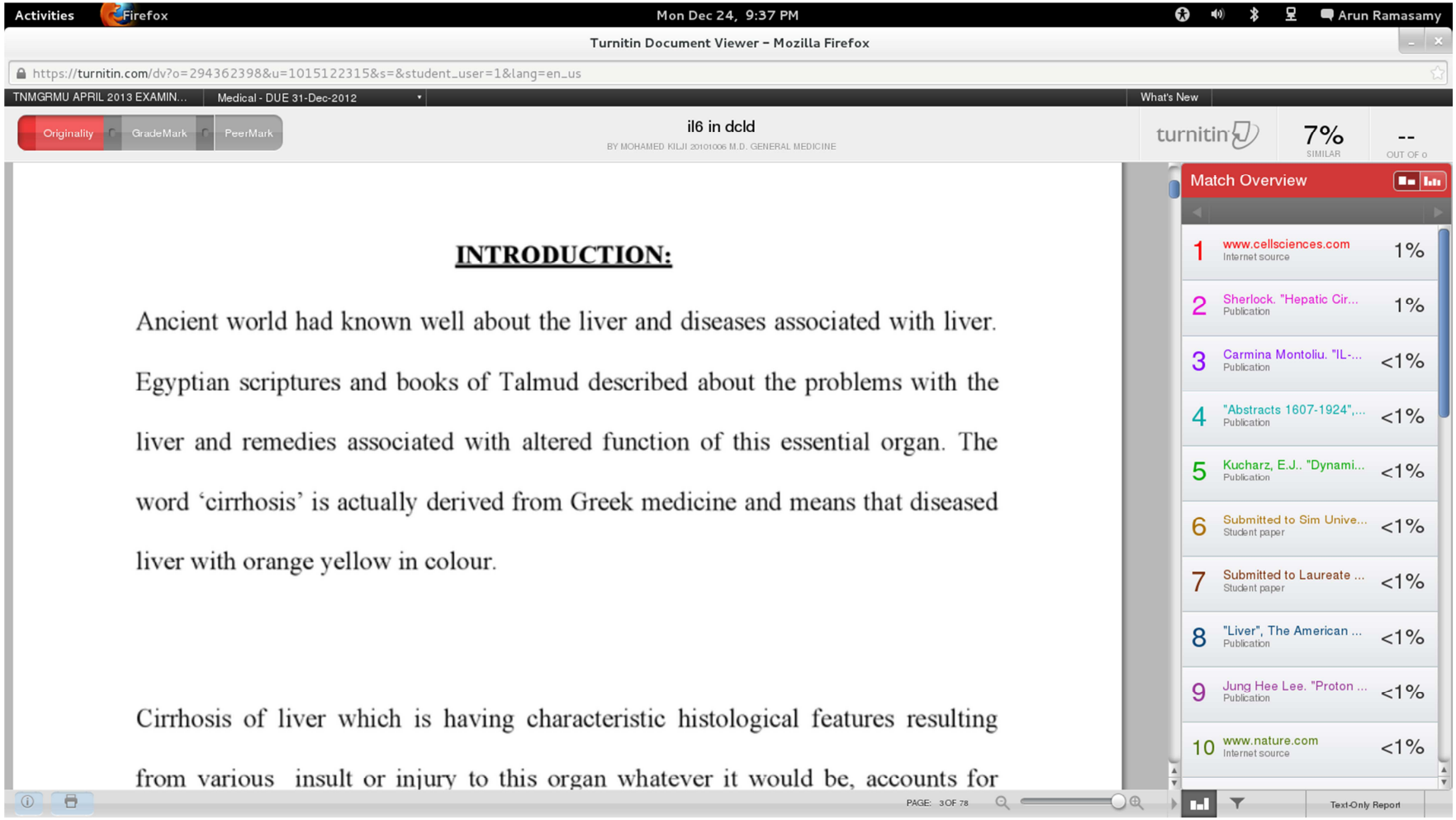
Total words	8578

First 100 words of your submission

1 INTRODUCTION: Ancient world had known well about the liver and diseases associated with liver. Egyptian scriptures and books of Talmud described about the problems with the liver and remedies associated with altered function of this essential organ. The word 'cirrhosis' is actually derived from Greek medicine and means that diseased liver with orange yellow in colour. Cirrhosis of liver which is having characteristic histological features resulting from various insult or injury to this organ whatever it would be, accounts for fourth major cause of mortality world wide, and one of the leading cause of mortality in india. Since the diagnosis of liver diseases went through various stages of...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INTRODUCTION:
Ancient world had known well about the liver and diseases associated with liver. Egyptian scriptures and books of Talmud described about the problems with the liver and remedies associated with altered function of this essential organ. The word 'cirrhosis' is actually derived from Greek medicine and means that diseased liver with orange yellow in colour.
Cirrhosis of liver which is having characteristic histological features resulting from various insult or injury to this organ whatever it would be, accounts for
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Text-Only Report

MASTER CHART

ID	IP NO	AGE	SEX	DURATION	Hb	PLATELET	PT	TB	ALP	HBsAg	HCV	Ascites	Encephalopathy
1	110505	36	m	2 years	4.2	1.22	2	3.9	152	neg	neg	yes	no
2	112154	35	m	IP	7.2	1.32	1	3.5	138	neg	neg	yes	no
3	112045	50	m	3 years	8.5	1.14	2	0.8	131	neg	neg	yes	no
4	107493	49	m	6 years	8.8	1.21	0.2	5.7	148	neg	neg	no	no
5	40342	42	m	IP	9.2	1.02	1.2	1.6	112	neg	neg	yes	no
6	41899	46	m	2 years	4.8	1	1.8	1.4	106	neg	neg	no	no
7	40111	49	m	2 years	9.3	0.9	1.9	6.6	140	neg	neg	yes	no
8	59539	48	m	1 year	8	0.65	0.4	2.5	182	neg	neg	no	no
9	107001	45	m	6 years	6	1.8	4.2	8.8	194	neg	neg	no	yes
10	101113	50	m	5 years	7.2	1.15	0.4	1.9	116	neg	neg	yes	no
11	107934	41	m	IP	9.4	0.8	2	0.8	62	neg	neg	yes	no
12	109519	39	m	IP	7.1	1.16	0.6	10.6	237	neg	neg	yes	no
13	108484	44	m	7 years	10	0.66	5.2	3.6	151	neg	neg	no	yes
14	108614	48	m	IP	7	1.8	0.1	1.2	92	neg	neg	yes	no
15	33801	43	f	3 .5 years	3.5	1	0.3	0.7	173	neg	neg	yes	no
16	6037/12	48	m	2 years	5.9	0.8	2.2	2.2	162	neg	neg	yes	no
17	114296	50	m	3 years	10.6	1.81.	1.7	2.8	93	neg	neg	yes	no
18	6171/11	48	m	1.5 years	9	1.1	1.7	1.8	95	neg	neg	no	no
19	41322	45	m	6 years	9	2.5	4.6	2.2	108	neg	neg	yes	no
20	113818	48	m	5 years	5.7	1.2	4.2	8.7	145	neg	neg	no	yes

21	113690	32	m	4 years	8.6	1.56	2.1	15.8	268	neg	neg	yes	no
22	112489	45	m	1 year	14	2.2	0.4	7	173	neg	neg	yes	no
23	111697	40	m	3 years	7.4	1.25	2.3	5.9	153	neg	neg	no	no
24	113315	45	m	2.5 years	6.9	0.78	2.1	5.4	182	neg	neg	no	no
25	111345	38	m	IP	12.8	1.8	1.2	1.6	115	neg	neg	no	no
26	63744	27	m	1 year	5.9	0.66	3.7	1.9	127	neg	neg	yes	no
27	108976	50	m	6 years	3.8	1.12	2.6	3.9	84	neg	neg	yes	no
28	101456	50	f	Nonalcoholic	9.8	0.98	2.1	3	196	neg	pos	yes	no
29	101670	45	m	6 years	11.6	1.98	2.2	6.4	269	neg	neg	no	no
30	111094	38	m	Nonalcoholic	9.2	1.8	2	2.5	178	pos	neg	yes	no
31	63980	41	m	2 years	7.8	1.12	4.7	4.1	211	neg	neg	yes	no
32	110567	38	m	4 years	6.8	1.32	3.2	5.6	112	neg	neg	no	yes
33	66890	41	m	3.5 years	5.7	0.78	1.2	1.1	112	neg	neg	yes	yes
34	109845	45	m	2 years	11	2.1	4	4.7	134	neg	neg	no	no
35	66980	49	m	Nonalcoholic	10.7	1.12	1.7	2.5	173	pos	neg	no	no
36	103640	40	m	IP	12.8	2.52	1.8	1.8	98	neg	neg	yes	no
37	62167	31	m	IP	14.7	2.89	1.2	1.5	78	neg	neg	no	no
38	62289	35	m	1 year	10.9	1.23	2.5	2.7	167	neg	neg	yes	no
39	62289	48	m	nonalcoholic	5.9	0.76	6.2	9.2	212	neg	pos	no	yes
40	666110	46	f	nonalcoholic	6.7	0.91	0.2	1.6	145	pos	neg	yes	no
41	102876	39	m	4 years	8.9	2.98	3.2	7.2	187	neg	neg	yes	no
42	111004	47	m	1 years	9.8	1.76	1.2	2.8	101	neg	neg	yes	no
43	102834	41	m	2 years	7.9	1.09	1.8	2.2	178	neg	neg	yes	no

44	111460	45	m	0.5 years	10.9	1.45	2.2	1.2	103	neg	neg	yes	no
45	110650	50	m	5 years	11.9	0.45	4.2	6.7	301	neg	neg	yes	no
46	113088	45	m	IP	14	2.34	0.2	1.8	99	neg	neg	yes	no
47	114530	28	m	IP	15.2	2.89	1.2	1.1	95	neg	neg	yes	no
48	112674	35	m	6 years	4.6	0.68	3.8	5	289	neg	neg	no	yes
49	61329	48	m	1 years	9	1.4	1.5	1.8	101	neg	neg	no	no
50	102399	50	m	2 years	7.8	1.56	3.2	2.1	143	neg	neg	yes	no

ID	IP NO	AGE	SEX	TP	Serum Alb	Ascitic Alb	SAAG	PV Diameter	Variceal Grade	Child Class	Child Score	IL6
1	110505	36	m	6	3.2	2	1.2	14mm	2	B	8	14.2
2	112154	35	m	5.8	3.2	1.2	2	13mm	2	B	9	10.3
3	112045	50	m	5.9	2.9	1.2	1.5	14mm	4	B	7	12.2
4	107493	49	m	5.7	2.9	1.2	1.7	13mm	N	B	7	12.4
5	40342	42	m	6.5	3.8	nil	NA	11mm	N	A	6	9.8
6	41899	46	m	6.1	2.9	nil	NA	10mm	N	A	6	9.2
7	40111	49	m	5.7	2.6	1	1.6	14mm	4	C	11	17.4
8	59539	48	m	6.1	3.2	nil	NA	12mm	N	A	6	8.2
9	107001	45	m	6.2	3.5	1.4	2.1	14mm	4	C	10	16.9
10	101113	50	m	6.9	4.1	nil	NA	13mm	2	A	5	11.9
11	107934	41	m	6.8	3.7	nil	NA	13mm	1	A	6	9

12	109519	39	m	6.8	3.2	1.1	2.1	14mm	4	C	10	16.1
13	108484	44	m	6.5	3.7	1	2.7	14mm	2	C	10	16.4
14	108614	48	m	6.2	3.5	nil	NA	13mm	N	A	5	9.8
15	33801	43	f	6	3.8	2.1	1.7	12mm	N	A	5	9.4
16	6037/12	48	m	5.3	2.9	1.2	1.7	14mm	2	B	8	13.6
17	114296	50	m	6.8	3.2	1.4	1.8	14mm	4	B	8	13.9
18	6171/11	48	m	6	3.6	nil	NA	13mm	3	A	5	7.3
19	41322	45	m	5.7	2.8	1	1.8	15mm	4	C	10	18.3
20	113818	48	m	5.2	2.2	1	1.2	13mm	2	C	12	19.7
21	113690	32	m	5.7	2.9	1	1.9	14mm	4	C	10	18.1
22	112489	45	m	6	3.8	1	2.8	13mm	N	B	7	10.7
23	111697	40	m	6	3.2	1.3	1.9	14mm	2	B	8	12.8
24	113315	45	m	5.7	3.9	1.6	2.3	13mm	4	B	7	11.6
25	111345	38	m	5.9	3	nil	NA	13mm	1	A	6	12.3
26	63744	27	m	6.3	3.5	nil	NA	13mm	2	A	6	9.1
27	108976	50	m	6.2	2.5	1	1.4	14mm	4	C	10	16.8
28	101456	50	f	6.2	3.8	1.2	2.6	14mm	3	B	8	14.1
29	101670	45	m	7.8	2.8	0.9	1.9	15mm	2	C	10	16.8
30	111094	38	m	6	2.9	1.6	1.3	13mm	N	B	8	13.9
31	63980	41	m	5.2	2.7	1.1	1.6	14mm	4	C	11	21.2
32	110567	38	m	5	2.2	1	1.2	13mm	4	C	12	23.4
33	66890	41	m	6.4	3.6	1.4	2.2	11mm	2	B	5	13.6
34	109845	45	m	5.9	2.5	1	1.5	14mm	3	C	10	17.1

35	66980	49	m	6.4	3.1	1.2	1.9	13mm	N	B	7	12.5
36	103640	40	m	6.9	3.8	nil	NA	10mm	1	A	6	9.6
37	62167	31	m	6	3.4	nil	NA	11mm	N	A	5	6.1
38	62289	35	m	6.6	3.1	1.6	1.5	13mm	N	B	8	13.2
39	62289	48	m	4.7	2	0.8	1.2	13mm	3	C	15	25.3
40	666110	46	f	6.8	3.7	nil	NA	13mm	N	A	6	8.4
41	102876	39	m	5.1	2.6	1	1.6	14mm	4	C	10	13.5
42	111004	47	m	6.2	3	1.2	1.8	13mm	N	B	9	13.7
43	102834	41	m	6.4	3.2	1.8	1.4	14mm	3	B	8	14.1
44	111460	45	m	7	3.9	nil	NA	12mm	2	A	6	8.5
45	110650	50	m	4	1.9	0.3	1.6	15mm	4	C	13	22.9
46	113088	45	m	6.8	3.6	nil	NA	10mm	N	A	6	9.9
47	114530	28	m	6.5	3.9	nil	NA	11mm	N	A	6	8.3
48	112674	35	m	5.6	2.3	0.7	1.6	13mm	4	C	11	17.9
49	61329	48	m	6.2	3.5	nil	NA	11mm	N	A	5	4.1
50	102399	50	m	6.8	3.4	1.4	2	13mm	2	B	8	14.9